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Supplement to Gynecologic Oncology

GYNECOLOGIC ONCOLOGY

ABSTRACTS PRESENTED FOR THE 42ND ANNUAL MEETING OF THE SOCIETY OF GYNECOLOGIC ONCOLOGISTS

Edited by
Daniel Clarke-Pearson, MD and
Robert Bristow, MD, MBA

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GYNECOLOGIC ONCOLOGY

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GYNECOLOGIC ONCOLOGY

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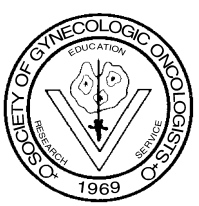
Aims and Scope: *Gynecologic Oncology*, an international journal, is devoted to the publication of clinical and investigative articles that concern tumors of the female reproductive tract. We welcome the submission of investigations relating to the etiology, diagnosis, treatment, and prevention of female cancers, as well as research from any of the disciplines related to this field of interest. Research areas include: cell and molecular biology, chemotherapy, clinical trails, epidemiology, genetics, immunology and vaccines, 'omics', pathology and cytology, quality of life, radiation therapy, surgery, and translational research. All aspects of scholarship related to tumors of this region are welcome, with originality, quality, and clarity the chief criteria of acceptance.



The Society of Gynecologic Oncologists was founded in 1969 to further the education, research and service of gynecologic oncologists, as well as the subspecialty of gynecologic oncology. In 2003, with the introduction of a new SGO logo, the original logo, as seen here, was honored with the designation as the Society's corporate seal.

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BRIEF SUMMARY

Description: Seprafilm® Adhesion Barrier (membrane) is a sterile, bioresorbable, translucent adhesion barrier composed of two anionic polysaccharides, sodium hyaluronate (HA) and carboxymethylcellulose (CMC). Together, these biopolymers have been chemically modified with the activating agent 1-(3-dimethylaminopropyl) -3- ethylcarbodiimide hydrochloride (EDC). Seprafilm should be stored between 36-86°F (2-30°C) until the package expiration date.

Indications: Seprafilm Adhesion Barrier is indicated for use in patients undergoing abdominal or pelvic laparotomy as an adjunct intended to reduce the incidence, extent and severity of postoperative adhesions between the abdominal wall and the underlying viscera such as omentum, small bowel, bladder, and stomach, and between the uterus and surrounding structures such as tubes and ovaries, large bowel, and bladder.

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Warnings: Seprafilm Adhesion Barrier should not be wrapped directly around a fresh anastomotic suture or staple line, whether or not the anastomosis was diverted. An increased potential for abdominal events related to anastomotic leak was identified in a post-approval study when Seprafilm Adhesion Barrier was wrapped directly around a fresh anastomotic suture or staple line. Seprafilm Adhesion Barrier is supplied sterile and must not be re-sterilized.

Precautions: The safety and effectiveness of Seprafilm Adhesion Barrier in combination with other adhesion prevention products and/or in other surgical procedures not within the abdominopelvic cavity have not been established in clinical studies. The safe and effective use of Seprafilm Adhesion Barrier in pregnancy has not been evaluated. No clinical studies have been conducted in pregnant women or women who have become pregnant within the first month after exposure to Seprafilm Adhesion Barrier. Therefore, this product is not recommended for use during pregnancy and avoidance of conception should be considered during the first complete menstrual cycle after use of Seprafilm Adhesion Barrier.

Foreign body reactions may occur with Seprafilm Adhesion Barrier, as with any implanted material.

The safety and effectiveness of Seprafilm Adhesion Barrier has not been evaluated in clinical studies in the presence of frank infections in the abdominopelvic cavity. Seprafilm Adhesion Barrier did not promote the growth of test microorganisms within the abdominopelvic cavity in animal studies.

The safety and effectiveness of Seprafilm Adhesion Barrier has not been evaluated in clinical studies in the presence of malignancies in the abdominopelvic cavity.

A mean of two of the 5" x 6" Seprafilm membranes were applied to patients in the two pre-market studies. In the post-market study a mean of 4.4 of the 5" x 6" membranes were applied to patients. Long term clinical outcomes such as chronic pain and infertility have not been determined in clinical studies.

Adverse Events: Seprafilm Adhesion Barrier has been studied in five clinical trials involving 2133 patients. Two safety pilot studies enrolled a total of 32 patients, two pivotal studies enrolled a total of 310 patients. One of the pivotal studies enrolled ulcerative colitis and familial polyposis patients undergoing colectomy followed by ileal pouch anal anastomosis with temporary ileostomy. The second pivotal study enrolled uterine myomectomy patients.

A post-market study enrolled 1791 patients (882 Seprafilm, 909 Control) with similar baseline characteristics from the United States, Canada, and Europe, who underwent intestinal resections or adhesiolysis for treatment of bowel obstruction. Although there was no difference in the overall number of patients in this postmarket study with serious adverse events, a higher incidence of anastomotic leak related events was observed in patients who had Seprafilm wrapped around a fresh anastomotic site. These complications were not observed when Seprafilm was used throughout the abdomen, without deliberately covering the Anastomosis.

How supplied: Seprafilm Adhesion Barrier is packed in a Tyvek®† holder within a plastic sleeve and packed in an outer sealed foil pouch. The contents of the foil pouch are sterilized by gamma radiation.

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Seprafilm Adhesion Barrier should be stored between 36-86°F (2-30°C).

Caution: Federal law restricts this device to sale by or on the order of a physician.

References: 1. Beck DE, Cohen Z, Fleshman JW, Kaufman HS, van Goor H, Wolff BG; Adhesion Study Group Steering Committee; A prospective, randomized, multi-center, controlled study of the safety of Seprafilm adhesion barrier in abdominopelvic surgery of the intestine. Dis Colon Rectum. 2003 Oct;46(10):1310-9. 2. Becker JM, Dayton MT, Fazio VW, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double–blind multicenter study. J Am Coll Surg. 1996;183:297-306. 3. Burns, J.W., S. Cox, and A.E. Walts. Water Insoluble Derivatives of Hyaluronic Acid: United States Patent Number 5,017,229. 1991. 4. Diamond MP, For the Seprafilm Adhesion Study Group. Reduction of adhesions after uterine myomectomy by Seprafilm® membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. Fertil Steril. 1996;66:904-910. 5. Fazio VW, Cohen Z, Fleshman JW, et al. Reduction in adhesive small-bowel obstruction by Seprafilm adhesion barrier after intestinal resection. Dis Colon Rectum. 2006 Jan;49(1):1-11.

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Indication

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Important Safety Information

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Please see brief summary on the following page.

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References: 1. Becker JM, Dayton MT, Fazio VW, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. *J Am Coll Surg.* 1996;183(4):297-306. **2.** Kusunoki M, Ikeuchi H, Yanagi H, Noda M, et al. Bioresorbable hyaluronate-carboxymethylcellulose membrane (Seprafilm) in surgery for rectal carcinoma: a prospective randomized clinical trial. *Surg Today.* 2005;35(11):940-945. **3.** Fazio VW, Cohen Z, Fleshman JW, et al. Reduction in adhesive small-bowel obstruction by Seprafilm adhesion barrier after intestinal resection. *Dis Colon Rectum.* 2005;49(1):1-11.

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Foreword

The Society of Gynecologic Oncologists (SGO) is proud to host its 42nd Annual Meeting on Women's Cancer™, March 6–9, 2011 in Orlando, Florida. As the subspecialty's premier educational event, the Society wishes to express its sincere appreciation to those who have generously contributed their time in support of the scientific curriculum presented at this year's meeting; a meeting which routinely attracts more than 1,700 gynecologic oncologists and other health professional from around the world.

This supplement to *Gynecology Oncology* contains the selected abstracts scheduled for presentation at the 2011 Annual Meeting. This year, 651 abstracts, and 27 surgical films were submitted for consideration. After careful discussion and deliberation, 51 were selected for oral presentation (27 Plenary session papers, 24 Focused Plenary papers, and 42 Featured Posters, presented in a new, electronic format) along with 227 for poster presentation. Of the 27 surgical films originally submitted, five (5) were selected for presentation during a featured Focused Plenary session.

This year's abstracts were reviewed and selected by the 2011 Annual Meeting Program Committee, chaired by Robert Bristow, MD, MBA. Members of this year's Committee are:

Deborah Armstrong, MD
Dennis Chi, MD
John Farley, MD
Elise Kohn, MD
Andrew Li, MD
Sang Yoon Park, MD, PhD
Cheryl Saenz, MD
Ignace Vergote, MD, PhD
Wendy Brewster, MD, PhD
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Susan Modesitt, MD
Pedro Ramirez, MD
Alessandro Santin, MD
John V. Brown, MD
John Elkas, MD, JD
Robert Holloway, MD
Charles Landen, MD
Pamela Paley, MD
Anthony Russell, MD
Krishnansu Tewari, MD

In addition to the Program Committee, SGO members assisted with the review and grading of the abstracts. These additional abstract graders include:

David Boruta, MD
Linda Duska, MD
John Geisler, MD
Kenneth Kim, MD
Bradley Monk, MD
Mian Shahzad, MD
Israel Zighelboim, MD
Rebecca Brooks, MD
Mark Einstein, MD, MS
Whitfield Growdon, MD
Edward Kost, MD
John Schorge, MD
Pamela Soliman, MD
Linus Chuang, MD, MPH, MS
Paola Gehrig, MD
Amir Jazaeri, MD
Brigitte Miller, MD
Leigh Seamon, DO, MPH
Sean Tedjarati MD, MPH

While reviewing the abstracts included within this supplement, it is my hope that you are both educated and inspired. This new body of scientific research embodies what the Society truly represents; an organization that embraces the highest quality of new research findings, innovative patient care models and advanced surgical techniques that continue to contribute toward SGO's mission of one day eradicating women's cancers.

Again, on behalf of the SGO, I want to extend my appreciation to the member volunteers whose dedicated time assists in the Annual Meeting's overall success.

Dan Clarke-Pearson, MD
2010–2011 SGO President

0090-8258/$ – see front matter
doi:10.1016/j.ygyno.2010.12.323

Gynecologic Oncology 120 (2011) S2–S133

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Abstracts

Abstracts presented for the 42nd annual meeting of the Society of Gynecologic Oncologists

Opening Plenary Session I
Sunday, March, 6, 2011, 10:15AM–11:50AM
Floridian Ballrooms A-I
Moderator, Abstracts: 1-3: Anthony H. Russell, MD, Massachusetts General Hospital/Harvard University, Boston, MA

1

A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally advanced squamous cell carcinoma of the vulva: A Gynecologic Oncology Group study

D. Moore[1], S. Ali[2], M. Barnes[3], W. Koh[4], H. Michael[5], C. McCourt[6], H. Homesley[7], J. Walker[8]
[1]Gynecologic Oncology of Indiana, Indianapolis, IN, [2]GOG Statistical and Data Center, Buffalo, NY, [3]University of Alabama, Birmingham, AL, [4]Fred Hutchinson Cancer Research Center, Seattle, WA, [5]Indiana University School of Medicine, Indianapolis, IN, [6]Women & Infants Hospital/ Brown University, Providence, RI, [7]Wake Forest University Medical Center, Winston-Salem, NC, [8]University of Oklahoma, Oklahoma City, OK

Objective: The purpose of this study was to determine the efficacy and toxicity of radiation therapy and concurrent weekly cisplatin chemotherapy in achieving a complete clinical and pathologic response when used for the primary treatment of locally advanced vulva carcinoma.

Patients with locally advanced (T3 or T4 tumors not amenable to surgical resection via radical vulvectomy), previously untreated squamous cell carcinoma of the vulva were treated with radiation (180 cGy daily × 32 fractions = 5760 cGy) plus weekly cisplatin (40 mg/m^2) followed by surgical resection of residual tumor (or biopsy to confirm complete clinical response). Management of the groin lymph nodes was standardized but, along with survival, was not a statistical endpoint.

Results: A planned interim analysis indicated sufficient activity to reopen the study to a second stage of accrual. Among 58 evaluable patients there were 40 (69%) who completed study treatment. Reasons for prematurely discontinuing treatment included: patient refusal ($n=4$), toxicity ($n=9$), death ($n=2$), and other ($n=3$). There were 37 patients with a complete clinical response (37/58, 64%). Among these women there were 34 who underwent surgical biopsy and 29 (78%) who also had a complete pathologic response. Common adverse effects included leukopenia, pain, radiation dermatitis, pain and metabolic effects.

Conclusions: This combination of radiation therapy plus weekly cisplatin yielded a higher response rate than previously achieved with an alternative strategy of radiation and concurrent cisplatin plus 5-fluorouracil chemotherapy with acceptable toxicity.

doi:10.1016/j.ygyno.2010.12.008

2

From guidelines to the front line: Only a minority of the Medicare population with advanced epithelial ovarian cancer receive optimal therapy

M. Thrall, D. Flum, R. Symons, N. Weiss, H. Gray, B. Goff
University of Washington Medical Center, Seattle, WA

Objective: Optimal care for most patients with advanced ovarian cancer includes both surgery and chemotherapy. Little is known about the proportion of women in the United States who receive combination care or the sequence in which this care is delivered. This study evaluated patterns of care, frequency of completion of recommended therapy and factors associated with sequencing of therapy.

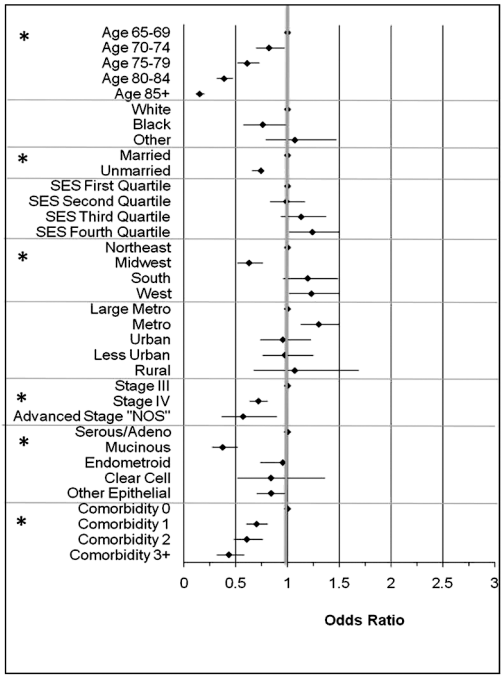
Using the SEER data with Medicare data, we identified a cohort of 8211 women with stage III/IV epithelial ovarian cancer diagnosed between 1995 and 2005. Receipt of chemotherapy or surgery was identified using Medicare claims. Logistic regression was used to evaluate factors associated with sequencing of treatment, the receipt of surgery and the completion of six cycles of chemotherapy.

Results: Four thousand three hundred seven (52.4%) women received both surgery and any chemotherapy, and only 3241 (39.1%) had surgery and at least six cycles of chemotherapy in any order in the year following their diagnosis of ovarian cancer. Surgery was performed initially in 4827 (58.8%), and 3658 of 4827 (75.8%) had subsequent chemotherapy. Two thousand seventeen (24.6%) had chemotherapy as their first treatment, and 649 of the 2017 (32.2%) had subsequent cancer-directed surgery. One thousand three hundred sixty-seven (16.7%) had no evidence of treatment in Medicare claims. Factors associated with receipt of initial chemotherapy included advancing age, nonwhite race, stage IV disease and increasing medical comorbidity (all $P<0.01$). These same factors, geographic location and nonmarried status are associated with the failure to receive both ovarian cancer-directed surgery and at least six cycles of chemotherapy in any order (all $P<0.01$). The use of surgery as initial therapy decreased from 67.5% in 1995 to 52.8% in 2005.

doi:10.1016/j.ygyno.2010.12.007

Conclusions: The majority of women in the Medicare population are not receiving optimal combination care, with only 39.1% receiving both surgery and at least six cycles of chemotherapy in any sequence. A large proportion of women are receiving chemotherapy as primary treatment for advanced ovarian cancer, and the majority of these patients do not go on to have surgery. Demographic factors such as age, race, marital status and geographic location are associated with the receipt of suboptimal care and may represent areas where quality improvement efforts can be focused.

Factors Associated with the Odds of Receiving Both Surgery and 6 Cycles of Chemotherapy in any Sequence (n=3157) Among Women Receiving Treatment with Primary Surgery or Primary Chemotherapy with Surgery Recommended (n=5785) for Advanced Ovarian Cancer



All Odds Ratios are multivariate and adjusted for age, race, marital status, median household income (reported as quartiles above), geographic region and size, stage, histology, comorbidity and diagnosis year. Odds <1 indicate a decreased likelihood having the combination of surgery and 6 cycles of chemotherapy in any order.
* indicates p<0.01 for the category

doi:10.1016/j.ygyno.2010.12.009

3

A 3' UTR KRAS variant as a biomarker of poor outcome and chemotherapy resistance in ovarian cancer

E. Ratner, F. Keane, H. Yu, D. Zelterman, T. Rutherford, A. Santin, P. Schwartz, F. Slack, D. Levine, J. Weidhaas
Yale University School of Medicine, Fairfield, CT

Objective: Ovarian cancer is a deadly disease, yet pathologic, and patient information does not accurately predict those who will ultimately succumb to their disease. We have reported an association between an inherited functional variant in the 3' UTR of the KRAS oncogene, rs61764370, and ovarian cancer. Here we evaluate the role of the KRAS variant as a biomarker of clinical outcome in ovarian cancer.

The following groups of women were tested for the KRAS variant: Women diagnosed with invasive epithelial ovarian cancer with known outcome ($n=821$); patients with ovarian cancer treated with neoadjuvant chemotherapy with known surgical outcome ($n=122$); and patients with ovarian cancer treated adjuvantly with platinum chemotherapy and evaluated for platinum resistance ($n=292$). MicroRNA expression patterns were compared in ovarian cancer tumor specimens with and without the KRAS variant.

Results: The KRAS variant predicts significantly worse outcome for patients with ovarian cancer by multivariate analysis (HR = 1.40, CI = 1.04–1.89, $P<0.029$). In addition, patients with KRAS variant-positive ovarian cancer respond poorly to neoadjuvant carboplatin and paclitaxel chemotherapy, with significantly more residual disease after surgery (OR = 24.18, CI = 1.29–453.26, $P<0.03$). Furthermore, patients with ovarian cancer who harbor the KRAS variant are platinum resistant (OR = 3.01, CI = 1.15–7.86, $P<0.024$). Potentially giving insight into this unique clinical behavior, miRNA expression patterns are significantly different in KRAS variant-positive ovarian tumors as compared with KRAS variant-negative tumors.

Conclusions: We have shown that the KRAS variant is a biomarker of poor outcome for women with invasive epithelial ovarian cancer. This appears to be due to resistance to platinum-based chemotherapy, currently the standard of care for treatment of ovarian cancer. These findings further expand the potential importance of the KRAS variant in ovarian cancer from being just a predictive marker to being a biomarker that may also allow optimization of treatment and ultimately reduced death from ovarian cancer.

doi:10.1016/j.ygyno.2010.12.010

Hugh Barber Outstanding Presentation Award
Sunday, March, 6, 2011, 11:25AM–11:50AM
Floridian Ballrooms A-I

Abstract: 4, Introduced by: Robert Bristow, MD, MBA, University of California, Irvine Medical Center, Orange, CA

4

Effectiveness of a program to prevent cervical cancer among HIV-infected women in Zambia

G. Parham[1], M. Mwanahamuntu[2], V. Sahasrabuhhde[3]
[1]University of Alabama, Birmingham, AL, [2]University of Zambia, Lusaka, Zambia, [3]Vanderbilt University, Nashville, TN

Objective: Cervical cancer kills more women in low-income nations than any other malignancy. With increased life expectancy associated with expanded antiretroviral therapy, yet without access to cervical cancer prevention services, HIV-infected women face a greater risk for persistent human papillomavirus (HPV) infections, cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (ICC). Herein we describe a programmatic evaluation of the first-ever large-scale public sector cervical cancer prevention program in Africa to be conducted alongside HIV/AIDS care and treatment programs.

In our public sector program in Lusaka, Zambia, we trained nurses to conduct screening with visual inspection with acetic acid (VIA) aided by digital cervicography. Women with visible lesions were offered same-visit cryotherapy or referred for histologic evaluation. Those with ICCs were referred for surgery or radiation. We evaluated predictors of programmatic and clinical outcomes and modeled program effectiveness by estimating the total number of ICC deaths prevented through the screening and treatment efforts.

Results: From 2006 to 2008, 21,010 women were screened for cervical cancer. Among the 31% (6572) who were infected with HIV, 53.6% (3523) had visible lesions, of whom 58.5% (2062) were eligible for cryotherapy and 41.5% (1461) were referred for histologic evaluation. Seventy-five percent (1095/1462) of patients referred for histologic evaluation complied and underwent therapy. Pathology results from 65% (715/1095) of women revealed benign abnormal-

ities in 21% (151), CIN 1 in 30% (214), CIN 2/3 in 33% (235), and ICC in 16.1% (115). Sixty-nine percent of the ICCs were early stage. Using a conditional probability model we estimate our program prevented 142 cervical cancer deaths (high − low range: 238 − 96) in 6572 HIV-infected women screened, or one cervical cancer death prevented per 46 (corresponding range: 28 − 68) HIV-infected women screened.

Conclusions: Our cervical cancer prevention efforts using setting-appropriate technology have reduced morbidity and mortality from cervical cancer among HIV-infected women in Zambia. Concerted efforts for implementing cervical cancer prevention programs integrated within HIV/AIDS care programs are warranted. Our prevention model can serve as the implementation platform for future low-cost HPV-based screening methods, and our results may provide the basis for comparison of programmatic effectiveness of future prevention efforts.

doi:10.1016/j.ygyno.2010.12.011

Plenary Session II
Sunday, March, 6, 2011, 12:10PM–1:05PM
Floridian Ballrooms A-I
Moderator, Abstracts: 5-7: Krishnansu Sujata Tewari, MD, UC Irvine Medical Center, Orange, CA

5

Incidence of nodal metastasis in endometrioid endometrial cancer risk groups: A Gynecologic Oncology Group multicenter review

M. Milam[1], J. Java[2], J. Walker[3], L. Parker[1], D. Metzinger[1], R. Coleman[4]
[1]University of Louisville, Louisville, KY, [2]Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY, [3]University of Oklahoma, Oklahoma City, OK, [4]University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: Recent Gynecologic Oncology Group (GOG) studies have demonstrated an approximate 40% rate of endometrial cancer in patients with a preoperative diagnosis of atypical endometrial hyperplasia. Management of patients with an incidental finding of endometrial cancer after a simple hysterectomy for benign indications is often based on single-institution practice patterns. The purpose of this study was to use the previously published GOG study of staging for uterine cancer (LAP2) and interrogate uterine primary characteristics (tumor size, grade, and depth of invasion) as to the risk for nodal metastasis.

This is a post hoc analysis of the previously identified 2516 women from 1996 to 2005 for the institutional review board-approved GOG study LAP2. Inclusion criteria for the patients in this analysis were women with uterine cancer of endometrioid histology and complete clinicopathologic data involving modified risk criteria. Patients identified as low risk (LR) for nodal metastasis were modified from the Mayo Clinic's criteria on endometrial cancer characteristics with three specific criteria on final pathology reports: (1) <50% invasion, (2) tumor size <2 cm, and (3) well or moderately differentiated histology. If the uterine specimen did not meet all three criteria it was viewed as high risk for nodal metastasis. Fisher's exact tests were used to compare categorical variables, and Wilcoxon rank-sum tests were used to compare continuous variables between the two groups.

Results: No statistical differences in median age, BMI, race, performance status, missing clinical data or open or minimally invasive technique were found among the risk groups or patients with and without nodal metastases. Patients with uterine specimens with high-risk characteristics were statistically at greater risk for nodal metastasis than patients with speciments with low-risk characteristics (10.7% vs 1%, $P<0.0001$). However, no significant differences were observed with respect to intraoperative complications, readmissions, reoperations or treatment-related deaths (see table).

Conclusions: In this multicenter post hoc analysis, low-risk endometrioid uterine cancer characteristics were associated with decreased risk of nodal metastasis. These criteria may be used to help guide treatment planning for reoperation in patients with incomplete surgical staging information.

Variable	Low risk ($n=389$)	High risk ($n=582$)	P value
Nodal metastasis	1% (3)	10.7% (62)	<0.0001
Both pelvic and paraaortic nodes removed	86.9% (338)	90.0% (524)	0.38
Intraoperative complications	7.5% (29)	10.1% (59)	0.15
Readmission	4.9% (19)	4.9%(29)	0.95
Reoperation	1% (4)	1.9% (11)	0.29
Treatment-related deaths	0.5% (2)	0.1% (1)	0.35

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6

MicroRNA as a novel predictor of response to bevacizumab in recurrent serous ovarian cancer: An analysis of The Cancer Genome Atlas

J. Chan[1], T. Kiet[1], A. Sherman[1], K. Fuh[1], S. Ueda[1], R. Brooks[1], D. Kapp[2], L. Chen[1], B. Monk[3]
[1]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, [2]Stanford University Medical Center, Stanford, CA, [3]Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, Phoenix, AZ

Objective: The aim of this study was to determine the association of miRNA expression and response to bevacizumab with survival in recurrent serous ovarian cancer.

Demographic, clinicopathologic, survival, and genomic data were extracted from The Cancer Genomic Atlas (TCGA) data portal. The χ^2 test, Kaplan–Meier survival estimates, and Cox proportional hazards models were employed for statistical analyses. Targetscan and Pictar genomic sequence analyses were used to identify gene targets of specific miRNAs.

Results: All patients had recurrent ovarian cancer and were treated with bevacizumab combined with chemotherapy (BC). All had serous histology and underwent primary surgery. The median time to primary recurrence was 11.3 months (range: 0.2–101.5) and five-year overall survival (OS) was $51.0 \pm 9.9\%$ with a median follow-up time of 46.0 months. The most common drugs used in combination with bevacizumab included cyclophosphamide, doxorubicin, and platinum/taxane combination. The median time to recurrence following BC treatment was 3.34 months (range: 0.23–20.46). After adjuvant chemotherapy, those who had an initial treatment-free interval (TFI) greater than the median of 3.0 months had a five-year OS of 78.3% versus 16.7% in those with less than a median TFI ($P=0.011$). Although TFI may predict for response, other prognostic factors such as age, stage, grade and optimal cytoreductive surgery did not. Correlating the clinical data with miRNA expression from the TCGA, we found that upregulation of miR-128 and miR-375 and downregulation of miR-214, miR-145*, miR-21*, miR-378 and miR-194 were associated with longer progression-free survival (PFS) after treatment with BC. On Kaplan–Meier analysis, the six-month and median PFS after BC in those with downregulation of miR-378 was 77.8% and 8.3 months compared with 33.6% and 2.8 months with normal Mir-378 ($P=0.035$). On multivariate analysis, TFI (HR = 0.754, 95% CI = 0.584–0.974, $P=0.030$) and miR-378 expression (HR = 2.042, 95% CI = 1.116–3.724, $P=0.020$) remained as independent predictors of response to BC treatment. Targetscan analysis reported that miR-378 is

likely to target genes associated with tumor angiogenesis: BMP2, MAPK1, and CBL.

Conclusions: Our data suggest that miR-378 may be associated with treatment response after chemotherapy with bevacizumab in recurrent ovarian cancer. Differential microRNA expression in ovarian cancer may have clinical utility in determining response to novel therapeutics. Further studies are warranted.

Up-regulated miR	p-value
miR-128	0.003
miR-375	0.042
Down-regulated miR	
miR-214	0.007
miR-145*	0.036
miR-21*	0.012
miR-378	<0.001
miR-194	0.001
Dis-regulated miR	
miR-222	0.028

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Prospective investigation of risk factors for gastrointestinal adverse events in a phase III randomized trial of bevacizumab in first-line therapy of advanced epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer: A Gynecologic Oncology Group study

R. Burger[1], M. Brady[2], M. Bookman[3], B. Monk[4], J. Walker[5], H. Homesley[6], J. Fowler[7], B. Greer[8], M. Boente[9], S. Liang[10]

[1]Fox Chase Cancer Center, Philadelphia, PA, [2]GOG Statistical and Data Center, Buffalo, NY, [3]Arizona Cancer Center, Tucson, AZ, [4]Creighton University School of Medicine, Phoenix, AZ, [5]University of Oklahoma, Oklahoma City, OK, [6]Wake Forest University Medical Center, Winston-Salem, NC, [7]Ohio State University, Columbus, OH, [8]University of Washington Medical Center, Seattle, WA, [9]Minnesota Oncology Hematology, P.A., Minneapolis, MN, [10]North Shore University Hospital, Manhasset, NY

Objective: The aim of this study was to prospectively evaluate potential risk factors (RFs) for the development of gastrointestinal (GI) adverse events (AEs) in patients enrolled in a double-blind, placebo-controlled phase III trial of bevacizumab (BEV) in first-line therapy of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC) or fallopian tube cancer (FTC).

Women with newly diagnosed, previously untreated stage III or IV EOC, PPC or FTC following tumor debulking and no evidence of GI obstruction were randomly allocated to three regimens: six cycles of platinum–taxane chemotherapy (CT) + placebo cycles (C) 2–22 (R1); CT + BEV (15 mg/kg) C2–6 + placebo C7–22 (R2); CT + BEV C2–22 (R3). They were treated until disease progression or development of unacceptable AEs. Patients were evaluated for a medical history (MEDH) of cardiovascular disease, diabetes, smoking, diabetes, autoimmune disease, GI disorders, chronic corticosteroid or NSAID use for any indication, small (SBR) or large (LBR) bowel resection at primary surgery, and several other factors. GI AEs were defined as grade ≥2 (NCI CTC Version 3) perforation, fistula, necrosis, or hemorrhage occurring as of C2 and ≤30 days of last protocol treatment. Fisher's exact test was used for univariate analyses of GI AEs versus RFs. A logistic model was used to estimate the relative odds of a GI AE due to BEV, adjusted for the putative RFs in the univariate analyses.

Results: The MEDH was available for 1759 (94%) of the 1873 patients enrolled; 2.8% (50/1759) had experienced a GI AE: 10 of 587 (1.7%), 20 of 587 (3.4%), and 20 of 585 (3.4%) for those assigned to R1, R2, and R3, respectively. Treatment of inflammatory bowel disease (IBD) ($P = 0.020$), SBR ($P = 0.032$), and LBR ($P = 0.016$) were significantly associated with a GI AE. The multivariate estimated relative odds of a GI AE were 13.4 (95% CI = 3.44–52.3) for treatment of IBD; 2.05 (95% CI = 1.09–3.88) for LBR; 1.95 (95% CI = 0.894–4.25) for SBR; and 2.15 for both groups receiving BEV (aggregated 95% CI = 1.05–4.40).

Conclusions: Treatment for IBD, SBR and LBR increases the risk of GI AEs in patients receiving first-line platinum–taxane chemotherapy for advanced EOC, PPC or FT. After accounting for these RFs, first-line BEV approximately doubles the odds of GI AEs, but is not increased by BEV maintenance treatment.

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Plenary Session III
Sunday, March, 6, 2011, 2:45PM–4:00PM
Floridian Ballrooms A-I

Moderator, Abstracts: 8-10: Deborah Armstrong, MD, Johns Hopkins Kimmel Cancer Center, Baltimore, MD

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First in human trial of the poly(ADP)-ribose polymerase inhibitor MK-4827 in patients with advanced cancer with antitumor activity in BRCA-deficient and sporadic ovarian cancers

R. Wenham[1], G. Wilding[2], R. Baird[3], L. Sun[4], C. Toniatti[5], M. Stroh[6], C. Carpenter[4], J. de-Bono[3], S. Sandhu[3], W. Schelman[2]

[1]H. Lee Moffitt Cancer Center, Tampa, FL, [2]University of Wisconsin Carbone Cancer Center, Madison, WI, [3]Drug Development Unit, Royal Marsden NHS Foundation Trust, Sutton, United Kingdom, [4]Merck & Company, Inc., Merck Research Laboratiories, North Wales, PA, [5]Merck & Company, Inc., Merck Research Laboratories, Boston, MA, [6]Merck Sharp and Dohme Corporation, West Point, PA

Objective: MK-4827 is a potent, selective poly(ADP)-ribose polymerase (PARP) 1/2 inhibitor with an IC_{50} of 3.8 nM. It induces selective synthetic lethality in homologous recombination (HR) repair-deficient tumors with BRCA1/2 loss and in tumor cell lines with non-BRCA-related HR defects, supporting its clinical utility in sporadic tumors. The objectives of this phase IA/IB study were to determine the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), recommended phase II dose (RP2D), pharmacokinetic and pharmacodynamic profiles, and a preliminary assessment of antitumor activity in patients with cancers likely to have HR DNA repair defects.

MK4827 was administered orally once daily in cohorts of three to six patients, enriched for BRCA-deficient and sporadic cancers associated with HR repair defects. Phase IA had enrichment for BRCA mutation carriers (BRCA-MC) with IB dose expansions in sporadic platinum-resistant high-grade serous ovarian cancer and hormone-refractory prostate cancer.

Results: Fifty-nine patients (13 males, 46 females; median age = 56 - years; 23 BRCA mutation carriers) were treated at 10 dose levels from 30 to 400 mg on days 1–21 of a 28-day cycle (C) in C1, followed by continuous dosing. Patients had received 1 or 2 ($n = 5$), ≥3 ($n = 11$), or ≥4 ($n = 40$) prior systemic treatments. Overall, DLT was observed in four patients: grade 3 fatigue in one of six patients treated with 30 mg, reversible grade 3 pneumonitis in one of six patients given 60 mg, and two cases of reversible grade 4 thrombocytopenia in six patients treated at 400 mg. The MTD was established at 300 mg. Other MK-4827-related grade 1/2 reversible adverse events included fatigue, anorexia, nausea and myelosuppression. Dose proportional pharmacokinetics was observed with a mean $t_{1/2}$ of 40 hours (range:

37–42 hours). Pharmacodynamic studies confirmed PARP inhibition in peripheral blood mononuclear cells at doses ≥80 mg. Antitumor activity was observed in both sporadic and BRCA-MC cancers. There were 11 patients with partial responses (nine ovarian, two breast, 9/11 BRCA-MC cancers, 8/11 with ongoing treatment) and four patients with stable disease (two ovarian, two NSCLC, 2/4 BRCA-MC) ≥120 days. Partial responses ranged from 75 to 483 days and stable disease from 136 to 354 days.

Conclusions: MK-4827 was well tolerated, exhibited linear pharmacokinetics, had evidence of target modulation, and had promising antitumor activity. Evidence of both PARP blockade in peripheral blood mononuclear cells and antitumor activity in both BRCA-MC and sporadic cancer has been observed. Specific cohort expansions are ongoing, and updated safety and response data will be available for the 2011 meeting.

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A unique microRNA locus at 19q13.41 sensitizes epithelial ovarian cancers to chemotherapy

C. Mach[1], J. Kim[2], C. Creighton[2], P. Gunaratne[1], M. Anderson[2]
[1]*University of Houston, Houston, TX,* [2]*Baylor College of Medicine, Houston, TX*

Objective: MicroRNAs (miRNAs) are recently discovered small, noncoding RNA transcripts that play a critical role in silencing patterns of gene expression. Although altered microRNA expression has been well documented in ovarian cancer, the function of individual microRNAs remains largely unexplored.

The genomic locations of known human microRNAs were determined using MirBase and correlated with genomic copy number variation identified by microarray. Established ovarian cancer cell lines were transfected with miRNA mimics, inhibitors, and controls as specified (Thermo). Stable clones were established by selecting cell lines transfected with pLemiR miR-express vectors (Open Biosystems) with puromycin. Proliferation and apoptosis were measured using standard MTS and caspase-3/7 assays (Promega).

Results: We identified a unique genomic locus at 19q13.41 that encodes more than 54 individual microRNAs. Using a data set of >400 specimens, copy number losses at this locus could be identified in ~37% of high-grade papillary serous cancers. Mimics and inhibitors for at least four of the microRNAs encoded by the 19q13.41 locus (mir-520a, miR-520 h, miR519d, and miR-529e) significantly impacted apoptosis in established ovarian cancer cell lines (SKOV4, HEY, OVCAR8, OVCAR5), with variable effects on proliferation when compared with cultures either sham-transfected or transfected with nonsilencing controls. Increased expression of either miR-520a and miR-520 h consistently decreased the IC_{50} values of all cell lines tested for cisplatin more than threefold ($P<0.01$) when compared with controls, irrespective of their effects on caspase-3 and -7 activity. Predicted targets for miR-520a and miR-520 h include >150 gene products previously implicated in DNA damage pathways and ovarian cancer, including BRCA1/2, ATM, BCL-2, FAS, AKT, and E2F.

Conclusions: Altered genomic copy number variation at the 19q13.41 microRNA locus occurs frequently in epithelial ovarian cancers. Individual microRNAs encoded by this locus significantly sensitize ovarian cancers to platinum-based chemotherapy. Future work will determine how these microRNAs exert their biologic effects, identify genetic signatures predictive of their ability to sensitize primary ovarian cancers to chemotherapy, and determine how best and when to deliver specific 19q13.41 microRNAs for optimal therapeutic impact.

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Ovarian cancer: Predictors of primary care physicians' referral to gynecologic oncologists

B. Goff[1], H. Andrilla[1], L. Baldwin[1], D. Lishner[1], B. Matthews[1], J. Miller[2], K. Trivers[2]
[1]*University of Washington School of Medicine, Seattle, WA,* [2]*Centers for Disease Control and Prevention, Atlanta, GA*

Objective: Recent studies in the United States have shown that 30–50% of patients with ovarian cancer are not receiving comprehensive surgery or being treated by high-volume surgeons. Our goal was to identify the factors associated with referral of a woman with suspected ovarian cancer to a gynecologic oncologist.

A vignette-based survey was mailed to 3200 physicians aged 64 and younger who were randomly sampled in equal numbers from American Medical Association Masterfile lists of family physicians (FPs), general internist (IMs), and obstetrician–gynecologists (OB-GYNs). In the vignette, a 57-year-old woman with pain, bloating and a right adnexal mass underwent an ultrasound that revealed a 10-cm complex mass with increased vascularity and ascites. We varied the patient's race and insurance. Using multivariate analysis we evaluated patient, physician and practice characteristics associated with a referral to a gynecologic oncologist.

Results: The response rate was 61.7%. After exclusions we included 564 OB-GYNs, 588 FPs, and 412 IMs. Referral to a gynecologic oncologist was recommended by 39.8% of FPs and 51.6% of IMs ($P=0.002$). Among the OB-GYNs, 191 (33.9%) indicated they would perform surgery and 371 (66.8%) recommended consultation or referral to another physician (97.5% gynecologic oncologists). For the IMs and FPs the only patient factor associated with lower referral rates was Medicaid insurance. Physician factors associated with lower referrals to gynecologic oncologists included male sex, FP specialty, solo practice, rural practice location, and high number of patient visits per week. For OB-GYNs, factors associated with primary surgical management included rural practice location and geographic census division.

Conclusions: When presented with a patient with a suspicious ovarian mass, the majority of primary care physicians do not recommend direct referral to a gynecologic oncologist and one-third of obstetrician–gynecologists perform primary surgical management. This may contribute to the high rates of noncomprehensive surgery for patients with ovarian cancer in the United States.

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Focused Plenary I – New Frontiers in Gynecologic Cancers
Sunday, March, 6, 2011, 4:15PM–5:25PM
Floridian Ballrooms A-I

Moderator, Abstracts: 11–15: Charles N. Landen, MD, University of Alabama at Birmingham, Birmingham, AL

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Uterine serous papillary carcinomas overexpress human trophoblast cell surface marker (Trop-2) and are highly sensitive to immunotherapy with hRS7, a humanized anti-Trop-2 monoclonal antibody

A. Santin[1], S. Bellone[1], J. Varughese[1], E. Cocco[1], E. Ratner[1], D. Silasi[1], T. Rutherford[1], P. Schwartz[1], M. Azodi[1], S. Pecorelli[2]

[1]Yale University School of Medicine, New Haven, CT, [2]University of Brescia, Brescia, Italy

Objective: Uterine serous papillary carcinoma (USPC) is an aggressive and chemotherapy-resistant variant of endometrial cancer. We evaluated the expression of human trophoblast cell surface marker (Trop-2) and the potential of hRS7, a humanized anti-Trop-2 monoclonal antibody, as a novel therapeutic strategy against USPC.

Trop-2 expression was evaluated by immunohistochemistry (IHC) in a total of 23 USPC paraffin-embedded tissues. Six primary USPC cell lines, half of which overexpress the epidermal growth factor type II (HER2/neu) receptor at the 3+ level, were assessed by flow cytometry and real-time PCR for Trop-2 expression. Sensitivity to hRS7 (Immunomedics, Inc.) antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) was tested in standard five-hour ^{51}Cr-release assays against primary USPC cell lines expressing different levels of Trop-2. Finally, to investigate the effect of interleukin-2 (IL-2) on hRS7-mediated ADCC, 5-hour ^{51}Cr assays also were conducted in the presence of low doses of IL-2 (i.e., 50–100 IU/mL).

Results: Expression of Trop-2 was found in 11 of 23 (65%) tumor tissues tested by IHC and in 50% (3/6) of the USPC cell lines tested by real-time PCR and flow cytometry (Trop-2 expression in USPC vs normal endometrial cells) ($P<0.005$). USPC cell lines overexpressing Trop-2, regardless of their intrinsic resistance to natural killer cytotoxicity or their high or low HER2/neu expression, were highly sensitive to hRS7-mediated ADCC in vitro (range of killing: 28.2–64.4%, $P<0.001$). Negligible cytotoxicity against USPC was seen in the absence of hRS7 or in the presence of rituximab control antibody (range of killing: 1.1–12.4%). Incubation with IL-2 in addition to hRS7 further increased the cytotoxic activity against USPC cell lines overexpressing Trop-2 ($P=0.008$).

Conclusions: Trop-2 is highly expressed in the majority of uterine serous carcinomas at mRNA and protein levels. Primary USPC cell lines are highly sensitivity to hRS7-mediated cytotoxicity in vitro. hRS7 may represent a novel therapeutic agent for the treatment of uterine serous papillary carcinomas refractory to standard treatment modalities.

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Common single-nucleotide polymorphisms in the BNC2, HOXD1 and MERIT40 regions contribute significantly to racial differences in ovarian cancer incidence

A. Berchuck[1], M. Pike[2], J. Schildkraut[1], C. Pearce[2]
[1]Duke University Medical Center, Durham, NC, [2]University of Southern California, Los Angeles, CA

Objective: Recently, an international ovarian cancer association consortium comprising more than 20,000 research subjects has discovered and validated six common low-penetrance single-nucleotide polymorphisms (SNPs) that affect ovarian cancer risk. These SNPs in the BNC2, HOXD1, 8q24, TiPARP, SKAP1 and MERIT40 regions have risk effects in the range of 10–20% per allele. Data from the U.S. SEER population-based tumor registry have indicated that ovarian cancer incidence is 31% lower in blacks than in whites. Differences in known epidemiologic risk factors such as parity explain only part of this difference. Because allele frequencies of many SNPs vary considerably between races, we sought to determine whether racial variations in the frequencies of the six known risk SNPs contribute to differences in ovarian cancer incidence between U.S. blacks and whites.

Data from the International HapMap Project were used to examine the allele frequency of the six ovarian cancer susceptibility SNPs for the population of individuals of African ancestry from the Southwest United States (ASW) compared with individuals of Northern and Western European ancestry in Utah from the CEPH group (CEU). For the ASW, there are 57 individuals/114 chromosomes and for CEU there are 113 individuals/226 chromosomes. Population-attributable risk percentages were calculated for each SNP for blacks and whites.

Results: Two of the SNPs (8q24, TiPARP) had risk allele frequencies that were essentially the same in blacks (ASW) and whites (CEU), and a third (SKAP1) could not be evaluated because data on the ASW population are not available. For three of the loci, the frequency of the risk allele is substantially higher in whites (CEU) compared with blacks (ASW): For rs3814113, which is near the BNC2 gene, the risk allele frequency for blacks is 42% compared with 63% for whites. For rs2072590, which is in the region of HOXD1 gene, the risk allele frequency is 9% in blacks compared with 36% in whites; and for rs8170, which is near the MERIT40 gene, the risk allele frequency in blacks is 11% compared with 21% in whites. The racial variation in the frequencies of these three risk alleles predicts a 17.6% lower incidence of ovarian cancer in U.S. blacks than in whites.

Conclusions: Although differences in epidemiologic risk factors such as parity likely contribute to the lower incidence of ovarian cancer in U.S. blacks compared with whites, racial variations in common risk SNPs in the BNC2, HOXD1 and MERIT40 regions also appear to play a significant role.

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XPC single-nucleotide polymorphisms correlate with prolonged progression-free survival in advanced ovarian cancer

N. Fleming, H. Agadjanian, C. Miller, S. Orsulic, B. Karlan, C. Walsh
Cedars–Sinai Medical Center, Los Angeles, CA

Objective: The nucleotide excision repair (NER) pathway recruits more than 20 gene products to areas of DNA damage to repair and restore DNA integrity. This pathway plays a key role in response to platinum-induced DNA damage, the cornerstone of treatment for advanced epithelial ovarian cancer. Effective removal of bulky platinum DNA adducts allows cells to repair chemotherapy-induced damage and survive. Therefore, altered NER pathway activity can affect platinum responsiveness. We sought to determine whether single-nucleotide polymorphisms (SNPs) in the NER pathway could predict response to platinum-based chemotherapy in ovarian cancer.

Under an institutional review board-approved protocol, we identified patients with advanced-stage, papillary serous ovarian cancers. All patients underwent primary cytoreductive surgery followed by platinum-based chemotherapy. Patients who received neoadjuvant chemotherapy or a non-platinum-based chemotherapeutic regimen were excluded. DNA was isolated from peripheral blood specimens. Sixteen SNPs within genes in the NER pathway (XPG, XPD, ERCC1, XPC, ERCC3, ERCC8, ERCC4, XPA, XPF) were genotyped by TaqMan PCR. Statistical analyses were performed with univariate and multivariate Cox proportional hazards regression analysis.

Results: We identified 139 patients with stage III and IV papillary serous ovarian cancer. Two SNPs in the XPC gene were significantly associated with prolonged progression-free survival (PFS). The presence of the minor allele in each XPC polymorphism predicted longer PFS. XPC (rs3731108) AG/GG versus AA was associated with a prolonged PFS of 21.3 months versus 13.4 months (HR = 0.63, 95% CI = 0.42–0.95, $P=0.03$). XPC (rs1124303) GT/TT versus GG was associated with a prolonged PFS of 22.8 months versus 14.9 months (HR = 0.47, 95% CI = 0.23–0.94, $P=0.03$). On multivariate analysis adjusting for BRCA status and optimal cytoreductive surgery, both XPC polymorphisms remained significantly associated with prolonged PFS.

Conclusions: XPC is a key component of the nucleotide excision repair pathway that participates in DNA damage recognition and repair protein complex formation. Single-nucleotide polymorphisms

in the XPC gene may represent a novel predictor of ovarian cancer response to platinum-based chemotherapy.

doi:10.1016/j.ygyno.2010.12.020

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Genomewide methylation analyses reveal a prominent role of HINF1 network genes, via hypomethylation, in ovarian clear cell carcinoma

K. Yamaguchi[1], T. Baba[2], N. Matsumura[2], M. Mandai[2], I. Konishi[2], A. Berchuck[1], S. Murphy[1]
[1]*Duke University Medical Center, Durham, NC,* [2]*Kyoto University, Kyoto, Japan*

Objective: Ovarian clear cell carcinomas (CCCs) exhibit frequent ARID1A mutations and HNF1B overexpression, but the epigenomic features that characterize CCCs are not known. We previously reported that several CCC-specific genes, including HNF1B, are regulated by promoter methylation. Our objectives were to: (1) use genomewide methylation data to develop a CCC-specific methylation signature, and (2) characterize the molecular features of these genes.

Methylation data as β values (scale 0–1; equivalent to percent methylation) were generated using the Illumina Infinium 27 k platform for 47 ovarian cancer cell lines (14 CCCs and 33 non-CCCs) and four normal specimens (three immortalized OSE and one endometriotic cell line). Comparisons of normal versus cancer lines identified differentially methylated genes using the criteria of $P<0.01$ (Student's t test) and β-value average difference >0.3. Categorical analyses were performed using the R Package Allez 1.0. Direct interactions between genes were analyzed and depicted using GeneGo pathway analysis software (St. Joseph, MI). P values <0.05 were considered significant.

Results: One thousand eight hundred eighty-eight genes were hypermethylated (HM) and 71 genes were hypomethylated (UM) in CCCs compared with normal lines, whereas 864 genes were HM and 78 genes were UM in the non-CCCs compared with normal cells. There were 748 HM and 36 UM genes that overlapped in these data sets ($P<0.0001$). Of the non-overlapping genes, CCCs showed more HM genes than non-CCCs (1140 genes vs 116 genes, respectively; $P<0.0001$). The number of non-overlapping UM genes did not differ between CCC and non-CCC cells (35 vs 42 genes, respectively; $P=0.62$). Allez indicated that the CCC UM genes included many with HNF1 binding sites ($P<0.01$). GeneGo showed no direct interactions among the non-CCC-specific gene sets. However, 336 CCC-specific methylated genes were grouped within one large network, whereas 10 CCC-specific UM genes were grouped within the HNF1 transcript network. Significantly more CCC UM than HM genes showed inverse correlations with expression ($P=0.025$). In external data set GSE6008, six of nine CCC UM HINF1 pathway genes were overexpressed in CCCs versus non-CCCs ($P<0.05$).

Conclusions: CCCs possess a distinct methylation profile compared to those of other histologic subtypes of ovarian cancer with hypomethylation of HINF1B as well as genes with HINF1 binding sites. These results support a prominent role for epigenetic deregulation of the HINF1 network, via loss of methylation, in CCCs.

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KLF6-SV1 is a novel uterine leiomyosarcoma gene: From transgenic mouse model to human disease

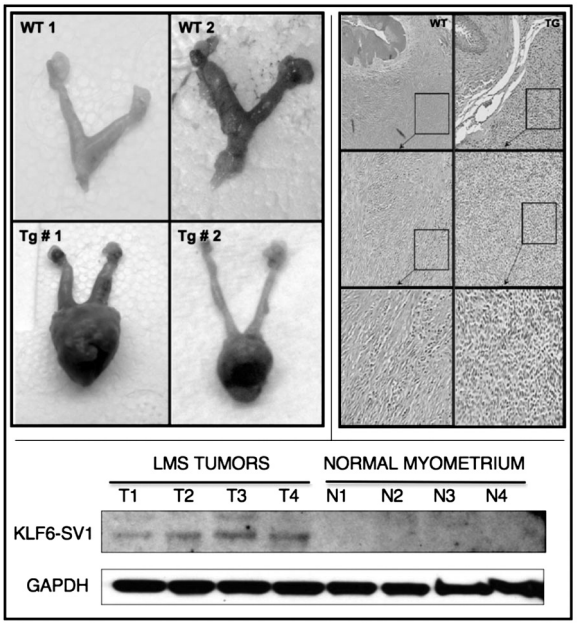
A. DiFeo[1], R. Sennet[1], F. Huang[1], D. Levine[2], T. Kalir[1], M. van de Rijn[3], P. Dottino[1], J. Martignetti[1]
[1]*Mt. Sinai School of Medicine, New York, NY,* [2]*Memorial Sloan–Kettering Cancer Center, New York, NY,* [3]*Stanford University Medical Center, Stanford, CA*

Objective: Uterine leiomyosarcoma (ULMS) is a rare sarcoma accounting for ~1% of all uterine malignancies, and the genetic etiology remains largely unknown. Existing therapies are unfortunately ineffective as evidenced by the high recurrence rate. These malignant mesenchymal neoplasms have complex karyotypic abnormalities and possess distinctive gene expression signatures. Understanding the genetic basis of these tumors will be critical to improved prognostic tools and rationally designed targeted therapies. KLF6-SV1 is an alternatively spliced isoform of the Kruppel-like tumor suppressor KLF6 and an antiapoptotic protein that regulates key cancer-relevant pathways in a p53-independent fashion, including proliferation, angiogenesis and invasion. We have now generated KLF6-SV1 transgenic mice that spontaneously develop ULMS.

Phenotypic analysis of postnatal transgenic mice was performed. KLF6-SV1 expression in human ULMS samples ($n=34$) and ULMS- and normal myometrium-derived cell lines was examined using quantitative RT-PCR and Western blotting. Loss-of-function and gain-of-function experiments were performed using siRNA and cDNA expression vectors, respectively.

Results: KLF6-SV1 transgenic mice displayed a range of phenotypes including the development of ULMS (figure, right and left). The markedly hypercellular, highly proliferative tumor mass arose from smooth muscle cells and was confined within the uterine wall. We therefore next analyzed human ULMS samples. KLF6-SV1 mRNA was overexpressed ~3-fold when compared with normal myometrial tissues ($P<0.05$), whereas protein expression differences were even greater: KLF6-SV1 was detected only in ULMS (figure, bottom). Functionally, targeted inhibition of KLF6-SV1 in ULMS cell lines increased apoptosis and cell cycle arrest, whereas overexpression in normal myometrium-derived lines led to increased proliferation.

Conclusions: The development of ULMS in KLF6-SV1 transgenic mice, KLF6-SV1 overexpression in patient-derived tumors, and the proliferative effect of KLF6-SV1 expression on myometrial cell lines suggest an important role for this gene in ULMS. In combination with our previous results that KLF6-SV1 inhibition can markedly prolong survival, demonstration that KLF6-SV1 inhibition results in cell cycle arrest and apoptosis in ULMS cell lines further supports KLF6-SV1 as a potential novel therapeutic target in ULMS.



doi:10.1016/j.ygyno.2010.12.022

Focused Plenary II – MMXI – Surgical Films From The Final Frontier
Sunday, March, 6, 2011, 4:15PM–5:25PM
Floridian Ballrooms J-L
Moderator, Abstracts: 16–20: David M. Kushner, MD, University of Wisconsin, Madison, WI
Abstracts 16–20 are Surgical Films and only require an objective.

16
Single-incision laparoscopic staging surgery for endometrial cancer
D. Boruta, C. McCann, W. Growdon
Massachusetts General Hospita/ Harvard University, Boston, MA

Objective: The objective of this Surgical Film submission is to demonstrate the performance of single-incision laparoscopic surgical staging for endometrial cancer.

doi:10.1016/j.ygyno.2010.12.023

17
Single-port paraaortic lymph node dissection
M. Liotta, P. Escobar
The Cleveland Clinic, Cleveland, OH

Objective: The goal was to demonstrate the use of the single-port laparoscopic technique for paraaortic lymph node dissection.

doi:10.1016/j.ygyno.2010.12.024

18
Robotic nerve-sparing radical hysterectomy type C1
J. Magrina[1], W. Pawlina[2], R. Kho[3], P. Magtibay[3]
[1]Mayo Clinic Scottsdale, Phoenix, AZ, [2]Mayo Clinic, Rochester, MN, [3]Mayo Clinic College of Medicine, Phoenix, AZ

Objective: The goal was to demonstrate the surgical aspects required to transform the conventional robotic radical hysterectomy into a nerve-sparing operation.

doi:10.1016/j.ygyno.2010.12.025

19
Urinary reconstruction after pelvic exenteration: Modified Indiana pouch
F. Khoury Collado[1], Y. Sonoda[2], B. Bochner[2]
[1]Memorial Sloan–Kettering Cancer Center, Staten Island, NY, [2]Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: Pelvic exenteration in gynecologic oncology is classically performed for a locally recurrent malignancy in a patient with a prior history of pelvic radiation therapy. Removal of the bladder will necessitate the reconstruction of the lower urinary tract, which is done using isolated bowel segments. Because of its location, the pelvic ureter is frequently involved in the radiation field. To avoid including radiated segments in the uretero-intestinal anastomosis, the ureter should be trimmed until the nonradiated level is reached. This could lead to a shortened ureter, which in turn can create tension on the anastomosis and increase the risk of anastomotic complications. In addition, direct anastomosis of the ureters onto the pouch favors the reflux of urine to the kidneys, which increases the risk of infection and deterioration of renal function. We present in this video a modified Indiana pouch, where a segment of small bowel is used as a conduit between the ureters and the pouch in an attempt to create a tension-free uretero-intestinal anastomosis with decreased risk of urine reflux to the kidney.

doi:10.1016/j.ygyno.2010.12.026

20
Intrathoracic cytoreductive surgery by video-assisted thoracic surgery in advanced ovarian carcinoma
J. Diaz[1], B. Park[2], Y. Sonoda[2], D. Chi[2]
[1]University of Miami Miller School of Medicine, Miami, FL, [2]Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: Primary surgical debulking is a fundamental component of ovarian cancer treatment in patients with advanced-stage disease at initial presentation. Our institutional practice has been to consider video-assisted thoracic surgery (VATS) in any patient with any evidence of intrathoracic disease. The goal is to obtain an intrathoracic residual disease burden <1 cm. This video demonstrates the algorithm used at our institution to select patients for a VATS and intrathoracic cytoreductive surgery, as well as the techniques used for simple and complex intrathoraic cytoreduction and lung wedge resection. The multidisciplinary surgical approach to patients with advanced ovarian carcinoma results in an increased number of patients who benefit from an optimal cytoreduction. *With video.

doi:10.1016/j.ygyno.2010.12.027

Focused Plenary III – Diagnosis, Treatment and Surveillance of Endometrial Cancer: Putting Evidence Into Practice
Sunday, March, 6, 2011, 4:15PM–5:25PM
Grand Ballroom I/II, Waldorf Astoria
Moderator, Abstracts: 21–25: John V. Brown, MD, Gynecologic Oncology Associates/Hoag Hospital Cancer Center, Newport Beach, CA

21
Prospective phase II trial of adjuvant pelvic radiation "sandwiched" between paclitaxel and carboplatin combination chemotherapy in women with uterine papillary serous carcinoma
M. Einstein, M. Frimer, R. Phaeton, L. Reimers, K. Mehta,
S. Mutyala, D. Kuo, G. Goldberg
Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

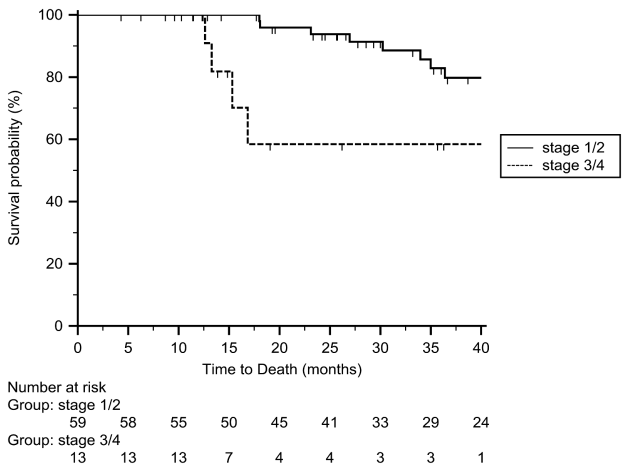
Objective: The purpose of this study was to prospectively evaluate safety, tolerability and survival in women with completely resected uterine papillary serous carcinoma (UPSC) treated with adjuvant pelvic radiation "sandwiched" between six cycles of paclitaxel (T) and carboplatin (C) chemotherapy (clinicaltrials.gov identifier: NCT00231868). These data represent the phase II trial updated from a prior pilot report.

Surgically staged patients with UPSC (updated FIGO stages I–IV) and no visible residual disease were enrolled. Treatment involved T (175 mg/m^2) and C (AUC = 6.0) every 21 days × three doses, followed by radiation therapy, which was brachytherapy (BT), external beam radiation therapy (EBRT), or EBRT + BT based on stage and physician preference, followed by an additional three cycles of T and C (AUC = 5–6). Fields were extended for N2-positive pelvic or confirmed paraaortic nodes. Toxicity was graded according to NCI CTC Version 4.0. Intent to treat survival analysis was performed with Kaplan–Meier methods.

Results: Seventy-eight patients were offered treatment at a single institution with this regimen between 1999 and 2010. Median age was 68 years (range: 43–82). Sixty-four of 78 (82%) had disease confined to

the uterus (stages I and II) and 12 of 78 (18%) had grossly completely resected extrauterine disease (stages III and IV). Sixty-five (83%) completed the protocol prescribed therapy. All patients, regardless of number of chemotherapy cycles, had radiation therapy. Fifty-five of 78 (84.6%) completed EBRT + BT. Of the 65 patients who completed all six cycles of chemotherapy, 6 (9.2%) completed EBRT alone and four (6.2%) completed BT alone. In the 72 patients for whom follow-up data were available, overall progression-free survival and overall survival for combined stage I and II patients were 48.5 ± 2.3 and 47.6 ± 1.6 months, respectively. Progression-free survival and overall survival for combined stage III and IV patients were 24.1 ± 3.5 and 34.0 ± 6.0 months, respectively. Three-year survival probablility for stage I and II patients was 81%, and that for stage III and IV patients was 58% (see Fig. 1). Of the 435 chemotherapy cycles administered, 63 (14%) were complicated by grade 3 hematologic toxicity and 56 (13%) by grade 4 hematologic toxicity, most commonly between cycles 4 and 5, after radiation therapy. There were 11 (2.5%) grade 3 or 4 nonhematologic toxic effects, of which the most common were infection (five) and deeo vein thrombosis (three). There were 21 (4.8%) cycles with dose reductions and 35 (8%) with delays secondary to toxicity. There were no treatment-related deaths.

Conclusions: In this prospective registered trial, radiation therapy "sandwiched" in T/P chemotherapy was well tolerated and highly efficacious in women with completely resected UPSC, including stage III and IV patients. This regimen should be considered as an arm for future phase III clinical trials in patients with UPSC.



doi:10.1016/j.ygyno.2010.12.028

22

Randomized controlled trial of laparoscopic approach to carcinoma of the endometrium (LACE): Prevalence and risk factors for surgical complications

S. Kondalsamy-Chennakesavan[1], M. Janda[2], V. Gebski[3], J. Nicklin[4], T. Jobling[5], R. Land[4], T. Manolitsas[6], A. McCartney[7], L. Perrin[8], A. Obermair[4]

[1]University of Queensland, Brisbane, QLD, Australia, [2]Queensland Institute of Technology, Brisbane, QLD, Australia, [3]University of Sydney, Sydney, NSW, Australia, [4]Queensland Centre for Gynaecological Cancer, Brisbane, QLD, Australia, [5]Monash Medical Centre, Melbourne, VIC, Australia, [6]VicHealth, Melbourne, VIC, Australia, [7]King Edward Memorial Hospital, Perth, WA, Australia, [8]Mater Hospital, Brisbane, QLD, Australia

Objective: The Laparoscopic Approach to Cancer of the Endometrium (LACE) randomized trial aims to establish the equivalence of laparoscopic and open surgery (laparotomy) for early-stage endometrial cancer.

Seven hundred sixty patients with clinical stage I endometrioid adenocarcinoma of the endometrium, ECOG status 0 or 1, were enrolled between 2005 and 2010. To date, 685 patients completed at least six months of follow-up; 319 were randomly allocated to total abdominal hysterectomy (TAH) and 366 to total laparoscopic hysterectomy (TLH). Three hundred seventy-three patients (49.4%) received pelvic and/or aortic lymph node dissection. Descriptive statistics were used to establish frequency of treatment crossovers (conversions). Serious adverse events or adverse events of grade 3+ were regarded as surgical complications (SCs), and $\chi 2$ tests were used to examine differences in proportions. Variables that showed significant association with SCs were entered into a multivariate stepwise logistic regression to determine independent predictors of SCs.

Results: Overall, 26 conversions (3.8%) were recorded, five from TAH to TLH because of patient decision after randomization, and 21 from TLH to TAH (13 for anatomical reasons: Sox needed an abdominal incision to remove the uterus, two for technical reasons, and six due to intraoperative complications). Overall, 112 patients (17%) developed at least one SC (TAH: 64/319, 20.1%; TLH: 48/366, 13.1%; $P = 0.014$). Factors predictive of SCs were TAH (OR = 2.1, 95% CI = 1.3–3.3), history of myocardial infarction, congestive heart failure, general or systemic conditions, ECOG performance status of 1 and elevated alkaline phosphatase levels (shown in the table). Lymph node dissection was not associated with a greater risk of SCs.

Conclusions: Within the LACE trial few conversions were observed, and of those, very few were due to surgical complications or anatomical restrictions. Patients receiving TAH experience twice as many SCs as patients who have a TLH. The surgical approach is the only potentially modifiable risk factor for the development of SCs in endometrial cancer surgery.

Covariate	Odds ratio	95% CI		p
TAH vs TLH	2.05	1.29	3.25	0.002
Platelet count	1.00	1.00	1.01	0.012
Myocardial infarction	3.98	1.49	10.59	0.006
Congestive heart failure	8.74	1.11	68.82	0.040
General/systemic conditions	2.37	1.39	4.04	0.001
ECOG	2.15	1.23	3.74	0.007
Alkaline phosphatase (log)	2.63	1.22	5.66	0.014

doi:10.1016/j.ygyno.2010.12.029

23

Postmenopausal endometrial cancer: Reevaluating the role of the endometrial echo complex

U. Chandavarkar[1], J. Kuperman[2], L. Muderspach[1], C. Morrow[1], A. Yessaian[1], H. Pham[1], Y. Lin[1], L. Roman[1]

[1]University of Southern California, Los Angeles, CA, [2]Columbia University, New York, NY

Objective: The goal of this study was to determine the preoperative ultrasonographic characteristics of the uterus and adnexae of

postmenopausal women diagnosed with endometrial cancer (EC) at our institution and to correlate the thickness of the endometrial echo complex (EEC) with histology (type 1 vs type 2) based on the hysterectomy specimen.

Postmenopausal women with EC who underwent preoperative pelvic ultrasound from 1999 to 2009 were identified from the gynecologic oncology database. Demographic information as well as bleeding history, hormone therapy status, and stage was gleaned from chart review. The histologic diagnosis was based on pathologic findings in the hysterectomy specimen. EEC thickness and ancillary ultrasound characteristics were abstracted from ultrasound reports. In all instances, ultrasound preceded the biopsy by a maximum of three months. Means with SD were calculated for all categorical data. Differences between type 1 and type 2 ECs were determined using t tests and χ^2/Fisher exact analyses, as appropriate. A P value <0.05 was considered statistically significant.

Results: Among 250 patients with postmenopausal EC, 88 had type 1 EC and 162 had type 2. The histologic type of EC was significantly associated with EEC measurement: 28% of patients with type 1 EC had an EEC <5 mm, whereas 46% of patients with type 2 EC had an EEC <5 mm ($P=0.006$). There were no statistically significant differences in ancillary ultrasound characteristics between the two histologic classes of EC with respect to adnexal masses, myomatous masses or free pelvic fluid. There were also no statistically significant differences between type 1 and type 2 ECs with respect to patient age at diagnosis, age at menopause, years since menopause, body mass index, gravidity, parity, race or use of hormone therapy. However, the median duration of hormone therapy was significantly longer among those diagnosed with type 2 EC ($P=0.03$).

Conclusions: ACOG currently recommends no further diagnostic procedure in a woman with postmenopausal bleeding and an EEC <5 mm because the risk of malignancy is low. Our results indicate that a significant proportion of women with EC have EECs <5 mm during their initial evaluation. Furthermore, we have identified that an EEC <5 mm is more common in the more aggressive type 2 ECs. Therefore, although an EEC <5 mm may be reassuring, it does not rule out endometrial cancer and cannot supplant definitive histologic evaluation.

doi:10.1016/j.ygyno.2010.12.030

24

Cost comparison of strategies for the management of venous thromboembolic event risk following laparotomy for ovarian cancer

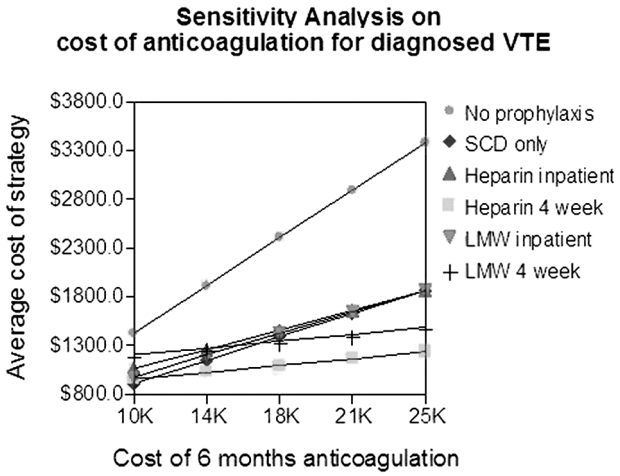
D. Teoh, E. Myers, A. Berchuck, A. Alvarez-Secord, P. Lee, W. Lowery, G. Sfakianos, L. Havrilesky
Duke University Medical Center, Durham, NC

Objective: Recent data suggest efficacy for extended postoperative prophylaxis to prevent venous thromboembolic events (VTEs). Our goal was to evaluate the cost and effectiveness of available strategies for management of VTE risk following laparotomy for ovarian cancer.

We constructed a decision model to evaluate five strategies for management of postoperative VTE risk: (1) inpatient sequential pneumatic compression (SCD); (2) inpatient unfractionated heparin (UFH) 5000 units three times daily; (3) inpatient low-molecular-weight heparin (LMWH) 40 mg daily; (4) UFH 5000 units three times daily for 1 month; (5) LMWH 40 mg daily for one month. Estimates associated with each strategy, including rate of symptomatic or asymptomatic VTE without prophylaxis (13%), heparin-induced thrombocytopenia (HIT; 0.2–2.6%) and significant postoperative bleeding (4.8–6.1%), were obtained from published literature. Costs of prophylaxis, treatment of VTE and complications (hemorrhage, HIT) were obtained using the Agency for Healthcare Research and Quality Nationwide Inpatient Sample database for 2008 (http://hcupnet.ahrq.gov/) and average wholesale pricing. Sensitivity analyses were performed to account for uncertainty in estimates.

Results: In the base case, UFH for 1 month was the least expensive and most effective strategy, with a mean cost of $1611 and a 1.9% risk of a VTE. LMWH for one month was equally effective (1.9% VTE) but more expensive than UFH, with a mean cost of $2197. Inpatient UFH (5.4% VTE), inpatient LMWH (5.9% VTE), and SCD (6.4% VTE) were less effective and more expensive than extended prophylaxis using UFH. In the sensitivity analysis, UFH for one month remained the least expensive strategy unless the probability of VTE without prophylaxis was assumed less than 6.5%, the cost of long-term anticoagulation following VTE was less than $19,000, or the cost of clinically significant bleeding exceeded $4500. Variation in the cost of HIT did not influence the model's results. If warfarin was used for long-term anticoagulation for VTE, then no prophylaxis became the least expensive strategy and the inpatient regimens became less costly than extended prophylaxis regimens.

Conclusions: Extended prophylaxis with UFH is the least expensive and most effective strategy to prevent postoperative VTEs for women undergoing laparotomy for ovarian cancer. Given recent data suggesting superior survival when VTE is treated with LMWH, this model supports the use of extended prophylaxis with UFH or LMWH.



doi:10.1016/j.ygyno.2010.12.031

25

Evaluation of the outcome benefit conferred by intensive surveillance strategies in women with early-stage endometrial cancer

J. Kesterson[1], G. Kiran[2], K. Ozerkan[3], M. Kanis[4], A. Groman[1], S. Lele[1]
[1]Roswell Park Cancer Institute, Buffalo, NY, [2]Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey, [3]Uludag University, Bursa, Turkey, [4]Mt. Sinai School of Medicine, New York, NY

Objective: The optimum follow-up regimen for women treated for early-stage endometrial cancer is unknown. Currently the National Comprehensive Cancer Network (NCCN) recommends a physical exam and vaginal cytology every three–six months for two years, then at six- to 12-month intervals with annual chest x-rays. The objective of this study was to determine if intensive surveillance, per NCCN guidelines, improved outcomes of women with recurrence of their early-stage endometrial cancer.

After institutional review board approval was obtained, the Roswell Park Cancer Institute Cancer Registry was used to identify patients with stage I and II endometrioid-type endometrial cancer treated at our institution from 1990 through 2007. Patients with recurrent disease were included in this analysis. Patients were divided into two groups: (1) asymptomatic women diagnosed as a result of routine screening, and (2) those who were symptomatic. The primary endpoint of interest was overall survival. Potential confounding effects of other variables associated with diagnosis method and the outcome were investigated using both univariate and multivariate methods. Overall survival (OS) associated with routine screening diagnoses and symptomatic diagnoses was compared using multivariate proportional hazards methods controlling for age, adjuvant treatment, grade, recurrence site, and stage. P values < 0.05 were deemed statistically significant.

Results: Of 850 patient with stage I and II endometrioid-type endometrial cancer, 52 with recurrent disease were identified. Twenty-three patients were diagnosed via routine screening methods and 29 were symptomatic at presentation. Groups were matched with respect to age, stage, grade, adjuvant therapy, site of recurrence (local, distant) and time to recurrence ($P > 0.05$). Median survival time was 79 months for those diagnosed during routine screening and 80 months for symptomatic patients ($P > 0.05$). Five years after diagnosis, 55% of routine screening patients were alive versus 59% of symptomatic patients.

Conclusions: The commonly implemented Pap smear and chest x-ray appear to be of questionable utility for surveillance in women treated for early-stage endometrial cancer as our study has shown that women diagnosed as a result of intensive surveillance did not have a better outcome than those who presented when symptomatic. Prospective, randomized studies in women who have been treated for endometrial cancer are needed to confirm or disprove any benefit of routine surveillance.

doi:10.1016/j.ygyno.2010.12.032

Focused Plenary IV – Contemporary and Future Management Issues in Ovarian Cancer: What You Need to Know
Monday, March, 7, 2011, 10:30AM–11:39AM
Floridian Ballrooms A-I
Moderator, Abstracts: 26-30: Ignace B. Vergote, MD, PhD, University Hospital, Leuven, Leuven, Belgium

26

Primary debulking surgery versus neoadjuvant chemotherapy in stage IV ovarian cancer

J. Rauh-Hain[1,2,3], W. Growdon[1,3], N. Rodriguez[2,3], A. Goodman[1,3], D. Boruta[1,3], N. Horowitz[2,3], M. Del Carmen[1,3], J. Schorge[1,3]
[1]Massachusetts General Hospital, Boston, MA, [2]Brigham & Women's Hospital, Boston, MA, [3]Harvard Medical School, Boston, MA

Objective: Recent data appear to support a paradigm shift toward neoadjuvant chemotherapy with interval debulking surgery (NACT-IDS). Patients with stage IV disease are least likely to be optimally cytoreduced at primary debulking surgery (PDS). We hypothesized that NACT-IDS would result in similar outcomes and less morbidity.

From the Cancer Registry database at our institutions we identified a subpopulation of patients with stage IV epithelial ovarian cancer who underwent primary therapy from January 1, 1995, to December 31, 2007. Each patient record was evaluated to subclassify stage IV disease according to the sites of tumor dissemination. Correlation between categorical variables was assessed with Fisher's exact test. The Kaplan–Meier method was used to generate overall survival data.

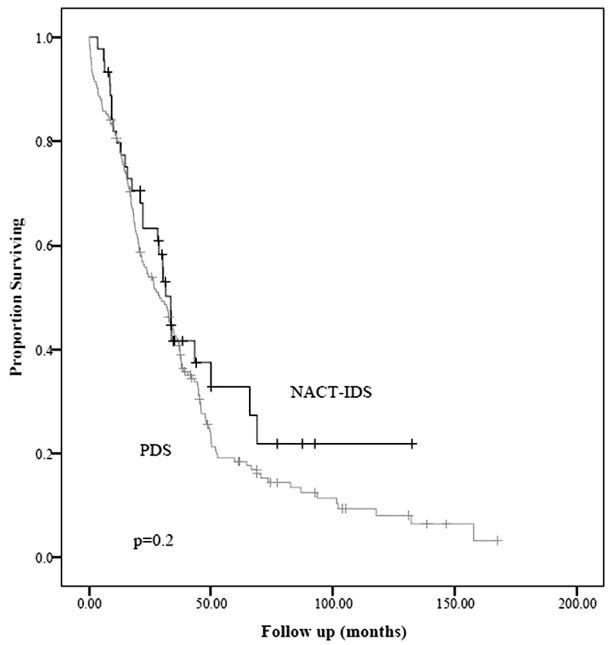
Results: Two hundred twenty-one newly diagnosed patients with stage IV disease underwent surgery. The median age was 61 years (range: 18–93). One hundred seventy-six women (79%) underwent PDS, and 45 (21%), NACT-IDS. The rates of optimal debulking to <1 cm residual disease were comparable for the PDS and NACT-IDS groups (58% vs 71%, $P = 0.1$). However, the rate of complete resection to no residual disease was significantly higher in patients with NACT-IDS than in those with PDS (27% vs 7.5%, $P < 0.001$). The rates of upper abdominal surgical procedures in patients who underwent PDS and NACT-IDS were comparable (41% vs 29%, $P = 0.1$). When compared with women treated with NACT-IDS, women with PDS had longer admissions (12 days vs 8 days, $P = 0.01$) and more frequent ICU admissions (12% vs 0%, $P = 0.01$) and exhibited a trend toward a higher rate of postoperative complications (27% vs 15%, $P = 0.08$). Eight women (5%) in the PDS group died within 30 days of their initial surgery, compared with none in the NACT-IDS group. Median follow-up was 28 months (range: 0.1–167). There was no difference in median overall survival between the PDS and NACT-IDS groups (29 months vs 33 months, $P = 0.2$) (Fig. 1). In the subgroup with liver metastases, patients who were treated with PDS had a median survival of 27 months compared with 43 months for patients treated with NACT-IDS ($P = 0.04$) (see table).

Conclusions: Survival for women with stage IV ovarian cancer appears equivalent for those treated with NACT-IDS or PDS. NACT-IDS was more likely to result in complete resection of stage IV ovarian cancer with reduced postoperative morbidity compared with PDS. The superior overall survival achieved with NACT-IDS for those presenting with parenchymal liver metastases suggests this may be the preferred course of therapy in this particular group.

Median progression-free survival and overall survival by site-specific distant metastasis.

	N	DFS (months)	*P*	OS (months)	*P*
Pleural effusion					
PDS	81	12	0.9	26	0.7
NACT-IDS	20	13		28	
Liver					
PDS	27	13	0.06	27	0.04
NACT-IDS	12	15		43	
Abdomen					
PDS	51	14	0.7	30	0.8
NACT-IDS	8	18		30	
Distant lymph nodes					
PDS	18	14	0.9	32	0.5
NACT-IDS	8	16		34	
Spleen					
PDS	17	14	0.5	38	0.6
NACT-IDS	8	23		69	

Patients who had metastases to multiple sites were included in each of the specific sites. That is, if a patient presented with malignant pleural effusion and liver metastasis, that patient was included in the survival analysis of patients with malignant pleural effusion, as well as in the group with liver metastasis.



doi:10.1016/j.ygyno.2010.12.033

27

Treatment of chemotherapy-induced anemia in patients with ovarian cancer: Does the use of erythropoiesis-stimulating agents worsen survival?

R. Rocconi[1], B. Long[2], P. Sullivan[2], M. Blaize[3], J. Brown[3], J. Arbuckle[3], K. Bevis[3], J. Estes[3], E. Reed[1], M. Finan[1]
[1]University of South Alabama Mitchell Cancer Institute, Mobile, AL, [2]University of South Alabama, Mobile, AL, [3]University of Alabama, Birmingham, AL

Objective: Emerging data have demonstrated that the use of erythropoiesis-stimulating agents (ESAs) worsens survival in cancer patients. A criticism of these studies is that ESAs are used to achieve "supratherapeutic" hemoglobin levels rather than treat chemotherapy-induced anemia (CIA). Considering the paucity of data specific to ovarian cancer, our objective was to evaluate the effect of ESAs as used for the treatment of CIA on survival in patients with ovarian cancer.

A multi-institution retrospective chart review was performed on patients with ovarian cancer. Data collected included patient demographics, surgicopathologic information, chemotherapy treatments, laboratory data, erythropoeisis stimulation data, transfusions, and survival data. Patients who underwent surgery or chemotherapy treatment outside the participating institutions were ineligible. Patients were stratified by ever-use of ESAs and compared using χ^2 test, Fisher's exact test, Student's t test, and Kaplan–Meier statistics for analysis.

Results: Five hundred eighty-one patients were eligible for analysis; 39% ($n=229$) patients had used ESAs at least once (ESA–YES) and 61% ($n=352$) had never used ESAs (ESA–NO). Mean age was 60.4, and the majority of patients had stage IIIC (60%) ovarian cancer of papillary serous histology (64%). The majority of patients received optimal cytoreduction (67%) followed by a mean number of 2.4 chemotherapy regimens and median follow-up of 27 months. The ESA–YES and ESA–NO groups were similar with respect to age, body mass index, race, stage, histology and debulking status. Compared with the ESA–NO group, ESA–YES patients were significantly more likely to experience recurrence (56% vs 80%, $P<0.001$) and death (46% vs 59%, $P=0.002$). Kaplan–Meier curves demonstrated a significant reduction in progression-free survival for ESA–YES patients (16 months vs 24 months, $P<0.001$); however, the two groups had statistically similar overall survival (38 months vs 46 months, $P=0.10$).

Conclusions: Our data demonstrate a negative impact on survival when using ESAs for chemotherapy-induced anemia. Considering that patients who receive ESAs are more likely to experience recurrence, death and decreased survival, the use of ESAs in patients with ovarian cancer should be restricted.

doi:10.1016/j.ygyno.2010.12.034

28

An economic analysis of intravenous carboplatin plus dose-dense weekly paclitaxel versus intravenous carboplatin plus every three-weeks paclitaxel in the upfront treatment of ovarian cancer

H. Dalton[1], X. Yu[2], L. Hu[3], B. Monk[1], I. Benjamin[1], J. Chan[3]
[1]Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, Phoenix, AZ, [2]University of Memphis School of Public Health, Memphis, TN, [3]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Objective: Recent results from the JGOG showed that dose-dense paclitaxel once a week plus carboplatin every three weeks (ddT) improved progression-free survival (PFS) and overall survival (OS) compared with the standard once every-three-weeks carboplatin plus paclitaxel (q3T) regimen in advanced ovarian cancer. We performed a cost analysis comparing ddT with q3T in the primary treatment of ovarian cancer.

Using a Markov decision model, a cost–utility study was performed to compare ddT (80 mg/m^2 IV weekly) with q3T (180 mg/m^2 IV every three weeks). Cost of drugs, rates of complication and PFS were derived from the published JGOG study (Lancet 2009;374:1331–8). An acceptable incremental cost-effectiveness ratio (ICER) per progression-free life-year saved (LYS) was established. The estimated costs of growth colony-stimulating factors and blood transfusion were also included in the model.

Results: Based on Medicare payment for administration of chemotherapy, the estimated cost of ddT is $107 versus $80 per cycle for q3T based on the body weight and surface of an average woman at the age of 63. The estimated total costs of treatment per cycle of combination chemotherapy and administration were $750 for ddT and $483 for q3T. The estimated cost of growth colony-stimulating factors is $1014 for four injections of 300 mg, and that for blood transfusion is $200 for each unit transfused. The median PFS was approximately 28 months with ddT versus 17 months with q3T. This resulted in an ICER of $3940 per LYS for ddT compared with the q3T arm. Using a maximum ICER of $10,000 per LYS as the cost-effective threshold, the ddT arm appears cost-effective. The ICER was sensitive to the median PFS difference between two treatment arms. A four-month difference in PFS resulted in an ICER of $7419 per LYS. The ICER is also sensitive to OS difference, rate of blood transfusion, and hematologic toxicity of treatment.

Conclusions: In this economic model, our data suggest that the dose-dense paclitaxel regimen is cost-effective. GOG 262 will confirm the efficacy of ddT compared with q3T (with bevacizumab at the discretion of the treating oncologist).

doi:10.1016/j.ygyno.2010.12.035

29

Should stage IIIC ovarian cancer be further stratified by intraperitoneal versus retroperitoneal-only disease? A Gynecologic Oncology Group study

B. Rungruang[1], A. Miller[2], S. Richard[1], C. Hamilton[3], N. Rodriguez[4], M. Bookman[5], G. Maxwell[3], T. Krivak[1], N. Horowitz[4]

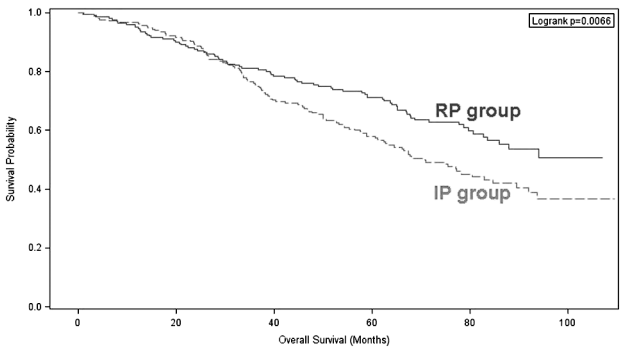
[1]Magee–Womens Hospital of UPMC, Pittsburgh, PA, [2]Gynecologic Oncology Group, Buffalo, NY, [3]Walter Reed Army Medical Center, Washington, DC, [4]Brigham and Women's Hospital, Boston, MA, [5]Fox Chase Cancer Center, Philadelphia, PA

Objective: FIGO recently modified endometrial, vulvar, and cervical cancer substaging to better reflect prognosis. For ovarian cancer, institutional studies have suggested improved survival in patients with stage IIIC on the basis of retroperitoneal disease only (no peritoneal dissemination). Our objective was to determine whether stage IIIC ovarian cancer patients with microscopic residual disease after cytoreductive surgery had different long-term outcomes depending on the site of tumor involvement within a large, multi-institutional trial.

A retrospective chart review examined patients with ovarian cancer patient in GOG 182 who underwent primary cytoreductive surgery to microscopic residual followed by adjuvant chemotherapy (without interval cytoreduction). Demographic, surgical, pathologic and outcome data were obtained. Patients were divided into two groups: those with stage IIIC disease based on positive pelvic or paraaortic lymph nodes only (RP group), and those with stage IIIC disease who had >2 cm intraperitoneal dissemination with lymph node involvement (IP group). Kaplan–Meier estimates and multivariate regression modeling were used to assess the associations between disease distribution and progression-free survival (PFS) and overall survival (OS).

Results: Of 4312 women with stage III or IV ovarian cancer who were enrolled on GOG 182, 825 underwent primary cytoreductive surgery to microscopic disease. Of these, 416 had stage IIIC disease with lymph node involvement and were included in this analysis. There were 202 (48.5%) patients in the RP group and 214 (51.5%) patients in the IP group. Patients in the IP group were more likely to have serous histology ($P<0.001$), ascites ($p<0.001$) and poor performance status ($P<0.005$). Multivariate regression revealed that IP was associated with worse PFS (HR = 1.483, 95% CI = 1.16–1.90) and OS (HR = 1.532, 95% CI = 1.13–2.08) compared with the RP group. With the RP group as a referent, the IP group had worse PFS (median time to recurrence: 25 months vs 47 months, respectively, $P<0.01$) and OS (median time to death: 70 months vs "not reached," respectively, $P<0.01$) (see the figure).

Conclusions: There is significant improvement in PFS and OS in patients with stage IIIC ovarian cancer who undergo optimal surgical cytoreduction to microscopic residual disease with retroperitoneal-only involvement compared with patients with intraperitoneal tumor. These results suggest that patients with retroperitoneal-only involvement may be further substratified within FIGO stage IIIC.



doi:10.1016/j.ygyno.2010.12.036

30

Efficacy of influenza vaccination in women with ovarian cancer

C. Chu[1], J. Boyer[2], A. Jawad[3], N. Prak[2], K. Sullivan[2]

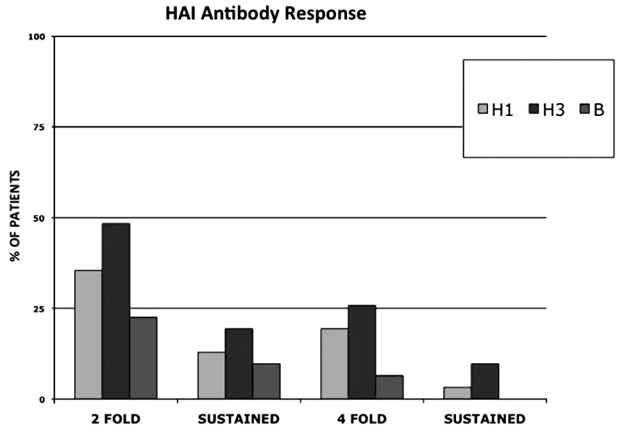
[1]University of Pennsylvania Medical Center, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA, [3]Children's Hospital of Philadelphia, Philadelphia, PA

Objective: The purpose of this study was to determine the immunogenicity of influenza vaccine in women undergoing treatment for ovarian cancer.

Under two institutional review board-approved protocols, patients with ovarian cancer undergoing treatment or in remission receiving a consolidation dendritic cell (DC) vaccination were administered seasonal trivalent killed influenza vaccine. Patients undergoing chemotherapy were vaccinated on day one of a respective cycle; patients receiving DC vaccine were treated on day one of the first vaccine. Peripheral blood was collected at day 0, weeks 10–12, and months four, nine and 12 for assessment. Serum was analyzed for hemagglutination inhibition (HAI) antibody titers. Peripheral blood mononuclear cells were isolated to quantify and characterize T- and B-cell populations. T-cell proliferation was measured by CFSE.

Results: Thirty-one patients were recruited: 6 in remission receiving DC vaccine alone, seven in remission receiving DC vaccine plus a single dose of low-dose cyclophosphamide, and the remaining 18 patients undergoing off-protocol therapy. The off-protocol group included two patients in first remission not undergoing chemotherapy, but the remainder were undergoing treatment with a mean of 2.3 prior regimens. In reaction to challenge with the three strains included in the seasonal vaccine, A (H1N1), A(H3N2), and B, only one (3%), three (10%), and 0 patients, respectively, were able to mount a sustained fourfold HAI antibody response. Even a transient fourfold response was observed in only 6 (20%), 8 (26%), and 2 (6%), respectively (Fig. 1). However, 15 (48%), 13 (42%), and 13 (42%) were noted to have antibody titers >1:40 at baseline to the three strains, respectively, prior to vaccination. All B-cell phenotypes were decreased below normal controls. Both maximal and influenza-specific T-cell proliferation were decreased compared with normal controls, though patients receiving prevaccine cyclophosphamide experienced transient elevated responses, correlating with a drop in regulatory T cells.

Conclusions: Despite CDC recommendations that patients undergoing chemotherapy receive flu vaccine, there is little evidence to support its efficacy. Patients with ovarian cancer either undergoing active chemotherapy or having recently completed chemotherapy are almost uniformly unable to mount a meaningful antibody response to flu vaccine, though most patients seem to have some baseline protection to the 2008–2009 seasonal strains. These findings have serious implications for future resource allocation for both seasonal and novel pandemic influenza outbreaks.



doi:10.1016/j.ygyno.2010.12.037

Focused Plenary V – Surgical Evolution and a Cautionary Tale
Monday, March, 7, 2011, 10:30AM–11:25AM
Grand Ballroom I/II, Waldorf Astoria
Moderator, Abstracts: 31-34: Pedro T. Ramirez, MD, The University of Texas, MD Anderson Cancer Center, Houston, TX

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Does the bedside assistant matter in robotic surgery: An analysis of patient outcomes in gynecologic oncology

M. Martino[1], R. Miller[1], J. Shubella[1], S. Williams[2], M. Thomas[1], R. Boulay[1]
[1]*Lehigh Valley Health Network, Allentown, PA,* [2]*University of South Florida College of Medicine, Tampa, FL*

Objective: Although gynecologic oncology training programs often incorporate practice for robotic surgical procedures, the resident's role regarding their level of participation during surgeries still remains uncertain. The purpose of this study is to determine the effect that resident involvement during robotic surgeries has on patient quality outcomes. Primary outcome measures were major perioperative complication rates and conversion rates. Secondary outcome measures included length of stay (LOS), estimated blood loss (EBL) and operative times.

This is a retrospective cohort study of all patients from June 3, 2008 to June 30, 2010 who were scheduled for a robot-assisted total laparoscopic hysterectomy with either a resident physician or a specially trained surgical assistant (co-surgeon or physician's assistant) as the primary assistant during surgery. All procedures were performed by gynecologic oncologists on the Da Vinci S surgical system. Demographic data reviewed included age, body mass index, stage, comorbidities and surgical pathology. Outcome measures reviewed were major perioperative complication rates, conversion rates, LOS, EBL and operative times. Data were analyzed using Pearson's χ^2 test and Student's t test in SPSS.

Results: Two hundred ninety-nine patients met the inclusion criteria. Thirty-three had a resident physician as the primary surgical assistant, and 266 had either a co-surgeon or physician's assistant as the primary assistant. There was no significant difference between the two groups in age, body mass index, stage, comorbidities or benign versus malignant pathology. LOS (1.6 days vs 1.3 days, $P=0.29$) and operative times (152 min vs 171 min, $P=0.07$) were also similar for the two cohorts. EBL (74 mL vs 120 mL, $P=0.05$) was lower for the cases staffed by resident physicians. However, conversion rates (9.1% vs 1.1%, $P<0.01$) and major perioperative complication rates (18.2% vs 7.9%, $P=0.05$) were significantly lower in the robotic cases staffed by a co-surgeon/physician assistant than in those assisted by a resident physician.

Conclusions: Patients who have a resident physician as the primary surgical assistant during their robotic procedure may have higher complication rates and conversion rates compared with patients who have a specially trained assistant. This study suggests that additional training for residents as bedside assistants may be necessary to improve patient outcomes in gynecologic oncology surgery.

doi:10.1016/j.ygyno.2010.12.038

32

Comparison of single-port laparoscopy versus standard laparoscopy versus robotic surgery in patients with endometrial cancer: A multi-institutional study

P. Escobar[1], M. Frumovitz[2], P. Soliman[2], H. Frasure[3], D. Starks[1], A. Nickles Fader[4], P. Ramirez[2]
[1]*The Cleveland Clinic, Cleveland, OH,* [2]*University of Texas M.D. Anderson Cancer Center, Houston, TX,* [3]*Case Western Reserve/MacDonald Women's Hospital, Cleveland, OH,* [4]*Greater Baltimore Medical Center/Johns Hopkins Medical Institutions, Baltimore, MD*

Objective: The aim of this study was to evaluate single-port laparoscopy (SPL) for the surgical treatment of presumed early-stage endometrial cancer and compare surgical outcomes with those for laparoscopy and robotics.

This was a multi-institutional, matched case–control study. All patients with clinical stage I or occult stage II endometrial cancer who underwent single-port laparoscopic hysterectomy and bilateral salpingo-oophorectomy ± lymphadenectomy from April 2009 to September 2010 were identified. Comparison was made with patients who had the same procedure by laparoscopy or robotics matched by age, BMI and FIGO stage. Data collected included patient demographics, comorbid conditions, histologic type, surgical procedure, operative times, estimated blood loss, pathologic results, length of stay, conversion rates and complications. Data were analyzed using Kruskal–Wallis one-way analysis of variance and $\chi 2$ test for frequency data. A P value <0.05 was considered significant.

Results: A total of 90 patients were matched by age, stage, and BMI (30 robotic, 30 laparoscopic, and 30 SPL). The median age and BMI for the entire cohort were 60.5 years and 32 kg/m^2, respectively. The median operating times for patients undergoing robotic, laparoscopy and SPL were 174.0, 219.5, and 155.0 minutes, respectively, ($P=0.61$). The median blood loss was 75, 100 and 100 mL, respectively ($P=0.62$). The median number of pelvic lymph nodes removed was 17.0 (range: 8–36), 13.0 (range: 3–18), and 16 (range: 11–21), respectively. Pelvic lymph node count was significantly higher for robotic and SPL when compared with laparoscopy ($P=0.04$). The median number of paraaortic nodes removed was 3.5 (range: 2–14), 6.0 (range: 1–10), and 6.0 (range: 2–12) ($P=0.53$). The mean length of hospital stay was 1.4, 1.3, and 1.4 days, respectively ($P=0.128$). There was no significant difference between the three groups in median age, BMI, comorbid conditions or complication rates ($P=0.17$).

Conclusions: SPL hysterectomy and lymphadenectomy for endometrial carcinoma is feasible and results in similar operating times, estimated blood loss, lymph node retrieval, hospital length of stay and complication rates, when compared with laparoscopy and robotics. Although SPL provides early surgical outcomes similar to those for laparoscopy and robotics, prospective trials are needed to assess the efficacy of this novel technique in the management of patients with endometrial cancer.

doi:10.1016/j.ygyno.2010.12.039

33

Adenocarcinoma of the cervix: Is radical vaginal trachelectomy safe?

L. Helpman[1], A. Covens[2], D. Grisaru[1]
[1]*Tel Aviv Sourasky Medical Center, Tel Aviv, Israel,* [2]*Sunnybrook Odette Cancer Center, Toronto, ON, Canada*

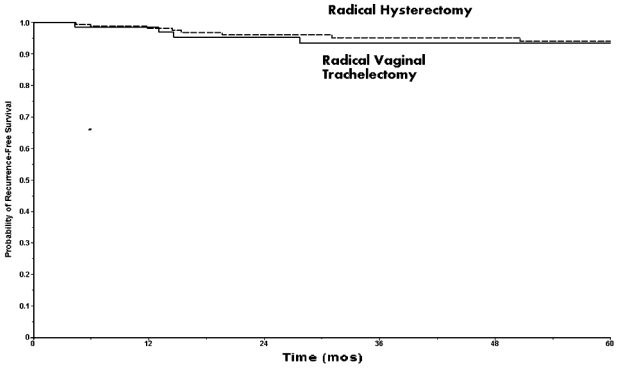
Objective: Radical vaginal trachelectomy (RVT) has, in the past 15 years, emerged as a revolutionary option for fertility preservation in young women with invasive cervical tumors. Several large series of RVTs have demonstrated oncologic outcomes comparable to those of radical hysterectomy (RH), but none have specifically addressed the influence of histology on outcome. We sought to evaluate the safety

of RVT specifically for adenocarcinoma and to compare it with that for squamous cell cancer (SCC).

Data were taken from the prospectively maintained University of Toronto Radical Surgery for Cervical Cancer Database. Demographic data, surgical data, and pathologic parameters including grade, depth of invasion and lymphovascular space invasion are all recorded, as are follow-up data at regular intervals. For this analysis, only adenocarcinomas and SCCs that underwent RVT or RH were included; all other histologic subtypes were excluded. Recurrence-free survival was calculated from the date of surgery, and distributions used the product-limit method of Kaplan and Meier. Differences between medians, proportions and survival curves were compared with the Mann–Whitney U test, the χ^2 test, and the log-rank test, respectively. Statistical significance was defined as $P<0.05$.

Results: Between March 1994 and April 2010, 74 patients with adenocarcinoma of the cervix and 67 patients with SCC underwent RVT with laparaoscopic pelvic lymphadenectomy at one gynecologic oncology center. One hundred eighty-eight cases of adenocarcinoma underwent RH during the same period. Patients undergoing RVT were younger than patients having RH (31 vs 40, $P<0.001$). Tumor characteristics were generally similar for the two groups, except depth of invasion and the incidence of high-grade lesions were both higher in the RH group (5 mm vs 3 mm, $P<0.001$; and 22% vs 36%, $P=0.04$). Adjuvant radiation was given more frequently in the RH group (10.9% vs 2.8%, $P<0.05$). Disease-free survival was ultimately similar for the two treatment modalities (see the figure). Disease-free survival was also comparable for patients with adenocarcinomas and SCCs treated by RVT.

Conclusions: Radical vaginal trachelectomy is equally efficacious for early-stage adenocarcinoma of the cervix and SCC and is a viable alternative to radical hysterectomy in patients wishing to preserve fertility. In carefully selected cases, disease-free survival is comparable to that of patients undergoing radical hysterectomy, and fewer cases require adjuvant radiation.



doi:10.1016/j.ygyno.2010.12.040

34

The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma

J. Park, S. Park, J. Kim, Y. Kim, Y. Kim, J. Nam
Asan Medical Center, Seoul, Republic of Korea

Objective: Uterine leiomyosarcoma (LMS) is a rare but aggressive disease. As there is no established preoperative diagnostic method, it is usually diagnosed after surgery for leiomyoma, and thus, tumor morcellation is frequently used. The purpose of this study was to evaluate the impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine LMS.

We performed a retrospective chart review of patients with stage I and II uterine LMS who underwent surgery between June 1989 and May 2010. The outcomes of the group that underwent upfront, total abdominal hysterectomy (TAH) without tumor morcellation (group A) and the group that underwent surgical management including tumor morcellation (group B) were compared.

Results: During the study period, 50 patients (27 in group A, 23 in group B) with stage I and II uterine LMS, were identified and included in this analysis. There were no significant differences between the two groups in mean age (47.8 vs 45.7, $P=0.368$), mean parity (2.4 vs 2, $P=0.151$), menopausal status (8, 29.6% vs 3, 13.0%, $P=0.158$), mean body mass index (24.2 vs 23.3, $P=0.237$), high-grade tumors (17, 63.0% vs 16, 69.6%, $P=0.623$), method of postoperative treatment ($P=0.084$) and follow-up months (40.7 vs 39.6, $P=0.931$). However, there were some differences in ovarian preservation (12, 44.4% vs 18, 78.3%, $P=0.015$) and tumor size (8.6 vs 6.3 cm, $P=0.048$). There were no significant correlations with 5-year disease-free survival and overall survival ($P>0.05$) in age at diagnosis, parity, menopausal status, body mass index, ovarian preservation, FIGO stage, tumor grade, mitoses and tumor sizes among the prognostic factors. However, five-year disease-free and overall survival rates were 79.0 and 71.9% in group A, and 50.4 and 45.8% in group B, respectively ($P=0.037$ and $P=0.096$). Nonmorcellated surgery improved five-year disease-free survival compared with morcellated surgery, suggesting that nonmorcellated surgery was an independent prognostic factor for improving disease-free survival.

Conclusions: These findings suggest that tumor morcellation during surgery may influence a worse prognosis than TAH for patients with early uterine LMS. Therefore, it is important to preoperatively determine the most accurate diagnostic methods. However, large-scale randomized controlled trials are needed to support these results.

doi:10.1016/j.ygyno.2010.12.041

Plenary Session V
Tuesday, March, 8, 2011, 8:00AM–9:45AM
Floridian Ballrooms A-I

Moderator, Abstracts: 35-39: Susan C. Modesitt, MD, University of Virginia, Charlottesville, VA

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Efficacy of the AS04-adjuvanted HPV-16/18 vaccine in reduction of abnormal cytology, colposcopy referrals and cervical excision therapies: PATRICIA end-of-study results

C. Wheeler[1], J. Paavonen[2], P. Naud[3], J. Salmeron[4], S. Chow[5], D. Apter[6], H. Kitchener[7], X. Castellsagué[8], J. Teixeira[9]
[1]University of New Mexico Health Sciences Center, Albuquerque, NM, [2]University of Helsinki, Helsinki, Finland, [3]Federal University of Rio Grande do Sul/Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [4]Unidad de Investigación Epidemiológica y en Servicios de Salud, Instituto Mexicano del Seguro Social, Morelos, Mexico, [5]College of Medicine and the Hospital, Taipei, Taiwan, [6]Family Federation of Finland Sexual Health Clinic, Helsinki, Finland, [7]University of Manchester Academic Unit of Obstetrics and Gynaecology, Manchester, United Kingdom, [8]Institut Català d'Oncologia, L'Hospitalet de Llobregat, Catalonia, Spain, [9]University of Campinas, Campinas, Brazil

Objective: The AS04-adjuvanted human papillomavirus (HPV)-16/18 vaccine shows high prophylactic vaccine efficacy (VE) against cervical intraepithelial neoplasia (CIN) 2+ associated with HPV-16/18. We present VE against abnormal cytology (ASCUS or greater [+]) and reduction in colposcopy referrals and cervical excision therapies.

Women aged 15–25 years were randomized to receive HPV-16/18 vaccine or hepatitis A vaccine as control at months 0, one and six. Cervical samples were collected every six months for HPV DNA typing and every 12 months for gynecologic/cytopathologic examinations. Women were referred for colposcopy and treatment according to predefined algorithms. We report VE for the total vaccinated cohort (TVC) (women who received one or more doses, regardless of baseline HPV DNA/serostatus) and for the TVC-naïve (women who received one or more doses, HPV-16/18 seronegative, DNA-negative for 14 oncogenic HPV types, normal cytology at baseline).

Results: At end-of-study (median follow-up: 47.4 months for TVC and 47.5 months for TVC-naïve), VE (95% CI) against ASCUS+ associated with HPV-16/18 was 68.4% (range: 64.1–72.3) and 91.9% (range: 88.8–94.3) in the TVC and TVC-naïve, respectively. For ASCUS+ irrespective of HPV type, VE was 12.2% (range: 7.2–16.9) and 23.2% (range: 16.9–29.0), respectively. Corresponding reductions in colposcopy referrals were 14.8% (range: 8.9–20.3) and 29.0% (range: 21.6–35.8), with reductions in cervical excision therapies of 33.2% (range: 20.8–43.7) and 70.2% (range: 57.8–79.3).

Conclusions: Vaccination with the AS04-adjuvanted HPV-16/18 vaccine reduced abnormal cytology rates with a corresponding reduction in colposcopy referrals and in cervical excision therapies, in both the TVC and TVC-naïve.

doi:10.1016/j.ygyno.2010.12.042

36

The utility of preoperative CA-125 in the management of apparent early-stage endometrial cancer

J. Nicklin[1], M. Janda[1], V. Gebski[1], T. Jobling[2], R. Land[1], T. Manolitsas[2], A. McCartney[3], M. Nascimento[1], L. Perrin[1], A. Obermair[1]
[1]Queensland Centre for Gynaecologic Cancer, Brisbane, QLD, Australia, [2]Monash University, Melbourne, VIC, Australia, [3]King Edward Hospital, Perth, WA, Australia

Objective: The purpose of this study was to evaluate the use of preoperative serum CA-125 levels in determining the presence of extrauterine disease in patients with apparent early-stage endometrial cancer. It is well established that elevated CA-125 is associated with advanced-stage endometrial cancer that can readily be identified on standard preoperative imaging with MRI and CT. This is the largest prospective study to evaluate the utility of CA-125 in apparent early-stage disease, as a preoperative prognostic determinant for the need for comprehensive intraoperative staging.

Between October 2005 and April 2010, 760 patients were enrolled in an international, multicenter, prospective randomized trial comparing laparotomy with laparoscopy in the management of endometrial cancer apparently confined to the uterus. Three hundred nine of 624 (49.5%) patients had full surgical staging. This study is based on data from 624 patients who had a preoperative serum CA-125 value and was undertaken to correlate preoperative serum CA-125 with final stage.

Results: Median preoperative serum CA-125 was 14 U/mL, and using a cutoff level of 40 U/ml, 12.3% of patients had elevated CA-125 levels. One hundred eighteen patients (18.9%) had stage 2+ (extrauterine) disease. On univariate logistic regression analysis both CA-125 ($P<0.001$) and poor grade of differentiation on D&C ($P=0.03$) were found to be associated with extrauterine spread of disease. On multivariate analysis, only CA-125 ($P<0.001$) was found to be associated with extrauterine metastatic spread of disease. CA-125 achieved a sensitivity, specificity, positive predictive value, and negative predictive value of 22.0, 93.3, 43.3, and 83.7%, respectively. When analysis was limited to patients who had full surgical staging, the outcomes remained unchanged.

Conclusions: Elevated CA-125 in patients with apparent early-stage disease is associated with a 47% risk of extrauterine disease. Preoperative identification of this risk factor may assist in triage of patients to tertiary centers and comprehensive surgical staging.

doi:10.1016/j.ygyno.2010.12.043

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BRCAness profile of ovarian cancer predicts disease recurrence

T. Pejovic[1], H. Li[1], S. Syriac[1], W. Zhang[2], P. Mhawech-Fauceglia[2]
[1]Oregon Health and Science University, Portland, OR, [2]Roswell Park Cancer Institute, Buffalo, NY

Objective: A subset of sporadic ovarian carcinoma (OC) may harbor anomalies of the homologous recombination (HR) pathway that could be associated with improved response rate and survival after treatment with platinum drugs. The proteins defining this BRCAness profile of sporadic OC have not been clearly defined, nor has the mechanism by which OC develops defective HR been elucidated. The objective of the study was to determine whether expression of PARP, FANCD2, PTEN, H2AX, ATM and P53 proteins in ovarian cancer correlates with response to treatment, recurrence rate, and survival. We specifically investigated whether PARP, FANCD2 and P53 in ovarian tissue predict cancer recurrence within five years.

A tissue microarray consisting of 203 sporadic ovarian cancer samples was stained with antibodies for each individual DNA repair protein as well as P53. Correlation with clinical and pathologic parameters was assessed.

Results: One hundred eighty-six patients (mean age: 62, range: 33–89) with serous histology type or stage II/IV or grade 3 ovarian cancers (cancer status) were evaluated using survival analysis (Kaplan–Meier method, Cox proportional hazards model, and cumulative incidence function). The median follow-up time (range) was 22 months (20 days–five years). Patients with serous histology type and late-stage cancer were more likely to have high levels of P53. High PARP expression positively correlated with high FANCD2 expression ($P<0.0001$), and one of three patients had high levels of both PARP and FANCD2 at baseline. Compared with patients with low levels of both PARP and FANCD2, patients with high levels of both proteins were twice as likely ($P=0.04$) to have a recurrence within five years after adjusting for age, cancer status and the presence of residual tumor. The estimated three-year recurrence probability and cumulative incidence rate were 48.9 and 41.4% for high levels of both proteins and 32.4 and 25.0% for low levels of both PARP and FANCD2.

Conclusions: Patients with coordinated high levels of PARP and FANCD2 proteins have a high risk for ovarian cancer recurrence. Dual targeting of these two HR pathway proteins may benefit patients with ovarian cancer.

doi:10.1016/j.ygyno.2010.12.044

38

Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes

F. Khoury Collado[1], M. Murray[2], Y. Sonoda[2], D. Levine[2], M. Leitao[2], D. Chi[2], R. Barakat[2], N. Abu-Rustum[2]
[1]Memorial Sloan–Kettering Cancer Center, Staten Island, NY, [2]Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The goal of this study was to compare the incidence of metastatic cancer cells in sentinel lymph nodes (SLNs) with the incidence of nonsentinel nodes (non-SLNs) in patients who had lymphatic mapping

for endometrial cancer and to determine the contribution of micrometastasis (MM) to the overall nodal metastasis rate.

We reviewed all patients who underwent SLN mapping for endometrial cancer. We used a cervical injection of blue dye in all cases. SLNs were examined by routine hematoxylin and eosin (H&E) and, if negative, by a standardized institutional pathology protocol that included additional sections and immunohistochemistry (IHC) to detect MMs.

Results: Between September 2005 and March 2010, 266 patients with endometrial cancer who underwent SLN mapping were analyzed. The histologic subtypes included: endometrioid, 220 (82%); serous, 22 (8%); carcinosarcoma, 18 (7%); and other types, six (2%). FIGO stage distribution was: stage I, 207 (78%); stage II, five (2%); stage III, 50 (19%), and stage IV, four (1%). SLN identification was possible in 223 (84%) cases. Positive nodes were diagnosed in 33 of 266 (12%) patients. In eight of the 33 (24%), the metastasis was detected only by additional section or IHC of the SLN, and would have been missed otherwise. The total number of SLNs removed was 801 (3.6 nodes/patient). The total number of non-SLNs removed was 2698 (10.1 nodes/patient). Excluding SLNs with MMs, 24 of 801 (3%) SLNs and 30 of 2698 (1%) non-SLNs were positive for metastatic disease ($P = 0.00027$).

Conclusions: Metastatic cells from endometrial cancer are more likely to be detected in the SLN than in the non-SLN. This finding strongly supports the concept of lymphatic mapping in endometrial cancer to fine-tune the nodal dissection topography. By adding SLN mapping to our current surgical staging procedures, we can increase the likelihood of detecting metastatic cancer cells in regional lymph nodes. An additional benefit of incorporating pathologic ultrastaging of SLNs is the detection of MMs, which may be the only evidence of extrauterine spread in 3% (8/266) of cases.

doi:10.1016/j.ygyno.2010.12.045

39

The role of lymphadenectomy in endometrial cancer: Was the ASTEC trial doomed by design and are we destined to repeat that mistake?

R. Naumann
Carolinas Medical Center, Charlotte, NC

Objective: This study examines the outcome of the ASTEC study with respect to lymph node (LN) dissection and explores future trial designs that address LN dissection in endometrial cancer (EC).

Data from several trials were used to create a decision analysis model that predicts the risk of LN spread and the effects of treatment on patients with EC. This decision model was applied to the population in the ASTEC trial as well as other future trial designs that might be used to address the role of LN dissection in EC.

Results: The model closely predicted the survival results of the ASTEC trial with and without LNs for the entire group, as well as the low-risk (LR) and intermediate-risk (IR) patients, with less than 4% difference between actual and predicted outcomes in all subgroups. The model predicts that there would be a survival difference of less than 2% between LNs and no LNs in the ASTEC trial, even if there was a 70% survival advantage associated with the removal of isolated positive pelvic LNs. This prediction is the same in both the LR and IR subgroups. Sensitivity analyses reveal that these conclusions are robust. Future trial designs comparing hysterectomy only, hysterectomy with radiation in IR, and hysterectomy with extended surgical staging with radiation reserved only for node-positive patients were also tested. Predicted survival rates with these respective strategies were 88, 90 and 93% in clinical stage I patients and 78, 82 and 89% in IR patients.

Conclusions: This decision analysis model confirms the futility of the ASTEC trial design and has important implications for future trials of surgical staging in EC. If trials comparing hysterectomy only with extended surgical staging and selective radiation are conducted in all stage I patients, only a 5% difference in outcome will be seen even if effective treatment for positive LNs is given. If trials using this design are limited to IR patients, a difference of greater than 10% in overall survival is expected and would significantly reduce the sample size needed.

doi:10.1016/j.ygyno.2010.12.046

Closing Plenary Session VII
Wednesday, March, 9, 2011, 7:35AM–11:25AM
Floridian Ballrooms A-I

Moderators, Abstracts: 40-51: John Farley, MD, Uniformed Services University of the Health Sciences, Bethesda, MD; Laura Jean Havrilesky MD, Duke University Medical Center, Durham, NC

40

Phase II trial of cetuximab in the treatment of persistent or recurrent squamous or nonsquamous cell carcinoma of the cervix: A Gynecologic Oncology Group study

A. Santin[1], G. Patricia[2], M. Sill[3], D. McMeekin[4], M. Leitao[5], J. Brown[6], G. Sutton[7], L. Van Le[8], C. Boardman[9]
[1]Yale University School of Medicine, New Haven, CT, [2]Upstate Carolina CCOP, Spartanburg, SC, [3]Roswell Park Cancer Institute, Buffalo, NY, [4]University of Oklahoma, Oklahoma City, OK, [5]Memorial Sloan–Kettering Cancer Center, New York, NY, [6]University of Texas M.D. Anderson Cancer Center, Houston, TX, [7]St. Vincent Hospital, Indianapolis, IN, [8]University of North Carolina School of Medicine, Chapel Hill, NC, [9]Medical College of Virginia, Richmond, VA

Objective: Epidermal growth factor receptor (EGFR, HER1/erbB-1) has been identified as a target for cancer therapy in multiple human tumors. The Gynecologic Oncology Group (GOG) conducted a phase II trial to assess the efficacy and tolerability of cetuximab, a human/murine chimeric monoclonal anti-EGFR1 antibody, in persistent or recurrent carcinoma of the cervix.

Eligible patients had cervical cancer, measurable disease, and GOG performance status 2. Treatment consisted of cetuximab 400 mg/m^2 as an initial dose followed by 250 mg/m^2 weekly until disease progression or prohibitive toxicity. The primary endpoints were progression-free survival (PFS) at six months and response. The study used a two-stage group sequential design.

Results: Thirty-eight patients were entered with three exclusions, leaving 35 evaluable for analysis. Thirty-one patients (88.6%) received prior radiation as well as either one ($n = 25$, 71.4%) or two ($n = 10$) prior cytotoxic regimens. Twenty-four patients (68.6%) had a squamous cell carcinoma. Grade 3 adverse events at least possibly related to cetuximab included dermatologic ($n = 5$), gastrointestinal ($n = 4$), anemia ($n = 2$), constitutional ($n = 3$), infection ($n = 2$), vascular ($n = 2$), pain ($n = 2$), and pulmonary, neurologic, vomiting and metabolic ($n = 1$ each). No clinical responses were detected. Five patients (14.3%, two-sided 90% CI = 5.8–30%) survived progression free for at least six months. The median PFS and overall survival times were 1.97 and 6.7 months, respectively. All patients with PFS at six months harbored tumors with squamous cell histology.

Conclusions: Cetuximab has limited activity in patients with recurrent cervical cancer in progression after palliative chemotherapy. Cetuximab seems to be well tolerated in this patient population and its activity seems to be limited to patients with squamous cell histology.

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Cervical cancer rates in clinical practice with co-testing, interval extension and current evaluation of women with pap-negative, human papillomavirus-positive screening tests

H. Dinkelspiel[1], N. Poitras[2], B. Fetterman[2], W. Kinney[2], T. Cox[3], T. Lorey[2], P. Castle[4]

[1]Kaiser Northern California, Sacramento, CA, [2]Kaiser Permanente Medical Center, Oakland, CA, [3]University of California, Santa Barbara, CA, [4]National Cancer Institute, Bethesda, MD

Objective: The purpose of this study was to characterize the cervical cancer rates in members of a large health maintenance organization following the introduction of Pap and human papillomavirus (HPV) co-testing in women aged 30+.

Age-adjusted rates of invasive cervical cancer (per 100,000) for female members, rescreening intervals following a negative screen, and follow-up information for women with two Pap-negative, HPV-positive screening tests were obtained from the organization's databases and the regional Cancer Registry. Women who had a positive Pap after a second Pap-negative, HPV-positive result and before histologic evaluation or who were no longer insured at 6 months following their second Pap-negative, HPV-positive screen were excluded.

Results: The median interval to rescreening in women who rescreened following a negative Pap was approximately 15 months prior to co-testing, and was 30 months for women who co-tested negative from 2003 to 2008.Cancer rates and the rates for histologic evaluation within six months following the second of two consecutive Pap-negative, HPV-positive screening tests are shown in the years 2003 through 2008 are shown in the table.

Conclusions: In clinical practice, cervical cancer rates are unchanged by doubling the screening interval for women with a negative Pap who also have a negative HPV test. This has not been previously demonstrated to the authors' knowledge despite national recommendations for interval extension with co-testing. However, the addition of HPV testing to cytology does not decrease cancer rates in the absence of prompt and complete evaluation of women with Pap-negative, HPV-positive results. Adding these observations to our previous report that the majority of cancers diagnosed following Pap-negative, HPV-positive screening tests were diagnosed after a single Pap-negative, HPV-positive screen argues for the development and implementation of sensitive and immediate triage of women with Pap-negative, HPV-positive screening tests rather than the current policy of deferring evaluation for a year.

	2000	2001	2002	2003	2004	2005	2006
Age-adjusted invasive cancer rate	6.5	6.3	6.5	5.1	5.6	5.8	6.1
No. of women with second consecutive Pap HPV+	0	0	0	18	324	1231	1304
No. of women with two consecutive Paps HPV+ and histology	0	0	0	2 (11%)	10 (3%)	131 (11%)	365 (28%)

	2007	2008	Total
Age-adjusted invasive cancer rate	7.6	6.2	
No. of women with second consecutive Pap HPV+	1177	1510	5564
No. of women with two consecutive Paps HPV+ and histology	502 (43%)	847 (56%)	1857

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Establishing an optimal sentinel lymph node mapping algorithm for the treatment of early cervical cancer

B. Cormier, J. Diaz, K. Shih, R. Sampson, Y. Sonoda, K. Park, D. Chi, R. Barakat, K. Alektiar, N. Abu-Rustum

Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The aim of this study was to establish a sentinel lymph node (SLN) mapping algorithm for the treatment of early cervical cancer that accurately detects lymph node (LN) metastasis but minimizes the need for complete lymphadenectomy.

A prospectively maintained SLN database of all patients with FIGO stage IA1 (with lymphovascular space invasion)/IIA cervical cancer who underwent SLN mapping from March 2003 to September 2010 was analyzed. Mapping was done after intracervical blue dye injection in all cases and was combined with preoperative intracervical ^{99m}Tc sulfur colloid injection in 64 cases. All patients underwent SLN mapping followed by a complete bilateral pelvic lymphadenectomy and parametrectomy combined with resection of the cervical cancer. We defined "detection rate" as identification of at least one SLN and "optimal mapping" as bilateral detection of at least one SLN. The surgical algorithm we evaluated included the following: (1) Any suspicious LNs are removed regardless of mapping. (2) If only unilateral mapping is noted, then a contralateral side-specific pelvic lymphadenectomy must be completed. (3) Parametrectomy (radical hysterectomy/trachelectomy) is done in all cases.

Results: One hundred twenty-two patients underwent SLN mapping. The median SLN count was three (range: 0–13), and the median total LN count was 20 (range: 2–74). Detection rate was 93% (114/122), and optimal mapping (bilateral) was achieved in 91 patients (75%). Twenty-eight patients (23%) had LN metastases. Nine had metastases detected in non-SLNs, but four of these also had a positive SLN. Of the five patients with LN metastases and negative SLNs, one had a grossly enlarged LN, positive on frozen section; two had only parametrial LN metastases detected on final pathology; one did not map but was found to have a positive LN on complete lymphadenectomy. The last patient had unilateral negative SLNs but a positive LN was found on the contralateral side-specific lymphadenectomy. When the algorithm was followed, all patients with LN metastases were detected, and a bilateral pelvic lymphadenectomy could have been spared in 75% of cases.

Conclusions: We established an optimal SLN mapping algorithm for the treatment of early cervical cancer that incorporates removal of any visible suspicious/gross disease and requires bilateral parametrectomy in conjunction with resection of the primary tumor and side-specific lymphadenectomy in cases where only unilateral SLN mapping is achieved. If followed, this algorithm allows for comprehensive detection of all patients with nodal disease and may spare a complete lymphadenectomy in the majority of cases.

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Comparison of radical hysterectomy with chemoradiation therapy for stage IB2 and IIA2 cervical cancer

J. Park[1], J. Kim[2], S. Park[2], J. Nam[1]

[1]Asan Medical Center, Seoul, Republic of Korea, [2]National Cancer Center, Goyang, Republic of Korea

Objective: Radical hysterectomy (RH) and concurrent chemoradiation therapy (CCRT) are used in the treatment of stage IB2 and IIA2 cervical cancer. However, optimal management is still controversial.

The aim of this study was to compare the outcomes of RH with those of CCRT in these patients.

From two tertiary centers, 191 patients with stage IB2 and IIA2 who underwent RH ($n=134$) or CCRT ($n=57$) were included in this retrospective analsysis. The primary endpoint was recurrence-free survival and the secondary endpoint was treatment-related complications.

Results: There were no between-group differences in age, body mass index, performance status, FIGO stage and histologic type. However, mean tumor size on imaging study was significantly larger in the RH group (3.8 cm vs 5.4 cm, $P<0.001$). The five-year, recurrence-free survival rates were 78 and 76% for the RH and CCRT groups, respectively ($P=0.928$). About 32% of patients in the RH group did not require adjuvant radiotherapy and none of them had a recurrence. Treatment-related complications were significantly lower in these patients than in the CCRT group.

Conclusions: Radical hysterectomy and concurrent chemoradiation therapy had similar efficacy in the treatment of patients with stage IB2 and IIA2 cervical cancer. However, significant proportions of the patients in these groups were successfully salvaged by surgery alone without significant treatment-related complications.

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Development of a preclinical serous ovarian cancer mouse model

V. Bae-Jump[1], C. Yin[1], X. Zong[1], T. Van Dyke[2]
[1]*University of North Carolina, Chapel Hill, NC,* [2]*National Cancer Institute, Frederick, MD*

Objective: Minimal improvements in overall survival for ovarian cancer have been made in the past several decades, and this can be partially attributed to the paucity of appropriate animal models of ovarian cancer, especially those recapitulating tumors of serous histology. Thus, our goal was to develop an inheritable genetically engineered mouse (GEM) model of serous ovarian cancer.

Given the high frequency with which pRb function is impaired in most epithelial ovarian cancers, we generated TgK18-gT_{121} conditional transgenic (Tg) mice, in which inactivation of all three Rb proteins by T_{121} (a fragment of the SV40 large T antigen) is driven by the keratin 18 (K18) promoter. A floxed stop codon upstream of the T[$_{121}$ transgene allows it to be silenced until being activated by Cre recombinase. We then crossed that mouse with conditional knockout mice floxed for the p53 and Brca1 tumor suppressor genes. This led to the creation of an ovarian cancer mouse model that specifically and somatically deletes the tumor suppressor genes of interest in adult ovarian surface epithelial cells (K18-g$T_{121}^{+/-}$; p53$^{fl/fl}$;Brca1$^{fl/fl}$ mouse model). The inactivation of the tumor suppressor genes, as well as induction of the T_{121} transgene, is achieved via injection of an adenoviral vector expressing Cre (AdCre) into the ovarian bursa cavity of adult female mice.

Results: Within three months of Cre-induced induction, ovarian carcinoma in situ was present within the injected ovary (4/4 mice). At six months postinduction, tumors developed in the injected ovary, while the contralateral un-injected ovary remained normal. At nine–14 months, mice developed ovarian tumors, most accompanied by ascites and/or carcinomatosis (5/5 mice). Examination of tumor histology revealed papillary growth surrounding fibrovascular cores, solid features, massive necrosis, and a high mitotic rate. These tumors expressed markers of serous tumors, including keratin 18, survivin, and WT-1.

Conclusions: We have developed an inheritable GEM model of serous ovarian cancer (K18-g$T_{121}^{+/-}$; p53$^{fl/fl}$; Brca1$^{fl/fl}$ mouse model). Most importantly, this model can be strategically altered to integrate other potential genomic attributes of this disease. Such a model system, which allows for the longitudinal study of serous ovarian cancer evolution, is paramount for understanding the sequence of malignant events required for this disease and is a critical tool needed in the search for better diagnostic and therapeutic interventions.

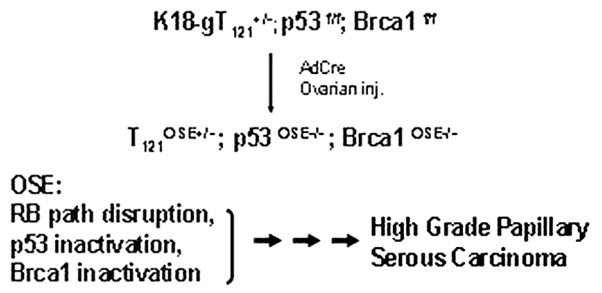

Figure 1. An inducible serous epithelial ovarian cancer model. T_{121} inactivates the Rb family proteins. The conditional transgene and conditional knockout of p53 and Brca1 are activated specifically in the OSE cells by ovarian bursa injection of AdCre.

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Impact of episodic transparent quality assessment on the staging of endometrial cancer

K. Podratz, S. Dowdy, J. Bakkum-Gamez, A. Weaver, M. McGree, W. Cliby, B. Gostout, T. Wilson, G. Keeney, A. Mariani
Mayo Clinic, Rochester, MN

Objective: The purpose of this study was to determine whether transparent episodic assessment of surgical quality by gynecologic oncologists within a single institution translates into improved staging of endometrial cancer (EC) and to identify patient-specific and process of care risk factors that influence surgical quality.

On January 1, 2004, a prospective treatment algorithm for EC including periodic analyses of the quality of pelvic and paraaortic lymphadenectomy (LND) was implemented. With the number of nodes harvested as a surrogate, staging quality during 2004–2008 (QA) was compared with that in the previous five-year interval (preQA). Since 2004, low-risk cases (e.g., grade 1/2, endometrioid, myometrial invasion (MI) <50%, and primary tumor diameter <2 cm) based on frozen section have not undergone LND and were excluded from both cohorts. Patient and perioperative risk factors influencing the quality of LND during both intervals were identified and compared.

Results: The inclusion of pelvic and paraaortic LND during the preQA era ($n=420$) was 77.9 and 48.8%, respectively, compared with 89.3 and 83.6% after initiation of QA ($n=561$) ($P<0.001$). The median number of pelvic and paraaortic nodes harvested in cases having LND was 29 and 10, respectively, during the preQA era compared with 34 and 16 after QA. Defining stringent LND adequacy as the mean node count minus 1 SD during QA, adequate pelvic (>22 nodes) and paraaortic (>10 nodes) LND occurred in 57.4 and 25.7% preQA compared with 77.9 and 70.8% during QA, respectively ($P<0.001$). Multivariable logistic regression analysis demonstrated the following

elements to be independent factors influencing adequate systematic pelvic and paraaortic LND: surgeon ($P<0.001$) and stage ($P<0.001$) during the preQA era compared with minimally invasive surgery ($P<0.001$), intraoperative ascites ($P<0.001$), BMI ($P<0.001$), surgeon ($P=0.002$), MI ($P=0.010$) and history of deep vein thrombosis ($P=0.011$) following QA.

Conclusions: The inclusion of transparent periodic assessment of surgical quality using number of nodes harvested and assessed as a surrogate translated into dramatic improvement in the quality of surgical staging for EC. Implementation of quality assessment was associated with a transition from predominantly disease-related factors influencing adequate LND to more patient-specific risk factors. Although surgical quality was markedly enhanced during QA, the persistent variability observed among surgeons renders continuous quality assessment and improvement obligatory.

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Defining the limits of radical cytoreductive surgery for ovarian cancer

J. Wright, S. Lewin, I. Deutsch, X. Sun, W. Burke, T. Herzog
Columbia University College of Physicians and Surgeons, New York, NY

Objective: We examined the morbidity and mortality of cytoreductive surgery for ovarian cancer and explored the effect of age and the performance of radical procedures on outcome.

Women who underwent cytoreductive surgery for ovarian cancer from 1998 to 2007 who were recorded in the Nationwide Inpatient Sample were analyzed. Patients were stratified by age: <50, 51–59, 60–69, 70–79, and >80 years. The following procedures were recorded for each patient: small bowel resection, rectosigmoid resection, other colectomy, bladder resection, splenectomy, hepatic resection and diaphragm resection. Each patient was further characterized by the number of radical procedures they underwent: none, one or more than two. Major perioperative morbidity and mortality were examined stratified by age, individual procedures and number of procedures performed using multivariable generalized estimating equations.

Results: A total of 28,651 patients, including 5660 (20%) aged 70–79 and 2208 (8%) aged >80, were identified. All of the individual complications increased with age. Surgical site infections increased from 6% in women <50 to 9% in patients aged 70–79 and 11% in those >80 ($P<0.0001$). Medical complications rose from 11% in women <50 to 21% in patients >80, while infectious complications increased from 3% in young women to 9% in patients >80 ($P<0.0001$ for both). Perioperative mortality was 0.5% in women <50, 3% in women 70–79, and 4% in patients >80 ($P<0.0001$). In multivariable analysis the odds ratio for perioperative death was 4.49 (95% CI = 3.09–6.52) in women 70–79 and 6.01 (95% CI = 3.93–9.18) in those >80. When stratified by the number of radical procedures performed, those who underwent no radical procedures had an all-cause complication rate of 20%, those with one procedure 34%, and those who underwent more than two procedures 44% ($P<0.0001$). These results were confirmed in multivariable analyses. The effects of age and number of radical procedures performed were additive. For each age group, morbidity increased with the number of radical procedures performed.

Conclusions: Perioperative morbidity and mortality for cytoreductive surgery are significant and increase with advancing age. Performance of radical debulking procedures increases morbidity significantly, particularly in patients >70 years of age. Given the substantial morbidity and mortality of extensive cytoreduction in the elderly, neoadjuvant chemotherapy should be considered in patients with substantial tumor burdens.

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Loss of *ARID1A* is a frequent event in clear cell and endometrioid ovarian cancers

W. Lowery[1], J. Schildkraut[1], L. Akushevich[1], R. Bentley[1], D. Huntsman[2], J. Marks[1], A. Berchuck[1]
[1]*Duke University Medical Center, Durham, NC,* [2]*University of British Columbia, Vancouver, BC, Canada*

Objective: The *ARID1A* gene plays a role in regulating expression of other genes through effects on chromatin remodeling. Inactivating somatic mutations in *ARID1A* have recently been described in a significant fraction of clear cell and endometrioid ovarian cancers, and these usually lead to loss of the corresponding protein (BAF250a). In this study we examined expression of BAF250a in clear cell and endometrioid ovarian cancers that were accrued prospectively in a molecular epidemiology study to determine whether loss of this gene is associated with clinical and epidemiologic features.

Immunostaining for BAF250a was performed using tissue sections cut from paraffin blocks of 186 clear cell and endometrioid ovarian cancers accrued in a prospective population-based molecular epidemiology study. All cases underwent centralized pathology review, and all subjects completed an interview regarding ovarian cancer risk factors. Loss of BAF250a was defined as staining of <10% of cancer cells in the presence of retention of expression in nonmalignant stromal elements. The association between loss of BAF250a and clinical and epidemiologic features was examined. Continuous variables were analyzed with the general linear model, and categorical variables were analyzed using χ^2 analysis.

Results: Loss of BAF250a expression was noted in 73 of 186 (39%) cancers, including 23 of 70 (33%) clear cell and 53 of 113 (47%) endometrioid cases. No relationship between the loss of BAF250a and stage, grade, or survival was identified. Epidemiologic variables such as birth control pill use, parity and infertility showed no correlation with loss of BAF250a. Because endometriosis is a precursor of many clear cell and endometrioid ovarian cancers, we examined the relationship between endometriosis and BAF250a expression. Endometriosis was reported by 15 of 72 (21%) cases with loss of BAF250a compared with 17 of 113 (15%) cases that retained BAF250a ($P=0.39$).

Conclusions: We have validated the finding that loss of the *ARID1A*-encoded protein BAF250a is a frequent event in the genesis of clear cell and endometrioid ovarian cancers. Loss of BAF250a is not associated with clinical or epidemiologic risk factors. One possible explanation for these findings is that inactivation of the chromatin remodeling pathway may be a requisite event in the development of all clear cell/endometrioid ovarian cancers. Confirmation of this hypothesis awaits future studies that seek to discover alterations in other genes in this pathway.

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Trends in utilization and cost of minimally invasive robotic surgery for endometrial cancer: A statewide analysis of 2296 patients

X. Yu[1], R. Brooks[2], D. Lum[2], T. Kiet[2], K. Fuh[2], R. Brooks[2], J. Orr[3], D. Kapp[4], J. Chan[2]

[1]University of Memphis, Memphis, TN, [2]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, [3]Florida Gynecologic Oncology, Lee Cancer Care, Ft. Myers, FL, [4]Stanford University Medical Center, Stanford, CA

Objective: The aim of this study was to analyze the trends in utilization and cost of robotic versus laparoscopic versus open surgery in patients with endometrial cancer.

Hospital discharge data for the period October 2008 to December 2009 for patients with endometrial cancer who underwent robotic surgery versus laparoscopic surgery versus open laparotomy were extracted from the State of Florida.

Results: Of 2591 patients with endometrial cancer (median age: 64), 649 (28.3%) underwent robotic surgery (RS), 228 (9.9%) laparoscopic surgery (LS), and 1419 (61.8%) open surgery (OS). Thirty-two percent of whites had RS versus 19.1% of nonwhites. Likewise, 10.3% of whites had LS versus 8.9% of nonwhites ($P<0.001$). The mean length of hospital stay was 1.9, 2.4, and five days for RS, LS and OS. The median total hospital charge was $51,569, $37,201 and $36,487, for RS, LS and OS, respectively. The major differences in the hospital charges were due to the operating room charges ($22,600, $13,684, and $11,183) and anesthesia facility charges ($4713, $2967, $3004) for RS, LS and OS. In a subset analysis of 40 facilities with one or more robotic systems, these hospitals accounted for 1403 (61.1%) of total surgeries. Among these facilities, the mean length of hospital stay was 1.9, 1.9, and 5.2 days, and the median total hospital charges were $51,569, $44,274, and $39,499 for RS, LS and OS, respectively. The trends in utilization and cost were further analyzed based on yearly quarters (Q1–Q4). The proportion of patients who underwent RS increased by 11%, from 22% in Q4 of 2008 to 28.5% in Q2 of 2009 to 33% in Q4 of 2009, whereas LS decreased by 3.9%, from 12.1% to 11% to 8.2%, and OS decreased by 7.1%, from 65.8% to 60.5% to 58.7% during the same periods ($P<0.001$). The proportion of nonwhites receiving robotic surgery also increased from 14% to 22.9% to 22.6% over time. Median length of hospital stay and hospital charges did not significantly change. More specifically, hospital charges for robotic surgery were $49,304 to $56,904 to $50,274 over the three periods.

Conclusions: In this statewide analysis of patients with endometrial cancer, our data suggest that the utilization of robotic surgery has increased with a corresponding decrease in both laparoscopic and open procedures. The higher hospital charges for robotic surgery were mostly attributed to operating room and anesthesia charges and have not decreased over time.

	Period 1	Period 2	Period 3	
Robotic	22%	28.5%	33%	$P<0.001$
Laparoscopic	12.1%	11%	8.2%	
Open	65.8%	60.5%	58.7%	

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BRCA1-deficient tumors demonstrate enhanced cytotoxicity and T-cell recruitment following doxil treatment

G. Mantia-Smaldone[1], E. Marsh[1], R. Loomis[1], S. Orsulic[2], S. Rubin[1], G. Coukos[1], S. Adams[1]
[1]University of Pennsylvania Medical Center, Philadelphia, PA, [2]UCLA Cedars–Sinai Medical Center, Los Angeles, CA

Objective: The aim of this study was to test the hypothesis that antitumor immune responses contribute to the increased efficacy of doxil in BRCA1-deficient (BRCA1–) tumors.

One hundred thousand BRCA1– or wild-type murine ovarian tumor cells were exposed to doxil (1 μg/ml) for 24 hours in vitro, then washed and bathed in drug-free medium. Cells were harvested at 24-hour intervals, counted to evaluate cytotoxicity, and analyzed for MHC I and Fas expression via multicolor flow cytometry. To determine the effect of doxil exposure on T-cell recruitment, 3×10^6 BRCA1– cells were injected intraperitoneally (IP) into FVB mice, and mice were treated with four weekly doses of intraperitoneal doxil (10 μg/100 μL phosphate-buffered saline [PBS], $n=10$) or PBS (100 μL, $n=10$) starting on day seven following tumor inoculation. Mice were euthanized when they reached a weight of 30 g due to ascites accumulation or at the end of the study (day 54). Immunohistochemical staining was performed on frozen tumor specimens using an anti-mouse CD3 antibody, and the frequency of intratumoral T cells was independently scored by two investigators.

Results: BRCA1– cells demonstrated enhanced cytotoxicity to in vitro doxil exposure compared with the wild-type cells (37% vs 76% survival, respectively; $P=0.0001$). Viable BRCA1– cells exhibited a fourfold increase in expression of MHC I and Fas following doxil exposure, with a 63% increase in the absolute number of double-positive cells, suggesting an enhanced susceptibility to T-cell killing. In contrast, there was no significant change in MHC I and Fas expression in the wild-type cells. Analysis of tumor biopsies also indicates a markedly increased frequency of intratumoral CD3 T cells in BRCA1-deficient tumors following doxil exposure compared with untreated mice.

Conclusions: We have previously reported that women with germline BRCA mutations have significantly longer progression-free and overall survival after doxil treatment compared with cases of sporadic ovarian cancer. Here we confirm that BRCA1– cells are more susceptible to the cytotoxic effects of doxil treatment in vitro and that surviving BRCA1– cells become better targets for T-cell killing after doxil exposure than wild-type cells. This response correlates with larger numbers of tumor-infiltrating T cells in BRCA1– tumor-bearing animals treated with doxil, suggesting an immunologic mechanism for the enhanced response to doxil by women with hereditary ovarian cancer.

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A history of breast carcinoma predicts worse survival in BRCA1 and BRCA2 mutation carriers with ovarian carcinoma

B. Norquist[1], R. Garcia[1], K. Agnew[1], J. Gross[2], R. Swensen[1], B. Goff[1], H. Gray[1], B. Karlan[2], E. Swisher[1]
[1]University of Washington Medical Center, Seattle, WA, [2]Cedars–Sinai Medical Center, Los Angeles, CA

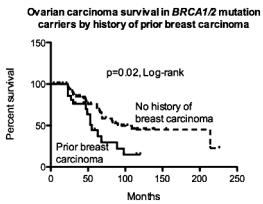
Objective: The purpose of this study was to identify factors that predict survival in a cohort of BRCA1 and BRCA2 (BRCA1/2) mutation carriers with ovarian, tubal and peritoneal carcinoma, compared with women with sporadic ovarian carcinomas.

Patients with BRCA1/2 mutations and ovarian, tubal, or peritoneal carcinoma were identified from two gynecologic oncology tissue banks and compared with patients with sporadic ovarian carcinomas without a significant family history of breast or ovarian cancer. The medical records were reviewed to determine age, stage, history of previous breast cancer, prior chemotherapy, optimal versus suboptimal debulking and survival. Data were analyzed using Prism or Instat software (Graphpad, Inc, San Diego, CA).

Results: Eighty-two patients with BRCA1 or BRCA2 mutations were identified, of whom 25 (30.5%) had a history of previous breast carcinoma, and 57 (69.5%) had no history of breast carcinoma. Two hundred thirty-two patients with sporadic ovarian carcinoma were identified. Median overall survival for all BRCA1/2 mutation carriers with ovarian carcinoma

was 82 months, compared with 49 months for women with sporadic ovarian carcinoma ($P=0.0002$, log-rank test, HR = 0.54, 95% CI = 0.39–0.75). BRCA1/2 mutation carriers with a prior history of breast carcinoma had a significantly worse overall survival compared with women with BRCA1/2 mutations and no previous history of breast cancer (median: 55 months vs 90 months, $P=0.02$, log-rank test, HR = 2.67, 95% CI = 1.20–5.91). BRCA1/2 mutation carriers with a prior breast cancer had an overall survival similar to that of women with sporadic ovarian carcinomas ($P=0.47$, log-rank test). Frequencies of stage I disease (8% vs 14%, $P=0.7$) and optimal debulking (95.2% vs 86.7%, $P=0.4$) did not significantly differ between BRCA1/2 mutation carriers with a history of breast carcinoma and those without.

Conclusions: Women with BRCA1/2 mutations and ovarian carcinoma have improved survival compared with women with sporadic ovarian carcinoma. BRCA1/2 mutation carriers with a history of breast carcinoma have significantly worse survival compared with those without a history of breast carcinoma, and similar survival compared with women with sporadic ovarian carcinoma. The diminished survival could result from the increased tendency of BRCA1/2 ovarian carcinomas in women with a history of breast cancer to manifest secondary mutations that restore BRCA1/2 in their recurrent ovarian carcinomas. Such secondary mutations result in resistance to platinum chemotherapy and could explain the decreased overall survival in women with previous breast cancer.



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Genetic variants in the mammalian target of rapamycin (mTOR) signaling pathway as predictors of clinical response and survival in women with ovarian cancer

L. Meyer[1], D. Liang[2], J. Lin[1], Y. Ye[1], M. Huang[1], X. Pu[1], K. Lu[1], X. Wu[1]
[1]University of Texas M.D. Anderson Cancer Center, Houston, TX, [2]Texas Southern University, Houston, TX

Objective: The mTOR pathway promotes cell survival and proliferation and is commonly altered in human tumors. Preliminary evidence suggests this pathway's involvement in chemoresistance to platinum and taxanes, first-line therapy for epithelial ovarian cancer. In this study,a pathway-based approach was used to identify individual germline single-nucleotide polymorphisms (SNPs) and cumulative effects of multiple genetic variants in mTOR pathway genes and their association with clinical outcome in women with ovarian cancer.

The case series was restricted to 319 non-Hispanic white women with high-grade ovarian cancer treated with surgery and platinum-based chemotherapy. One hundred thirty-five SNPs in 20 representative genes in the mTOR pathway were genotyped. Hazard ratios (HRs) for death and odds ratios (ORs) for failure to respond to primary therapy were estimated for each SNP using the multivariate Cox proportional hazards model and logistic regression model, respectively, while adjusting for age, stage, histology and treatment sequence. A survival tree analysis of SNPs with a statistically significant association ($P<0.05$) was performed to identify higher-order gene–gene interactions and their association with overall survival.

Results: There was no statistically significant difference in survival by tumor histology or treatment regimen. The median survival for the cohort was 48.3 months. Thirteen SNPs on five different genes were found to be significantly associated with a treatment response. Rare homozygous genotype of SNP rs6973428 showed a 5.5-fold increased risk compared with the wild type carrying genotypes. In the cumulative effect analysis, the highest risk group (individuals with ≥8 unfavorable genotypes) was significantly less likely to respond to chemotherapy (OR = 8.40, 95% CI = 3.10–22.75) compared with the low-risk group (≤4 unfavorable genotypes). Seven SNPs were significantly associated with decreased survival. Compared with those with no unfavorable genotypes, the HR for death increased significantly with the increasing number of unfavorable genotypes, and women in the highest risk category had a HR of 4.06 (95% CI = 2.29–7.21). The survival tree analysis also identified patients with different survival patterns based on their genetic profiles.

Conclusions: A pathway-based approach can demonstrate cumulative effects of multiple genetic variants on clinical response to chemotherapy and survival. Therapy targeting the mTOR pathway may help modify outcome in select patients.

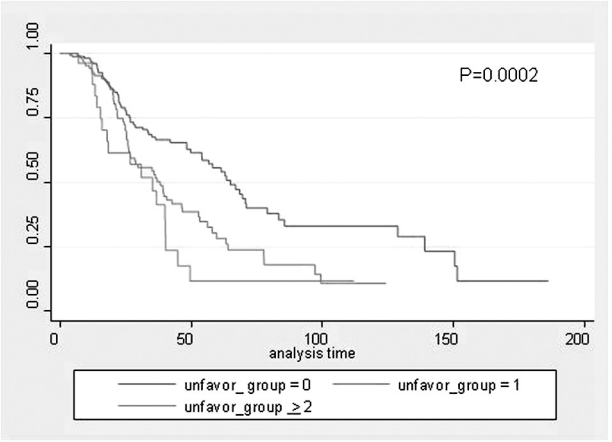

Figure 1. Kaplan Meier curve of overall survival stratified by risk group based on the number of unfavorable genotypes.

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Featured Poster Session
Sunday, March 6 – Wednesday, March 9, 2011
Abstracts 52–93
Bonnet Creek Ballroom Foyer

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A novel combination of a MEK inhibitor and fulvestrant shows synergistic antitumor activity in estrogen receptor-positive ovarian carcinoma

J. Hou[1], A. Rodriguez-Gabin[2], S. Horwitz[2], G. Goldberg[1], H. McDaid[2]
[1]Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [2]Albert Einstein Cancer Center, Bronx, NY

Objective: Although 40–60% of ovarian carcinomas express surface estrogen receptors, only about 15% respond to hormonal therapy. Expression of ERα is partially regulated via signaling changes in growth factor pathways such as the MAPK. MAPK signaling can occur

via mutation in RAS protein. Of note, K-ras is the most frequently mutated oncogene (15%) in ovarian carcinoma, predominately in clear cell and mucinous histologic subtypes. We evaluated the therapeutic efficacy of a highly selective MEK inhibitor, PD0325901, in combination with fulvestrant, an ERα antagonist, in human ovarian cancer cells and in an in vivo mouse model of ovarian carcinoma.

A panel of five ovarian cancer cell lines were analyzed for response to PD0325901 and fulvestrant using sulforhodamine colormetric growth assays. The Loewe additive model was used to evaluate the interaction of the two drugs in human ovarian SKOV-3 and A2780 carcinoma cells. Molecular determinants of response to MEK inhibition were determined by immunoblot. In addition, SKOV-3 xenograft-bearing mice were treated with PD0325901, fulvestrant, or a combination of both drugs given concurrently or sequentially to evaluate their antitumor efficacy and toxicity.

Results: In the ERα-positive ovarian cancer cell line SKOV3, inhibiting the MAPK pathway appears to stabilize and increase ER expression. This effect does not appear to be mediated by ERBB receptor tyrosine kinase or via the PI3K/AKT pathway. Phosphorylation status of AKT at serine 473 residue and S6 protein appears to be predictive of the sensitivity to PD0325901. The table summarizes the synergistic interaction between PD0325901 and fulvestrant over a range of concentrations that caused cytotoxicity in SKOV3. The interaction is minimally additive for A2780, an ER-negative cell line. In SKOV-3 xenograft-bearing mice, the combination is significantly superior to either agent alone and induces tumor stasis without significant toxicity.

Conclusions: Our data support the utility of MEK inhibitors as modulators of ERα expression and function in ovarian cancer cell lines. Treatment with the ER antagonist fulvestrant concurrently with PD0325901 has synergistic cytotoxicity. In an animal model of ER-positive ovarian carcinoma, this well-tolerated combination appears to induce disease stabilization. These data confirm the efficacy and support the development of MEK inhibitor and estrogen antagonists for potential targeted therapy in ER-positive ovarian cancer.

Synergistic interaction between PD901 and fulvestrant in human ovarian carcinoma cell lines.

Cell line	Effect of fulvestrant (200 nM)	Effect of PD0325901 (20–0.3 μM)	Effect of combination (observed) on growth	Effect of combination (expected range for additivity)
SKOV3 (ER+)	115% (proliferative effect)	30–10% Inhibition	30–25%	18–5%
A2780 (ER−)	20% Inhibition	80–30% Inhibition	80–31%	83–48%

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BAD apoptosis pathway expression and survival from cancer

J. Lancaster[1], D. Chen[1], D. Marchion[1], Y. Xiong[1], A. Berchuck[2], P. Judson[3], J. Gonzalez Bosquet[1], R. Wenham[1], S. Apte[1], W. Fulp[1]
[1]H. Lee Moffitt Cancer Center, Tampa, FL, [2]Duke University Medical Center, Durham, NC, [3]University of Minnesota, Minneapolis, MN

Objective: We previously determined the BCL2 antagonist of cell death (BAD) apoptotic pathway to be associated with the development of ovarian cancer (OVCA) chemoresistance. In the current study we explored associations between expression of the BAD apoptosis pathway, the development and progression of a variety of human cancers and clinical outcome.

Principal component analysis was used to derive a BAD pathway gene expression signature and a corresponding score that represents an overall measure of expression of BAD pathway genes. Associations between the BAD pathway signature score and a series of clinical variables were explored in genomic data sets from 1258 patients with ovarian, breast, colon and brain cancer. The influence of BAD protein phosphorylation on survival was evaluated in a series of OVCA patient samples.

Results: We developed a 47-gene BAD pathway signature, the expression score of which was associated with overall survival from OVCA (two data sets: $n=143$, $P<0.001$; $n=237$, $P=0.02$), colon cancer ($n=205$, $P=0.0045$), brain cancer (two data sets: $n=50$, $P=0.01$; $n=182$, $P=0.14$), and relapse-free survival from breast cancer (two data sets: $n=208$, $P<0.0001$; $n=286$, $P<0.01$. In multivariate analysis, BAD pathway score was independently associated with overall survival from OVCA ($P<0.001$). Incorporation of debulking status into the BAD pathway score analysis yielded a statistically significant association with overall survival ($P<0.01$). Interestingly, patients subject to suboptimal debulking of OVCAs with a high BAD pathway score had superior survival compared with patients subject to optimal debulking of OVCAs with a low BAD pathway score ($P=0.08$) (see the figure). Phosphorylation levels of the BAD protein were associated with overall survival for patients with OVCA ($P<0.0001$).

Conclusions: BAD pathway gene expression is associated with survival from many human cancers, and is an independent determinant of overall survival for patients with OVCA. The pathway represents an appealing human cancer prognostic biomarker and therapeutic target.

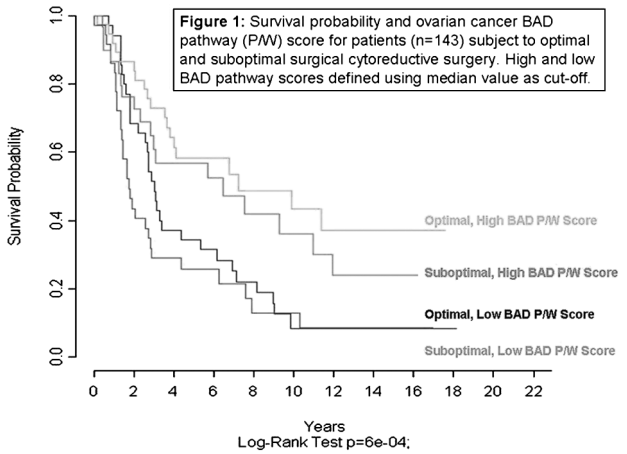

Figure 1: Survival probability and ovarian cancer BAD pathway (P/W) score for patients (n=143) subject to optimal and suboptimal surgical cytoreductive surgery. High and low BAD pathway scores defined using median value as cut-off.

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Examination of matched primary and recurrent ovarian cancer specimens supports the cancer stem cell hypothesis

K. Bevis[1], A. Steg[2], A. Katre[2], B. Erickson[2], T. Backes[2], K. Zhang[2], P. Frederick[2], M. Conner[2], C. Landen[2]
[1]University of Alabama, Trussville, AL, [2]University of Alabama, Birmingham, AL

Objective: Within heterogeneous tumors, subpopulations labeled cancer stem cells (CSCs) have been identified that have significantly enhanced tumorigenicity and chemoresistance in ex vivo models. However, whether these populations are truly more capable of surviving chemotherapy in de novo tumors is not known. We hypothesized that CSCs make up a greater portion of recurrent tumors and, therefore, may represent the subpopulation within ovarian cancers predominantly contributing to chemoresistance and recurrent disease.

Forty-five matched primary/recurrent tumor pairs of high-grade papillary serous or endometrioid ovarian adenocarcinomas were subjected to immunohistochemistry (IHC) for populations shown to have CSC properties in ex vivo studies: CD44, CD133 and ALDH1. Additionally, 12 pairs in which recurrent tumors were collected immediately after completion of primary therapy were laser microdissected and analyzed with quantitative PCR array for expression of stem cell pathway members.

Results: The percentages of positive CD44, CD133, and ALDH1 cells in primary samples averaged 6.2, 7.1, and 23.4%, respectively. In recurrent samples, there was a moderate increase in CD44-positive cells (to 11.0%, $P = 0.11$) and ALDH1-positive cells (to 29.2%, $P = 0.28$). However, for CD133, there was a dramatic increase, with 29.6% of cells CD133 positive ($P = 0.0004$). Interestingly, when patients were stratified based on the clinical scenario in which the recurrent tumor was sampled, the increases were more pronounced. Of tumors collected immediately after completion of primary therapy, 53.4% of cells were CD133 positive ($P = 0.001$), 54.9% were ALDH1 positive ($P = 0.018$) and 21.2% were CD44 positive ($P = 0.16$). Samples collected at first recurrence (before initiating secondary therapy) were composed of similar percentages of each population, suggesting the tumor was repopulated with marker-negative differentiated cells. Of 86 members of the Notch, Hedgehog, Wnt, and TGF-α pathways examined, 16% were overexpressed in recurrent specimens collected immediately after completion of primary therapy.

Conclusions: These data indicate that chemoresistant tumor subpopulations are enriched in CD133 and ALDH1 populations, suggesting a contribution of these subpopulations to surviving initial chemotherapy and ultimately recurrent disease. Expression profiling in recurrent samples supports the hypothesis that select subpopulations within a heterogeneous tumor have enhanced chemoresistance due, at least in part, to activation of stem cell pathways.

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Hypoxia-mediated activation of signal transducer and activator of transcription 3 (STAT3) in ovarian cancer: A novel therapeutic strategy using HO-3867, a STAT3 inhibitor

G. McCann[1], K. Selvendiran[1], K. Hideg[2], D. Cohn[1], P. Kuppusamy[1]
[1]Ohio State University, Columbus, OH, [2]Institute of Organic and Medicinal Chemistry, University of Pecs, Pecs, Hungary

Objective: Hypoxia plays a role in tumorigenesis and the development of resistance to radio- and chemotherapy. Specifically, we have shown that hypoxic exposure increases the phosphorylation of STAT3 at the Tyr705 residue in A2780 cell lines, and that this is associated with an increase in chemotherapeutic resistance. HO-3867, a novel curcumin analog designed with our institution, induces cell cycle arrest and apoptosis via inhibition of the STAT3 signaling pathway. The goal of this study was to examine the utility of HO-3867 as a means of reversing chemoresistance in hypoxic ovarian cancers and to understand the mechanistic pathways involved.

The study was performed using A2780 and SKOV3 human ovarian cancer cell lines grown under normoxic (21% O_2) and hypoxic (1% O_2) conditions for 24 hours. Hypoxia-exposed cells were subsequently treated with 10 or 20 μM HO-3867 for 12 and 24 hours. The expression levels of pSTAT3, associated proteins and apoptotic markers were evaluated by Western blot. Quantification of apoptosis was performed by staining with annexin V. We also examined cell viability and involvement of ubiquitin-dependent degradation of pSTAT3. Human tumor samples were analyzed for levels of pSTAT3 and associated proteins.

Results: Treatment with HO-3867 under hypoxic conditions resulted in decreased protein expression of pSTAT3 Tyr705 and Ser727. Downregulation of STAT3 correlated with accelerated ubiquitin-dependent degradation of pSTAT3 Tyr705. Treatment was associated with decreased levels of JAK1- and STAT3-targeting genes VEGF, Bcl-xL, and cyclin D1. An induction of apoptosis contributed to inhibition of cell proliferation as HO-3867-exposed A2780 cells exhibited elevated levels of cleaved caspase-3, caspase-7, and PARP, as well as an increase in apoptotic cell count measured by flow cytometry. Preliminary work in human ovarian cancer specimens suggests that pSTAT3 Tyr705 is highly expressed compared with Ser727 in advanced stages.

Conclusions: Under hypoxic growth conditions, HO-3867 demonstrates cytotoxicity via inhibition of the JAK/STAT3 signaling pathway. The use of HO-3867 may be a potential adjunct in the treatment of hypoxia-mediated chemotherapy-resistant ovarian cancers.

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Modeling of early events in serous carcinogenesis: Molecular prerequisites for transformation of fallopian tube epithelial cells

A. Jazaeri[1], J. Bryant[1], H. Park[1], J. Ferriss[2], H. Li[1], A. Dutta[3]
[1]University of Virginia Health System, Charlottesville, VA, [2]Temple University Hospital, Philadelphia, PA, [3]University of Virginia, Charlottesville, VA

Objective: Fallopian tube epithelial cells have emerged as the likely origin of most serous ovarian and peritoneal cancers. Our objective was to establish a dynamic model for serous carcinogenesis whereby relevant oncogenic molecular alterations and their necessity for malignant transformation could be tested.

Primary cultures of fallopian tube epithelial (FT) cells were transduced using a mixture of retroviral particles targeting ovarian cancer-relevant molecular pathways or a control retroviral mix. Ovarian cancer-relevant transgenes included: dominant negative p53, shRNAs targeting BRCA1, oncogenic RAS, C-MYC, hTERT, SV40 large T antigen and cyclin D1-CDK4. The control mixture contained empty and GFP-expressing vectors. Transduced FT cells were propagated under natural rather than antibiotic selection with the rationale that cells transduced with growth-promoting combinations of oncogenes would predominate the culture over time. Transformation was assessed by colony formation assays and xenograft formation in immunodeficient mice. Expression of retroviral targets was assayed using real-time RT-PCR and Western blot analysis.

Results: Primary FT cell lines transduced with the oncogenic mixture underwent malignant transformation as evidenced by colony formation assays and formation of xenografts in immunodeficient mice. The histologic and immunohistochemical features of these xenografts were very similar to those of human serous tumors. In contrast, FT cells infected with control retroviruses underwent senescence. Analysis of the molecular phenotype of transduced FT cells is ongoing and, thus far, has revealed p53, hTERT, RAS and C-MYC protein accumulation over time.

Conclusions: We have established a dynamic in vitro model of FT transformation that can be used to investigate the earliest molecular

alterations involved in serous carcinogenesis. The transformed FT xenografts resemble human serous carcinomas and provide direct evidence in support of the FT origin of serous cancers.

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Molecular profiling of advanced pelvic serous carcinoma associated with serous tubal intraepithelial carcinoma

D. Levine, F. Bogomolniy, F. Dao, N. Olvera, G. Han, R. Soslow
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: Ovarian cancer has traditionally been thought to develop from the ovarian surface epithelium or cortical inclusion cysts, but recent data suggest that a majority of advanced pelvic serous carcinomas (APSCs) originate from the distal fallopian tube, with serous tubal intraepithelial carcinoma (STIC) as the putative precursor lesion. We hypothesized that APSCs with and without associated STIC would have similar gene expression profiles reflecting a common cell of origin.

Fresh-frozen tumor tissues were collected at the time of initial surgery from 21 patients with stage IIIC or IV high-grade serous carcinoma classified as ovarian (16), peritoneal (two), or tubal (three) based on traditional criteria. All patients had comprehensive processing of the fallopian tubes using the SEE-FIM protocol. Gene expression profiles were generated from Affymetrix U133A 2.0 and Agilent Version 3 human microRNA (miRNA) oligonucleotide microarrays. Copy number assessment was performed using the Agilent 1 M Human Genome CGH microarray. Unsupervised clustering was performed using Pearson's correlation coefficient as the distance metric and average linkage as the method to join clusters. Supervised class comparison was performed to identify differentially expressed genes between APSCs with and without associated (±) STIC using a per gene two-sample *t* test.

Results: STIC was identified in nine of 21 (43%) cases. Unsupervised cluster analysis of both RNA and miRNA data identified two reproducible main clades with no segregation between APSCs ± STIC. Class comparison of the RNA data using the 10,631 most variable probe sets identified only 58 differentially expressed probes between APSCs ± STIC at a relaxed *P* of 0.01, fewer than the 106 expected by chance alone. At a more stringent *P* of 0.001, only three differentially expressed genes were identified, fewer than the 11 expected by chance alone. Class comparison of the miRNA data using the 543 most variable genes identified only two differentially expressed genes between APSCs ± STIC at a *P* of 0.01, fewer than the five expected by chance alone. Copy number alterations are currently being analyzed.

Conclusions: The data suggest that molecular differences between APCS with and without associated STIC are not identifiable, indicating a common biologic origin among all cases. We propose that APSC originates in the distal fallopian tube and a STIC lesion is identifiable in only ~50% of cases prior to intraperitoneal shedding of malignant cells.

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Prospective identification of epigenetic signatures that predict clinical outcomes in high-risk human papillomavirus-positive early cervical intraepithelial neoplasia

M. Einstein, T. Belbin, L. Adrien, G. Goldberg, H. Strickler, R. Burk, N. Schlecht
Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

Objective: Biomarkers for predicting cervical intraepithelial neoplasia (CIN) I outcomes have clear clinical implications. DNA hypermethylation of tumor suppressor genes has been described for CIN and cervical cancer in cross-sectional studies, but there are few prospective data. We prospectively recruited and followed women with incident CIN I with high-risk HPV to determine epigenetic profiles that correlate with disease outcomes.

After institutional review board approval, women with incident high-risk HPV-positive CIN I were followed every six months with (1) Pap, (2) colposcopy and directed biopsy of lesion(s), (3) biopsy adjacent to the lesion, and (4) biopsy of histologically confirmed colposcopic specimens of normal cervix. All biopsies were snap frozen within a minute of procurement for DNA and RNA analyses. Methylation analyses were performed with the Infinium Array (Illumina, San Diego, CA). Candidate genes were confirmed using bisulfite treatment and direct sequencing after PCR.

Results: Sixteen women with CIN I and biopsies from at least three subsequent time points were included in this analysis. Sufficient DNA for methylation analysis was available from 15 of 16 subjects. Ten confirmed normal adjacent cervical biopsies from nine subjects were also analyzed. Of the 15, 7 (47%) regressed, 7 (47%) continued to have CIN I, and 1 (1%) progressed over 18 months. Differences in methylation between the lesion and normal biopsies within the same subject were measured across 27,578 CpG sites. There was little difference in methylation across all CpG sites (mean $\beta = 0.002 \pm 0.026$). When the initial lesion biopsy was compared with follow-up at a later point in the same subject, there were 158 genes that differed, with one gene, MGMT, that had a significant change in methylation that was predictive of persistence (stable disease [SD])/progressive disease (PD) at a later date, suggesting these subjects accumulated methylation in this region. When baseline biopsies from subjects who had SD/PD were compared with those from subjects with regression to normal, 83 genes were identified, of which three (CCND2, MTMR4, and TEX2) were found to differ in methylation status between lesion and normal biopsies. By use of a second platform, MGMT was confirmed to be hypermethylated in subjects with SD/PD. This cohort continues to be followed and new subjects are being recruited.

Conclusions: This is the first prospective evaluation of epigenetic profiles in subjects with CIN I at consecutive six-month points. Methylation of MGMT is correlated with SD/PD, and might be a possible biomarker for early progression of CIN and a future target for therapy. With more time and recruitment, other hypermethylated genes might also be identified.

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The ubiquitin ligase EDD mediates platinum resistance and is a target for therapy in epithelial ovarian cancer

A. Ziebarth[1], H. Zheng[2], A. Bradley[2], W. Sakati[2], S. Eier[2], G. Lopez-Berestein[3], A. Sood[3], S. Eblen[2], C. Landen[4]
[1]University of Alabama, Birmingham, AL, [2]Medical University of South Carolina, Charleston, SC, [3]University of Texas M.D. Anderson Cancer Center, Houston, TX, [4]UAB Comprehensive Cancer Center, Birmingham, AL

Objective: Ovarian cancer remains the most lethal gynecologic cancer largely because of its ability to develop chemotherapeutic resistance. The protein E3 ubiquitin ligase identified by differential display (EDD) is overexpressed in 83% of recurrent, platinum-resistant ovarian cancers. Our objective was to evaluate EDD expression in

ovarian cancer to determine whether it may be therapeutically targeted.

EDD expression was analyzed in multiple ovarian cancer cell lines by Western blot. Transient knockdown of EDD was achieved with lipofectamine-mediated transfection of siRNA, and stable knockdown was achieved with shRNA, in the A2780ip2 and ES2 ovarian cancer cell lines. Cell viability was assessed by MTT assay and apoptosis by cell cycle analysis of PI incorporation, the Trevigen TACS 2 TdT-Blue Label apoptosis kit and PARP cleavage. Cos-7 cells were transfected with GFP, wild-type EDD or a ubiquitin ligase-deficient point mutant, EDD-C2768A, plasmid. In vivo, DOPC-encapsulated siRNA provided transient knockdown of EDD. Mice with intraperitoneal A2780ip2 or ES2 xenografts were randomized to treatment with control siRNA, EDD-targeting siRNA, cisplatin or combination therapy. Tumor weights were obtained and compared with Student's t test or the Mann–Whitney test.

Results: EDD expression was noted in ES2, A2780ip2, OV2008, OVCAR3 and OVCAR5 cells. In A2780ip2 and ES2 cell lines, EDD downregulation deceased cell viability 80% and increased apoptosis 2.5-fold compared with control siRNA ($P<0.001$). ES2 clones with stable EDD knockdown demonstrated four-fold increased platinum sensitivity. In Cos-7 cells transfected to overexpress EDD, cisplatin-induced apoptosis was reduced by 64%, whereas transfection with EDD-C2768A increased apoptosis by 17%. In vivo, mice treated with EDD siRNA exhibited a trend toward less tumor than those treated with control siRNA (27.7% reduction in ES2, 42.5% in A2780ip2, $P=0.23$ and 0.19, respectively). Mice treated with combined EDD siRNA and cisplatin had significantly less tumor than controls (77.9% reduction in ES2, 75.9% in A2780ip2, $P=0.004$ and 0.042, respectively) and cisplatin alone (60.3–64.4% reduction, $P=0.035$).

Conclusions: EDD overexpression is common in ovarian cancer and contributes to platinum resistance through its ubiquitin ligase activity. Targeting EDD induces apoptosis and sensitizes cells to platinum in vivo and in vitro. EDD ubiquitin ligase may be a viable target for overcoming chemoresistance in ovarian cancer.

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Does a uterine manipulator affect cervical cancer pathology or identification of lymphovascular space involvement?

J. Rakowski, M. Radi, S. Ahmad, L. Brudie, J. James, R. Holloway
Florida Hospital Cancer Institute, Orlando, FL

Objective: Uterine manipulators are helpful in the performance of robotic hysterectomy, but many surgeons have avoided their use in robotic radical hysterectomy for theoretical risks of altering the pathology or perhaps even increasing lymphovascular space invasion (LVSI). This study compared clinicopathologic data and a random selection of pathology specimens from open and robotic radical hysterectomy cases.

All radical hysterectomy cases from January 1997 to June 2010 at a single institution were reviewed. Clinical data included: tumor histology, grade, FIGO stage, lymph node status, LVSI, depth of invasion and tumor size. A ConMed V-CARE manipulator was used in all robotic cases. H&E-stained slides from 10 robotic cases and 10 open stage IB1 cases were reviewed by a pathologist, blinded to the procedure type for analysis of tissue artifact and LVSI characteristics. Statistical analyses were performed using Student's t test and z test.

Results: A total of 236 cases (185 open and 51 robotic) of stage IA2, IB1 and IB2 cervical cancer were reviewed. There were no significant differences with respect to stage (e.g., IB1: 70.3%, $n=130$, vs 80%, $n=41$; $P>0.1$), histology (e.g., squamous cell carcinoma: 65%, $n=120$, vs 51%, $n=26$; $P=0.1$), positive lymph node status (11.3% vs 13.7%; $P>0.1$), IB1 lesion size (<2 cm: 62%, $n=81$, vs 61%, $n=25$; $P>0.1$), and LVSI [34%, $n=63$, vs 39%, $n=20$; $P>0.1$) between the open and robotic groups, respectively. Similarly, depths of stromal invasion for IB1 lesions by thirds did not statistically differ ($P>0.1$). Examination of histologic sections failed to reveal any artifact that was more common in the robotic than in the open cases.

Conclusions: There was no difference in clinicopathologic findings, including depth of invasion and LVSI, between laparotomy and robotic cases of radical hysterectomy that used an intrauterine manipulator. Uterine manipulators are unlikely to significantly alter the histopathologic interpretation of radical hysterectomy specimens.

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Pap-negative, human papillomavirus-positive screening results: Compliance with follow-up and results of follow-up

H. Dinkelspiel[1], N. Poitras[2], B. Fetterman[2], W. Kinney[2], T. Cox[3], T. Lorey[2], P. Castle[4]
[1]Kaiser Northern California, Sacramento, CA, [2]Kaiser Permanente Medical Center, Oakland, CA, [3]University of California, Santa Barbara, CA, [4]National Cancer Institute, Bethesda, MD

Objective: The purpose of this study was to characterize the compliance with rescreening following a Pap-negative, high-risk human papillomavirus (HPV)-positive screen in routine clinical practice, the screening test results occurring in follow-up, and the compliance with and results of histologic assessment for a second consecutive Pap-negative, HPV-positive screen.

Follow-up data were obtained from a large health maintenance organization database. Conventional Pap smears and Hybrid Capture 2 (Qiagen) high-risk HPV tests were used for screening.

Results: In the year 2007, 8007 women aged 30+ had a Pap-negative, HPV-positive screening result. Follow-up frequencies within the 18 months following the Pap-negative, HPV-positive result are described next. Three hundred fifty-four women had Pap or HPV tests without co-tests within 18 months. Five thousand four hundred ninety-eight women had co-tests within 18 months. One thousand fifty-six women had no rescreening within 18 months and were no longer members at 18 months. One thousand ninety-nine women were noncompliant; they had no rescreening within 18 months and were still members at 18 months: $(354+5498)/(354+5498+1099)=84.2\%$ of continuing members with Pap-negative, HPV-positive screens were rescreened with any test within 18 months and 79.1% underwent a second co-test. The worst result of follow-up screening within 18 months of a Pap-negative, HPV-positive result is shown in the table. In the six-month period from 1 January 2009 to 30 June 2009, 1153 women aged 30+ had a second consecutive Pap-negative, HPV-positive screening result (any interval). Of the 1126 of 1153 women who were still members six months after their second Pap-negative, HPV-positive result, 763 (67.8%) had undergone histologic evaluation, with the finding of CIN2+ in 80 of 763 (10.5%) and CIN3+ in 32 of 763 (4.2%).

Conclusions: This first large evaluation of the histology associated with two Pap-negative, HPV-positive screens supports the recommendation for colposcopy. However, if 84.2% of Pap-negative, HPV-positive women receive follow-up screening and 67.8% of those with a second Pap-negative, HPV-positive screen undergo colposcopy, more than 40% of the CIN3 and cancer in the Pap-negative, HPV-positive population may be missed. Reduction in cancer rates will

require colposcopy of all HPV-positive women over a given age regardless of cytology (as demonstrated by Ronco et al., Br Med J 2009;339:b3005) or effective triage testing of Pap-negative, HPV-positive women.

Negative for intraepithelial lesion and malignancy or HPV– or cotest	No Pap HPV+	Pap-HPV+	ASC HPV–	ASC HPV+	ASC no HPV	Unsatis-factory	LSIL	ASC-H	AGC AIS	HSIL	Cancer
2895	12	1481	139	806	32	11	278	101	46	50	1

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Reproductive outcomes of patients undergoing radical trachelectomy for early-stage cervical cancer

C. Kim, N. Abu-Rustum, D. Chi, G. Gardner, M. Leitao, J. Carter, R. Barakat, Y. Sonoda
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The aim of this study was to report the reproductive outcomes of patients undergoing fertility-preserving radical trachelectomy for the treatment of early-stage cervical cancer at a single institution.

A retrospective review was conducted of our institution's first 105 patients who underwent attempted fertility-preserving surgery with radical trachelectomy (RT), pelvic lymphadenectomy and purse string cerclage from November 2001 to October 2010.

Results: Of the 105 patients who underwent attempted RT, 76 (72%) did not require an immediate radical hysterectomy and/or adjuvant therapy. Four patients were of pediatric age (6–15 years) and were excluded from this study. Of the remaining 72 patients, 35 were actively attempting conception six to 12 months after surgery. The median age was 32 years (range: 25–38), and 17 patients (49%) were nulligravid. Among 22 patients (63%) who successfully conceived, 18 (82%) had one pregnancy, and four (18%) had two pregnancies. Eighteen pregnancies were carried to the third trimester: six (33%) delivered between 32 and 36 weeks and 12 (67%) delivered at >37 weeks. All fpur patients who had two pregnancies delivered their second pregnancy between 32 and 36 weeks. The other pregnancies included one (4%) first-trimester miscarriage, three (12%) second-trimester miscarriages and three (12%) elective pregnancy terminations. The cerclage eroded through the vaginal wall in six cases and was treated by removal. One of these patients experienced a second-trimester miscarriage. Several factors may have contributed to the remaining 12 patients who were unsuccessful in achieving pregnancy: persistent cervical stenosis (three), poor oocyte quality (one), lack of follow-up with reproductive endocrinologists (four), failed in vitro fertilization due to unknown etiologies (two) and social issues (two). After RT, 77% of patients who desired to conceive used some form of assisted reproductive technology. Spontaneous conceptions accounted for 55% of pregnancies.

Conclusions: In our trachelectomy population, the majority of patients who attempted to conceive after radical trachelectomy were successful and most resulted in full-term births. Assisted reproductive technology played a significant role in this group of women. Cerclage may also contribute to a patient's ability to carry a pregnancy to the third trimester.

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Residing in a county with higher percentage of language isolation is associated with increased incidence of invasive squamous cell carcinoma of the cervix among Hispanic women

K. Ward[1], A. Roncancio[2], S. Plaxe[1]
[1]*University of California at San Diego/Kaiser San Diego, La Jolla, CA,* [2]*University of Texas School of Public Health Center for Health Promotion and Prevention Research, Houston, TX*

Objective: The goal of this study was to evaluate the association of language isolation (LI) with incidence of invasive squamous cell carcinoma (SCC) of the cervix among Hispanic women as compared with non-Hispanic women.

A LI household is defined as one in which all members 14 years of age and older speak a non-English language and also speak English less than very well. Percentage LI (%LI) quantifies the proportion of LI households in a given county. Average annual age-adjusted incidence rates/100,000 women (AAAAIR) and 95% confidence intervals (CI) for invasive SCC of the cervix were calculated from data reported in the Surveillance, Epidemiology and End Results (SEER) Program's 17 Registries from 2000 to 2007. Patients were stratified by non-Hispanic versus Hispanic ethnicity and by residence in a county with high versus low %LI (greater or less than the sample median).

Results: Of the 18,596 patients in the data set who met inclusion criteria, 24.0% (4463) were Hispanic and 90.6% of Hispanic patients lived in counties with high %LI. Less than half (49.1%) of non-Hispanic patients lived in high %LI counties. The range of %LI was 0.0–4.62% in the low %LI group (47.44% of the sample) and 4.72–20.05% in the high %LI group. Overall, the AAAAIR of SCC was significantly higher among Hispanic women: 5.0 (95% CI = 4.8–5.1) compared with 2.8 (95% CI = 2.8–2.9) in non-Hispanic women. The difference in AAAAIR was magnified among those residing in high %LI counties. Among Hispanic women living in high %LI counties, the AAAAIR of SCC was 5.1 (95% CI = 4.9–5.3), nearly double the AAAAIR of SCC among non-Hispanic women, 2.6 (95% CI = 2.5–2.7). In low %LI counties, the AAAAIR of SCC was 3.8 (95% CI = 3.4–4.2) among Hispanic women and 3.0 (95% CI = 3.0–3.1) among non-Hispanic women.

Conclusions: Prior to this report, the magnitude of the association between LI and the incidence of SCC of the cervix among Hispanic women had not been reported. It is recognized that language barriers contribute to low screening rates in Hispanic women. A more precise understanding of contributing factors, such as LI and other socioeconomic factors, may facilitate the design of targeted research studies and interventions. As examined here, LI is a county, or community, characteristic, rather than an individual characteristic, making it plausible that community-level public policy interventions might be effective in reducing the unequal burden of cervical cancer in Hispanic-American women.

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Stage IB2 cervical cancer: A decision analysis comparing quality-adjusted survival associated with chemoradiation versus radical surgery with tailored adjuvant chemoradiation

M. Einstein[1], J. Hollenberg[2], E. Hartenbach[1], R. Chappell[1], D. Kushner[1], A. Evans[1], J. Connor[1]
[1]*University of Wisconsin, Madison, WI,* [2]*Weill Medical College of Cornell University, New York, NY*

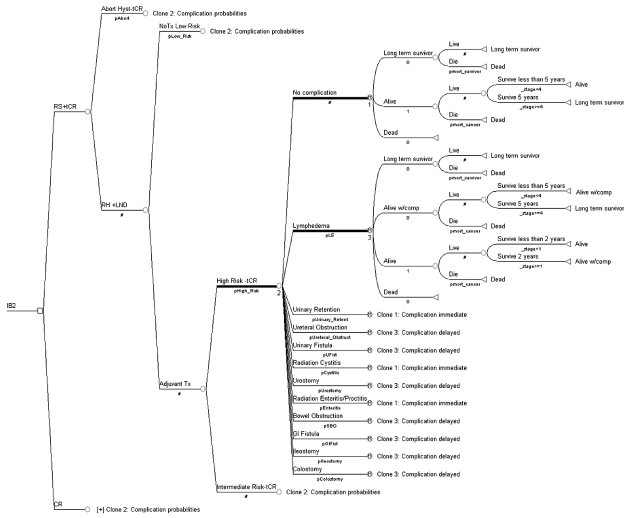
Objective: Optimal treatment of stage IB2 cervical cancer has not yet been determined. Treatment side effects pose serious survivorship issues. We hypothesized that the long-term increased side effects associated with surgery plus chemoradiation would make the

quality-adjusted survival (QAS) among women receiving primary chemoradiation (CR) preferable to that of women having radical surgery with tailored chemoradiation (RS-tCR).

A Markov transition model was created using TreeAge decision tree software comparing CR with RS-tCR in a cohort of 45-year-old women with IB2 cervical cancer. Surgical patients who met high-risk (positive lymph nodes and/or margins) or intermediate-risk (deep stromal and/or lymphovascular space invasion) criteria received adjuvant chemoradiation. Outcomes were overall survival (OS) and quality-adjusted life years (QALY). Five-year survival rates and probabilities were obtained by systematically searching Pubmed, Cochrane Review and Web of Science. Utilities (measurements of quality of life) associated with complications were obtained by interviewing patients with early cervical cancer using the standard gamble. One-way sensitivity analyses were performed.

Results: Overall survival was slightly better with RS-tCR than with CR (29.79 years vs 29.01 years). QAS was almost identical (28.23 QALY vs 28.11 QALY). QAS was sensitive to small changes in survival rates. If five-year survival was >79% with CR or <85% with RS-tCR meeting intermediate-risk criteria, CR was preferable. Although QAS was sensitive to the percentage of patients with aborted hysterectomy or high-risk disease (and, therefore, lower 5-year survival) in the RS-tCR arm, the model was not sensitive to the ability to forgo adjuvant therapy. Even when only 1% of patients were low risk, RS-tCR was preferable to CR. However, if five-year survival with CR was >79%, the model became sensitive to the need for adjuvant therapy in the RS-tCR group. The model was not sensitive to probabilities or utilities associated with complications, except the utilities of lymphedema and urinary retention.

Conclusions: In patients with IB2 cervical cancer, QAS is almost identical to RS-tCR and CR. The negative effect of combination radical surgery and chemoradiation on QAS is less than expected. In the model, QAS is more dependent on survival estimates than the percentage of patients requiring adjuvant chemoradiation. RS-tCR is a reasonable treatment for IB2 cervical cancer, even when considering survivorship issues.



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The vaginal radical trachelectomy: An update of a series of 125 cases and 106 pregnancies

M. Plante, J. Grégoire, M. Renaud, M. Roy
L'Hôtel-Dieu de Québec, Quebec City, QC, Canada

Objective: The goal of this study was to review our first consecutive 125 vaginal radical trachelectomies (VRTs) to assess the oncologic, fertility and obstetric outcomes.

Data from our prospective database were used to identify all VRTs planned between October 1991 and March 2010 in patients with early-stage cervical cancer (stages IA, IB, and IIA). The χ^2 test, Fisher's exact test and Student's *t* test were used to compare baseline characteristics; and Kaplan–Meier survival curves were constructed and compared with the use of the log-rank test.

Results: During the study period, 140 VRTs were planned and 125 were performed. The median age of the patients was 31, and 75% were nulliparous. The majority of the lesions were stage IA2 (21%) or IB1 (69%), and 41% were grade 1. In terms of histology, 56% were squamous and 37% were adenocarcinomas. Vascular space invasion was present in 29% of cases, and 88.5% of the lesions measured ≤2 cm. The mean follow-up was 93 months (range: 4–225). There were six recurrences (4.8%) and two deaths (1.6%) following VRT. The actuarial five-year, recurrence-free survival was 95.8% (95% CI = 0.90–0.98], whereas it was 79% (95% CI = 0.49–0.93] in the group in which VRT was abandoned ($P = 0.001$). Higher tumor grade, lymphovascular space invasion and size >2 cm appeared to be predictive of the risk of abandoning VRT ($P = 0.001$, 0.025, and 0.005, respectively). Tumor size >2 cm was statistically significantly associated with a higher risk of recurrence ($P] = 0.002$). In terms of obstetric outcome, 58 women conceived a total of 106 pregnancies. The first- and second-trimester miscarriage rates were 20 and 3%, respectively, and 77 (73%) pregnancies reached the third trimester, of which 58 (75%) delivered at term. Overall, 15 (13.5%) patients experienced fertility problems, 40% of which were due to cervical factors. Twelve (80%) were able to conceive, the majority with assisted reproductive technologies.

Conclusions: VRT is an oncologically safe procedure in well-selected patients with early-stage disease. Lesion size >2 cm appears to be associated with a higher risk of recurrence and a higher risk of abandoning the planned VRT. Fertility and obstetric outcomes post VRT are excellent.

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An economic analysis of bevacizumab in recurrent treatment of ovarian cancer

J. Chan[1], B. Monk[2], K. Fuh[1], R. Urban[1], L. Hu[1], A. Caughey[1], X. Yu[3]
[1]*UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA,* [2]*UC Irvine Medical Center, Orange, CA,* [3]*University of Memphis, Memphis, TN*

Objective: The purpose of this study was to determine whether the addition of bevacizumab (B) to chemotherapy for the recurrent treatment of advanced ovarian cancer is cost effective.

An economic analysis compared the two arms of the OCEANS trial: gemcitabine, carboplatin = GC versus gemcitabine, carboplatin with concurrent and maintenance bevacizumab (GCB + B). Based on Medicare payment for administration of chemotherapy, the actual and estimated costs of treatment (GC = $2363/cycle and GCB + B = $8813/cycle + $6540/maintenance cycle) plus the cost of potential complications were determined. Second, recurrence rates were estimated from published data. Estimated cost of drugs, rates of

bowel perforation, and progression-free survival (PFS) were analyzed to determine cost and efficacy and establish a favorable incremental cost-effectiveness ratio (ICER) per life-year saved (LYS).

Results: For the 240 patients entered into each arm of the OCEANS trial, and with the baseline estimates of PFS (8.6 months for the GC group and 11 months for the GCB + B group, assuming 21% improvement of new treatment) and bowel perforation, the cost of GC was $4.0 million, compared with $36.5 million for GCB + B. These costs resulted in an ICER of $677,250 per LYS for GCB + B compared with GC. If one were to assume a PFS of 15 months (six additional months of benefit) associated with GCB + B, then this results in an ICER of $253,968. Using a maximum ICER threshold of $100,000 per LYS to deem an intervention as cost effective, the cost of B would have to be decreased by 76% or the PFS extended to 25 months for GCB + B. If no additional risk of intestinal perforation is attributed to the addition of B (2% all arms and 25% of them are fatal perforation), the ICER in GCB + B would continue to exceed $665,229 per LYS.

Conclusions: In this exploratory analysis of the OCEANS trial, the addition of bevacizumab to combination chemotherapy for the treatment of recurrent ovarian cancer is associated with significant costs with potential benefits. Further investigations are warranted.

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Intraperitoneal chemotherapy for recurrent ovarian cancer appears efficacious with high completion rates and low complications

M. Skaznik-Wikiel, J. Lesnock, W. McBee, S. Taylor, S. Beriwal, A. Smith, K. Zorn, S. Richard, T. Krivak, R. Edwards
Magee–Womens Hospital of the UPMC, Pittsburgh, PA

Objective: Three prospective phase III clinical trials have shown a benefit of intraperitoneal (IP) chemotherapy as a front-line therapy in the treatment of ovarian cancer. However, little is known about the use of IP chemotherapy in recurrent ovarian cancer. The purpose of this descriptive study was to determine progression-free survival (PFS), overall survival (OS), completion rates, and frequency of complications in patients with epithelial ovarian cancer (EOC) treated with IP chemotherapy for recurrent disease.

A retrospective, single-institution analysis of women who received IP chemotherapy for recurrent EOC between January 2005 and April 2010 was conducted. Study patients were identified from the tumor registry. PFS and OS were estimated by Kaplan–Meier methods.

Results: A total of 56 women who received IP chemotherapy for their first EOC recurrence were identified. Their mean age was 56.7 years (range: 43–79). All patients had previously undergone primary surgical cytoreduction followed by intravenous platinum-based chemotherapy. Fifty-four patients (96.4%) had previously completed at least six cycles of IV chemotherapy. All patients were considered platinum sensitive. Among the patients, 80.4% were initially diagnosed with advanced-stage disease (stage IIIA–IV). All patients underwent secondary cytoreduction at the time of IP port placement; 65.3% were considered optimally cytoreduced (<1 cm residual disease) at the end of the secondary debulking surgery. Forty-four patients (78.6%) were able to successfully complete at least six cycles of IP chemotherapy. Reasons for noncompletion were: disease progression (five patients), allergic reaction (three patients), elevated creatinine (one patient), pain (one patient), severe nausea and vomiting (one patient), death (one patient), and patient refusal (one patient). Six patients (10.7%) developed port complications: pain around port site (two patients), port malfunction (one patient), pain and port malfunction (two patients), port erosion into small bowel (one patient). Median PFS since the initiation of IP chemotherapy was 12 months (95% CI: 7.5–16.4) and median OS was 51 months (95% CI: 40.8–61.1).

Conclusions: Intraperitoneal chemotherapy is an efficacious option for patients with recurrent epithelial ovarian carcinoma, with high completion rates, low frequency of complications and meaningful extension in survival. Further assessment in randomized controlled trials is warranted.

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Clinical practice guidelines decrease unnecessary Pap tests in survivors of gynecologic malignancies

L. Meyer[1], K. Schmeler[1], J. Wallbillich[2], D. Urbauer[1], P. Soliman[1], M. Frumovitz[1], C. Burke[1], D. Bodurka[1], C. Levenback[1]
[1]*University of Texas M.D. Anderson Cancer Center, Houston, TX,* [2]*University of Texas Medical School, Houston, TX*

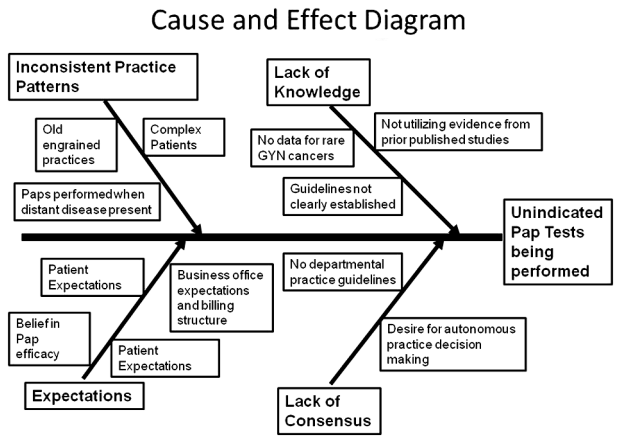
Objective: Widespread use of the Pap test has had minimal impact on the early diagnosis of recurrent disease in survivors of gynecologic cancers. The use of clinical practice guidelines (CPGs) is a well-described approach to reduce practice variation, control cost, and improve quality of health care. The objective of this study was to demonstrate the effectiveness of performance improvement strategies to alter practice patterns with the aim of decreasing the number of unindicated Pap tests performed for surveillance in gynecologic cancer patients by 50%.

A multidisciplinary operations team oversees outpatient care provided by 13 gynecologic oncologists and 20 midlevel providers who perform 13,400 patient visits annually at a single institution. The team identified Pap test utilization as a target for improvement, used a fishbone diagram to identify specific barriers (see figure), approved the new CPGs, and constructed a communication plan and project map. A convenience sample of patient visits to the practice during weeks two and four of August 2009 and August 2010 was used to represent practice patterns before and after the implementation of the CPG. For analysis, the percentage of total and unindicated (based on newly adopted CPGs) Pap tests performed out of all visits during each two-week period were calculated. Fisher's exact test was used for comparison. We estimated 80% power to detect a difference as low as 10.5%.

Results: Four hundred sixty-six patient visits occurred in the 2009 study period. One hundred two of the 466 (21.88%) patients had Pap tests performed during the two-week interval in 2009. Unindicated Pap tests were performed at 41 of 466 visits (8.80%). Four hundred thirty-eight patient visits occurred in the 2010 study period. Sixty-six of 438 (15.06%) had Pap tests performed. Unindicated Pap tests were performed at 19 of 438 (4.34%) visits, indicating a 50% reduction. The introduction of the CPGs correlated with a significant decrease in the proportion of total Pap tests performed (OR = 0.63, $P = 0.01$), as well as in the proportion of visits on which an unindicated Pap test was performed (OR = 0.47, $P = 0.01$). The cost per test is estimated at $170. By decreasing Pap test utilization from 22 to 15% of visits, 938 fewer tests would be performed annually with an estimated savings of $159,535.

Conclusions: The quality improvement process can successfully effect meaningful change in complex clinical settings. We now aim to eliminate all unindicated Pap tests. We are using the same tools to

reduce practice variation and costly overutilization in other aspects of our practice.



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A phase II study of gemcitabine, carboplatin and bevacizumab for the treatment of platinum-sensitive recurrent ovarian cancer

E. Eisenhauer[1], V. Zanagnolo[2], D. Cohn[1], R. Salani[1], D. O'Malley[1], G. Sutton[3], B. Cobb[1], M. Vaughan[1], J. Fowler[1], L. Copeland[1]
[1]Ohio State University, Columbus, OH, [2]European Institute of Oncology, Milan, Italy, [3]St. Vincent Hospital, Indianapolis, IN

Objective: The doublet gemcitabine and carboplatin is FDA approved for the treatment of recurrent ovarian cancer, with a response rate of 47%. Multiagent chemotherapy with bevacizumab has been shown to improve survival in many disease settings. We set out to determine the activity of gemcitabine, carboplatin and bevacizumab in the setting of first recurrence of platinum-sensitive ovarian cancer.

This is a phase II study of gemcitabine 1000 mg/m², carboplatin AUC 3, and bevacizumab 10 mg/kg administered intravenously on days one and 15 every 28 days for six cycles or up to 24 cycles if clinical benefit occurred. Eligible patients had platinum-sensitive recurrent EOC, primary peritoneal cancer or fallopian tube cancer without prior treatment for recurrence. Study objectives included response rate, toxicity and survival. Response rate was defined by Response Evaluation Criteria in Solid Tumors, or CA-125 criteria for patients without measurable disease.

Results: Forty-five patients were accrued and received treatment. Of these, 45 were evaluable for toxicity and 39 were evaluable for response (five patients completing therapy, one patient not assessable). Of those patients evaluable for response, the overall response rate was 70%; there were 12 complete responses (30%) and 16 partial responses (40%). Seven patients had stable disease (16%), and four patients progressed (10%). Grade 3 and 4 hematologic toxic effects included neutropenia (71%), thrombocytopenia (31%), and anemia (11%); there were no episodes of febrile neutropenia. Grade 3 and 4 nonhematologic toxic effects included fatigue (16%), pain (9%), nausea (4%) and vomiting (4%). Other noted toxic effects included one small bowel abscess, one cerebrovascular accident and intracranial hemorrhage. Survival endpoints are not yet mature.

Conclusions: Gemcitabine, carboplatin and bevacizumab constituted an effective regimen with acceptable toxicity in platinum-sensitive recurrent EOC. The response rate compared with that reported for the doublet gemcitabine and carboplatin is provocative. The degree to which schedule, dosing and the addition of bevacizumab improved response merits further study, and future testing of this regimen is warranted.

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A phase I clinical trial of a novel infectivity-enhanced suicide gene adenovirus with gene transfer imaging capacity in patients with recurrent gynecologic cancer

K. Kim, M. Wang, M. Barnes, J. O'Malley, Z. You, M. Preuss, G. Siegal, K. Zinn, D. Curiel, R. Alvarez
University of Alabama, Birmingham, AL

Objective: To circumvent limitations in cancer cell infectivity and invasive means of assessing gene transfer, we developed an infectivity-enhanced adenovirus, Ad5.RGD.TK/SSTr, which expresses a therapeutic thymidine kinase suicide gene and a somatostatin type 2 receptor. Preclinical studies have previously validated the therapeutic and imaging potential of this novel reagent. The purpose of this phase I study was to identify the maximum tolerated dose, the spectrum of toxicity, the potential clinical efficacy, and biologic effects of Ad5.RGD.TK/SSTr in patients with recurrent ovarian or other select gynecologic cancers.

Eligible patients were treated intraperitoneally with Ad5.RGD.TK/SSTr for 3 consecutive days in one of three dose cohorts ranging from 1×10^{9} to 1×10^{12} vp/dose and subsequently treated with intravenous ganciclovir for 14 days. Octreoscans were obtained on patients before and after Ad5.RGD.TK/SSTr treatment to assess for gene transfer. Toxicity was assessed using standard CTC grading. Clinical efficacy was evaluated using RECIST criteria 1 month after treatment. Ascites, serum, and other samples were obtained to evaluate for gene transfer, generation of wild-type virus, viral shedding and antibody response.

Results: A total of nine patients were treated in three treatment cohorts. Clinical adverse events classified as possibly or definitely associated with the administration of Ad5.RGD.TK/SSTr included three episodes of flu-like symptoms, one episode of fever and one episode of abdominal pain. All were grade 1 and transient in nature. There were no vector-specific laboratory adverse events. The maximum feasible dose was 1×10^{12} vp/dose. Three patients had stable disease; all others progressed. On further follow-up, one of the three patients with stable disease had normalization of her CA-125 and near-complete resolution of measurable disease. Octreoscans did not demonstrate evidence of gene transfer in the first two cohorts of patients. Ancillary studies demonstrated gene transfer in ascites cellular samples in eight of nine treated patients, limited viral shedding and robust anti-adenoviral immune response.

Conclusions: This study further validates the feasibility, tolerability, and potential clinical utility of infectivity-enhanced adenovirus-based gene therapeutics in gynecologic cancer. Further development of Ad5.RGD.TK/SSTr appears to be warranted.

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A phase I study of a novel lipopolymer-based interleukin-12 gene therapeutic in combination with chemotherapy for the treatment of platinum-sensitive recurrent ovarian cancer

R. Alvarez[1], K. Anwar[2], M. Barnes[1], J. Fewell[2]
[1]University of Alabama, Birmingham, AL, [2]Expression Genetics, Inc., Huntsville, AL

Objective: The safety and activity of EGEN-001, an interleukin (IL)-12 gene plasmid formulated with a lipopolymer gene carrier (PEG-PEI-cholesterol), as a single agent have been previously demonstrated in patients with platinum-resistant ovarian cancer. The purpose of this study was to examine the safety and activity of escalating doses of EGEN-001 in combination with intravenous carboplatin/docetaxel for the treatment of platinum-sensitive recurrent ovarian cancer.

Eligible patients with recurrent platinum-sensitive ovarian cancer were treated intraperitoneally with escalating dosages (12, 18, and 24 mg/m^2) and cycles (4–8) of EGEN-001 in combination with intravenous docetaxel (75 mg/m^2) and carboplatin (AUC 5). A final evaluation of patients for safety, antitumor activity, and various biologic endpoints was performed six months after EGEN-001 treatment.

Results: A total of 13 patients were enrolled in the study, with three patients each in cohorts 1–3 and four patients in cohort 4. All patients in cohorts 1–3 received four treatments of EGEN-001 every 10 days. Patients in cohort 4 received six to eight doses of EGEN-001 every 10 days. EGEN-001 treatment administered in combination with carboplatin/docetaxel was reasonably tolerated at all treatment doses and dosing cycles. The most commonly reported EGEN-001-related adverse events were abdominal pain, abdominal discomfort and low-grade fever. At 24 mg/m^2, one patient in cohort 4 experienced a grade 3 serious adverse event of low blood pressure, which was managed by fluid infusion, resolved without sequelae, and was considered to be related to the study drug. No other patients in that cohort experienced any EGEN-001-specific grade 3/4 toxicity. Hematologic toxicity observed in several patients was attributed to chemotherapy. Increases in interferon-γ and tumor necrosis factor α concentrations were noted in peritoneal fluid following repeated EGEN-001 treatment. At the six-month post-treatment follow-up, 38% of patients had a complete or partial response, 15% of patients had stable disease and 46% of patients had progressive disease. The CA-125 levels remained below treatment levels in 61% of patients at the six-month follow-up.

Conclusions: Intraperitoneal administration of the IL-12 gene therapeutic EGEN-001 in combination with chemotherapy is feasible and demonstrates potential antitumor activity in patients with recurrent ovarian cancer. Additional trials evaluating EGEN-001 in patients with ovarian cancer are planned.

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AMG 386 combined with either pegylated liposomal doxorubicin or topotecan in patients with advanced ovarian cancer: Results from a phase Ib study

R. Wenham[1], R. Schilder[2], C. Pippitt[3], S. Wong[4], S. Ananda[5], S. Scudder[6], R. Melara[7], N. Nanayakkara[8], H. Adewoye[7], I. Vergote[9]
[1]H. Lee Moffitt Cancer Center, Tampa, FL, [2]Fox Chase Cancer Center, Philadelphia, PA, [3]Piedmont Hematology–Oncology Associates, LLC, Winston-Salem, NC, [4]Western Hospital, Footscray, VIC, Australia, [5]Royal Women's Hospital, Melbourne, VIC, Australia, [6]UC Davis Medical Center, Davis, CA, [7]Amgen, Inc., Thousand Oaks, CA, [8]Quintiles, San Diego, CA, [9]University Hospitals Leuven, Leuven, Belgium

Objective: AMG 386, a first-in-class investigational peptide-Fc fusion protein (peptibody), blocks angiogenesis by inhibiting the interaction between angiopoietin-1 and -2 and the Tie2 receptor. Reported here are results from an ongoing, open-label phase Ib study of AMG 386 in combination with pegylated liposomal doxorubicin (PLD) or topotecan (T) in patients with advanced ovarian cancer.

In Part 1 of this two-part, dose de-escalation study with a 6 + 3 design with expansion to 25 patients, adult patients with advanced recurrent, epithelial ovarian, fallopian tube, or primary peritoneal cancer and GOG PS 0 or 1 received either PLD at 50 mg/m^2 every four weeks (Arm A, $n = 6$ planned) or T at 4 mg/m^2 every week (3 on/1 off; Arm B, $n = 6$ planned) plus AMG 386 at 10 mg/kg (cohorts A1 and B1) or 15 mg/kg (cohorts A3 and B3) intravenously every week until progression or unacceptable toxicity. Dose-limiting toxicity (DLT) in ≤1 of 6 or ≤2 of 9 patients triggered cohort expansion to a total of 25 patients (Part 2). The primary endpoint was DLT incidence; secondary endpoints included were safety, pharmacokinetics and response per RECIST or CA-125 (GCIG criteria).

Results: Sixty-three patients have been enrolled and received one or more doses of study medication (cohorts A1, B1, A3, and B3, $n = 25, 25, 6$, and 7). As previously reported (J Clin Oncol 2010;28(15 S):Abstract 5049), no DLT occurred in Part 1 of the study in cohorts A1 and B1, and there was one case of DLT in the A1 expansion. Subsequently, the expanded B1 cohort had two cases of DLT, and the AMG 386 15 mg/kg cohorts (A3 and B3; median follow-up time of 15 and 12 weeks, respectively) had no DLT. The A3 and B3 cohorts are part of the expansion phase. Safety results are summarized in Table 1. There were two grade 5 adverse events in cohort A1 (intestinal perforation, $n = 1$, and ovarian cancer, $n = 1$; neither was considered AMG 386 related) and six grade 4 adverse events in cohort B1 (neutropenia, $n = 2$; hypokalemia, $n = 1$; granulocyte count decreased, $n = 1$; dyspnea, $n = 1$; chest pain, $n = 1$; only the granulocyte count decrease was considered AMG 386 related); no other grade 5 or 4 adverse events occurred. In patients with sufficient follow-up time to confirm a response per RECIST (cohorts A1, B1, A3, and B3: 92, 92, 83, and 57%), the objective response rates (complete + partial) were 39, nine, 20, and 0%; 22, 30, 20, and 75% of patients had progressive disease. In patients evaluable (84, 92, 83, and 57%) for CA-125 response per GCIG criteria, the response rates were 48, 35, 20, and 67%; 28, 12, 0, and 17% of patients had CA-125 progression. Co-administration of AMG 386 with PLD or T did not appear to affect the pharmacokinetic parameters of either agent.

Conclusions: AMG 386 administered at 10 or 15 mg/kg in combination with PLD or T appears tolerable in patients with advanced recurrent ovarian cancer.

Adverse Events

	Cohort A1 (PLD 50 mg/m^2 + AMG 386 10 mg/kg) n = 25		Cohort B1 (T 4 mg/m^2 + AMG 386 10 mg/kg) n = 25		Cohort A3 (PLD 50 mg/m^2 + AMG 386 15 mg/kg) n = 6		Cohort B3 (T 4 mg/m^2 + AMG 386 15 mg/kg) n = 7	
	All %	Grade ≥3, %	All %	Grade ≥3, %	All %	Grade ≥3, %	All %	Grade ≥3, %
Peripheral edema	48	8	52	8	83	0	86	0
Palmar-Plantar Erythrodysesthesia Syndrome	56	4	0	0	33	17	0	0
Stomatitis	44	4	12	0	33	0	0	0
Neutropenia	20	12	36	20	33	17	29	0
AMG 386-related AEs of interest								
Hypertension	12	0	0	0	0	0	0	0
Proteinuria	0	0	4	0	17	0	0	0

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A phase II evaluation of carboplatin/paclitaxel/bevacizumab in the treatment of advanced-stage endometrial carcinoma: Report of toxicity

D. OMalley, P. Gary, R. Salani, E. Eisenhauer, J. Fowler, L. Copeland, D. Cohn
Ohio State University, Columbus, OH

Objective: The objective is to report the toxicity profile of carboplatin, paclitaxel, and bevacizumab (C/T/Bev) in patients with stage III/IV endometrial cancer who have undergone surgical treatment. This phase II trial has completed enrollment (August 2010).

On day one, carboplatin (AUC 5), paclitaxel (175 mg/m^2), and bevacizumab (15 mg/kg) were given every 21 days in single-arm open-label phase II for a maximum of six cycles in patients with or without measurable disease. Toxicity was reported using CTCAE Version 3 for every cycle and summarized for maximum grade per patient. Growth factor support could be given at the treating physician's discretion though not encouraged unless neutropenic toxicity was observed. Thirty-eight patients were enrolled to assess whether the 24-month failure rate is at most 50% against the alternative that the 24-month failure rate is at least 70% ($\alpha = 0.1$, $\beta = 0.1$, power = 90%).

Results: Following surgery, 38 patients with endometrial cancer initiated therapy, with six continuing to receive study therapy as adjuvant treatment. Of the 32 patients who have completed the study therapy, 26 (81%) completed the six cycles. Four patients were removed secondary to a serious adverse event (one fascia dehiscence after three cycles, one vaginal dehiscence after one cycle, one pulmonary embolism after three cycles, one neutropenic sepsis after one cycle). One patient withdrew from the study therapy after one cycle and one patient was removed after five cycles secondary to grade 2 neuropathy. Seventeen of 32 (53%) experienced grade 3/4 neutropenia. Thirteen-percent (4/32) of patients experienced febrile neutropenia. Additional Bev-specific toxicity affected two patients with grade 3 hypertension. There were no bowel perforations or fistulas.

Conclusions: C/T/Bev is a relatively well-tolerated regimen with manageable acute toxicity. Two patients in this trial had an evisceration (one fascia, one vaginal). Consideration should be given to omit Bev until cycle 2 to allow for improved wound healing in future trials with patients with uterine cancer. C/T/Bev caused 50% grade 3/4 neutropenia in more than 50% of patients and febrile neutropenia in 13%. Growth factor support should be considered in patients treated with this regimen. Final efficacy data will not be mature until 2012. Final toxicity will be able to be reported at presentation.

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Do uterine risk factors or lymph node metastases drive overall recurrence risk in patients with endometrial cancer?

E. Bishop, E. Nugent, C. Mathews, K. Moxley, M. Tenney, R. Mannel, J. Walker, L. Landrum, K. Moore, D. McMeekin
University of Oklahoma, Oklahoma City, OK

Objective: Several models for predicting risk of recurrence and need for postoperative treatment in endometrial cancer have been described. In PORTEC 1 and PORTEC 2, age and uterine factors were used to define risk in unstaged patients. Controversy continues over the importance of determining lymph node status in predicting recurrence and treatment. The objective of this study was to determine how the additional knowledge of lymph node status affects recurrence and survival compared with risk based on uterine factors alone in patients with clinical stage I endometrioid cancer.

A retrospective review of patients who underwent complete surgical staging for clinical stage I endometrioid adenocarcinoma of the uterus was performed. Patients were grouped by depth of invasion (DOI) and tumor grade. Our patients were then assessed based on PORTEC 1 inclusion criteria, PORTEC 1 high intermediate risk (HIR) criteria (presence of two factors: age >60, grade 3, >50% DOI), and PORTEC 2 eligibility criteria. Rates of nodal involvement were then evaluated for each group. Recurrence rates, progression-free survival (PFS), and survival were compared between groups.

Results: We identified 519 patients with clinical stage I disease. Of the 174 patients who met PORTEC 1 eligibility criteria, 32 (18%) had positive lymph nodes, and of these, eight (25%) recurred. From the PORTEC 1-eligible subset, 65 met HIR criteria with 18 (28%) recurrences. Twelve (18%) of these 65 patients had positive lymph nodes. Five (42%) of these node-positive patients recurred, whereas 13 (25%) of the HIR node-negative patients recurred ($P = 0.29$). Within the HIR subset all node-positive patients received post-operative treatment, compared with 58% of node-negative patients. The PFS at 48 months for HIR node-negative patients was 73% versus 50% in HIR node-positive patients ($P = 0.38$). Of the 92 patients who met PORTEC 2 criteria for treatment, 19 (21%) had positive lymph nodes. Seven (37%) of those with positive lymph nodes recurred compared with 17 (24%) node-negative patients from the same group. PFS at 48 months in node-negative patients from this group was 78% versus 58% for node-positive patients ($P = 0.60$).

Conclusions: In this study, patients with HIR disease based on uterine characteristics have a substantial risk of nodal involvement. Patients with positive lymph nodes have a higher risk of recurrence and worse PFS compared with the HIR group as a whole and those with negative lymph nodes. Knowledge of nodal status may better define risk and prognosis and may alter postoperative treatment in this group.

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Outcomes in patients with surgically staged, high-intermediate risk endometrial cancer in the absence of adjuvant therapy

K. Moxley, C. Mathews, D. McMeekin, L. Landrum, J. Walker, R. Mannel, K. Moore
University of Oklahoma, Oklahoma City, OK

Objective: The objective of this study was to calculate rates of recurrence and disease-specific survival in a surgically staged population of woomen with high-intermediate risk (H-IR) endometrial cancer who received no adjuvant therapy and to compare the results with the rates observed in similar patients receiving adjuvant therapy.

Records of patients diagnosed with endometrioid carcinoma of the endometrium between 2000 and 2005 at the University of Oklahoma were identified. All patients underwent complete surgical staging including hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymph node dissection, and collection of peritoneal cytology. Demographics, therapy received, recurrence patterns and survival data were abstracted from the records of patients defined as H-IR by GOG-99 criteria. Rates of recurrence and disease-specific survival were then compared between patients who received observation and those who received adjuvant radiation with or without chemotherapy.

Results: Two-hundred forty-four patients were identified who met H-IR criteria. One-hundred forty underwent surgery followed by observation, and 104 received adjuvant radiation therapy with or without chemotherapy. Recurrence rates for the two groups were similar at 11 and 8%. A univariate analysis was performed to assess the significance of individual predictors in the H-IR model as defined by H.M. Keys et al. (Gynecol Oncol 2004;92:744–51) in GOG 99. Both lymphovascular space invasion (LVSI) and invasion of the outer half of the myometrium were found to be significant predictors of recurrence ($P=0.003$ and $P=0.05$). On multivariate analysis, however, only LVSI remained significantly associated with disease recurrence. Kaplan–Meier curves were created for disease-specific survival in patients with and without adjuvant therapy. No difference in five-year disease-specific survival was observed between these cohorts on log-rank analysis ($P=0.39$).
Conclusions: In patients with surgically staged high-intermediate risk endometrial cancer, the overall risk of recurrence is low and is not significantly reduced when patients receive adjuvant therapy. Moreover, no survival benefit was demonstrated when adjuvant radiation therapy alone or in combination with chemotherapy was administered. Additionally, the use of adjuvant therapy in these generally low-risk patients does expose them to the risks of "multimodality treatment," which may increase overall complication rates.

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Retrospective review of an intraoperative algorithm to predict lymph node metastasis in low-grade endometrial adenocarcinoma

P. Convery[1], L. Cantrell[2], S. Modesitt[2],
A. Alvarez-Secord[1], L. Havrilesky[1]
[1]Duke University Medical Center, Durham, NC, [2]University of Virginia, Charlottesville, VA

Objective: The role of lymphadenectomy (LND) is controversial in endometrial cancer (EMCA), and algorithms to identify women most likely to benefit from LND are required. We sought to validate the "Mayo" algorithm to identify women intraoperatively who do not require a lymphadenectomy.

A multicenter retrospective chart review was completed using two independent institutional EMCA databases. Between 1977 and 2007, patients were identified with preoperative grade 1 or 2 EMCA. Inclusion criteria for the study were: (1) low-risk preoperative histology, excluding serous and clear cell; (2) no evidence of metastatic disease at surgery; (3) LND in which at least eight pelvic lymph nodes were sampled; (4) intraoperative pathology assessment. Patients were designated as satisfying the Mayo criteria if at the time of intraoperative assessment tumors were found to be grade 1 or 2 with endometrioid or endometrioid-like histology, myometrial invasion $\leq$50%, and tumor diameter $\leq$2 cm on intraoperative or final (if not measured intraoperatively) pathology. Nodal metastases and final staging were analyzed.
Results: Of 442 patients meeting inclusion criteria, 110 satisfied the Mayo criteria. Two (1.8%) patients had positive lymph node metastases; final pathology in node-positive cases was stage IIIC1 papillary serous adenocarcinoma and stage IIIC1 endometrioid adenocarcinoma. The negative predictive value of the Mayo algorithm was 98.2%. One hundred four of 110 (94.5%) patients meeting the Mayo criteria were stage IA on final pathology using the 2009 FIGO staging criteria. Two patients each (1.8%) had stage IB, IIIA, and IIIC1 disease. Intraoperative analysis was consistent with final grade in 54 patients (49.1%), upgraded on final analysis in 13 patients (11.8%), and downgraded in two patients (1.8%). For 41 patients (37.3%), grade was not available on either intraoperative or final pathology assessments because no invasive lesion was seen.
Conclusions: At several institutions with more traditional pathology systems, the Mayo algorithm identified with a 98.2% negative predictive value women who would not benefit from a lymphadenectomy for endometrial cancer. Discrepancies between intraoperative and final pathology results may limit the general applicability of this algorithm.

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Identifying Lynch syndrome in women with endometrial cancer

L. Chen, J. Holstein, A. Blanco, J. Chan, C. Powell, J. Rabban,
J. Grenert, P. Conrad
UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Objective: Approximately 2% of endometrial cancers are attributable to Lynch syndrome. Selecting a subgroup of patients with endometrial cancer at higher risk for Lynch syndrome may identify a cohort for genetic counseling and testing.

From January 2008 to June 2010, 328 women underwent hysterectomy for endometrial carcinoma. Mismatch repair protein (MMR) immunohistochemistry was prospectively performed for MLH1, MSH2, PMS2 and MSH6. Microsatellite instability (MSI) testing was performed by PCR and reported as microsatellite stable (MSS), low instability (MSI-low) or high instability (MSI-high). Inclusion criteria included: (1) age $<$50; (2) personal history of a Lynch cancer (colorectal, endometrial, urothelial, gastric, small bowel, brain, etc.); (3) a first-degree family member with a Lynch cancer, or pathology characteristics suggestive of Lynch cancer (tumor-infiltrating lymphocytes, peritumor lymphocytic infiltrate, mixed undifferentiated and well-differentiated carcinomas, lower uterine segment tumors, etc.).
Results: One hundred twelve of 328 (34%) tumors fulfilled at least one criterion: 48 were under age 50, five had a personal history of colorectal cancer, 11 were diagnosed with a synchronous ovarian cancer, 36 had a notable family history, and 51 had suspicious pathologic features. All patients had MMR IHC performed on their tumor; 88 (79%) also had MSI testing. Thirty-one patients (28%) had loss of at least one or more MMR by IHC: 22 had loss of MLH1 and PMS2, one had loss of MSH2 and MSH6, four had loss of MSH6 only, and four had loss of PMS2 only. Among patients with loss of MMR by IHC, 26 of 31 (84%) underwent MSI testing and all but one were MSI-high. Two patients with MSI-high tumors had intact MMR by IHC. All 31 patients with loss of MMR by IHC were contacted for genetic counseling; only 13 (42%) accepted. Nine of 13 patients underwent genetic testing, and two of the nine were found to have Lynch mutations (1 MLH1, 1 PMS2): one patient had a mother with uterine cancer, and the other was 42 years of age.
Conclusions: The integrated use of clinical, histopathologic, and molecular markers may help identify women with endometrial cancer at risk for Lynch syndrome. Patient access and awareness of genetic counselors may help improve the identification process.

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Ten-year relative survival for epithelial ovarian cancer

L. Baldwin[1], R. Ware[1], B. Huang[2], T. Tucker[2], S. Goodrich[1],
I. Podzielinski[1], C. DeSimone[1], F. Ueland[1], J. van Nagell[1], L. Seamon[1]
[1]University of Kentucky Medical Center, Lexington, KY, [2]Kentucky Cancer Registry, Lexington, KY

Objective: The overall survival rate of patients with epithelial ovarian cancer (EOC) is poor and most of the patients who are alive at five years have active disease. Thus, 10-year survival may be a more appropriate endpoint. By definition, relative survival (RS) adjusts for the general survival rate of the population for that race, sex, age and date at which the diagnosis was coded. The 10-year RS for ovarian cancer using SEER data has previously been reported, but was not limited to epithelial histologies. Our objective was to measure RS in EOC over 10 years, stratified by stage, race, age, classification of residence and surgery as the first course of treatment.

Using the SEER 1995–2007 database, cases were identified using the International Classification of Diseases codes for EOC. Inclusion criteria included malignant behavior, first primary, actively followed, and age $\geq$20 years. Exclusion criteria included death certificate- or autopsy-only cases. Using the actuarial life table method, RS over 10 years was calculated, stratified by stage, classification of residence, surgery as the first course of treatment, race and age.

Results: Forty thousand six hundred ninety-two patients met inclusion criteria. Stage distribution was 20, eight, 39, 27, and 7% for stages I, II, III, and IV, and unknown, respectively. The first course of treatment was surgery in 78%. Overall RS was 65, 44, and 36% at two, five and 10 years, respectively. The slope of decline in RS was reduced for years five–10 as compared with years one–five after diagnosis. RS at five years was 89, 70, 36, and 17% for stages I, II, III, and IV, respectively. RS at 10 years was 84, 59, 23, and 8% for stages I, II, III, and IV, respectively. RS was comparable for patients living in rural and urban settings. At all stages, patients who underwent surgery as their first course of treatment had better RS than those who did not have surgery. When RS was compared between races, blacks had the poorest survival. At all stages, advanced age at time of diagnosis was associated with decreased RS.

Conclusions: Although advanced EOC is associated with a poor prognosis, updated data demonstrate that survival rates adjusted for survival in the general population (RS) at five years are improved over historic reports and the 10-year RS for stage III is higher than expected. These data provide the physician and the patient with more accurate prognostic information, particularly for advanced-stage disease.

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Availability of gynecologic oncologists for ovarian cancer care

D. Cooney[1], B. Spruell[1], S. Rim[2], S. Foster[2], S. Lawvere[1], L. Richardson[2], C. Thomas[2], S. Stewart[2]
[1]SciMetrika LLC, Durham, NC, [2]Centers for Disease Control and Prevention, Atlanta, GA

Objective: Women with ovarian cancer (OC) treated by gynecologic oncologists (GOs) receive guidelines-based treatment more often and have better clinical outcomes than those who are not. Disparities in OC treatment include some race- and age-specific populations receiving standard care less often. To assess whether geographic distribution of GOs contributes to these disparities, we used Geographic Information Systems (GIS) methods to describe a relationship between OC incidence rates and practicing GOs in the United States.

Cancer incidence data were obtained from SEER and CDC's National Program of Cancer Registries. OC cases diagnosed from 2002 to 2006, covering 97.4% of the U.S. population, were age-adjusted using U.S. Census estimates (n = 106,391). County-level demographic, rural–urban and descriptive data were collected from census and area resource file data. A list of current GOs (n = 866) and their addresses was obtained from the Society of Gynecologic Oncologists; GO addresses were geocoded to determine county of location and distance measures from each county centroid to the nearest GO. Maps were generated using GIS to examine clustering and spatial relationships of GOs and OC incidence rates. Spatial analytic methods and correlation analyses were used to examine county-level characteristics. Multivariable logistic regression was conducted using dichotomous and polytomous categorization of incidence rates to determine the relationship between the availability of GOs and OC incidence.

Results: The mean U.S. 5-year incidence rate of OC was 15.1 per 100,000 women in counties within 100 miles of a GO versus 18.0 for counties without a GO within 100 miles ($P<0.0001$). There was a statistically significant ($P<0.0001$) correlation between incidence rates and distance to a GO. Most GOs (99%) were located in the 1048 metropolitan counties, less than 1% were located in the 1271 urban counties, and none were located in the 597 rural counties. Conversely, OC incidence rates were higher in rural counties (19.2) than in urban (15.3) and metropolitan (14.1) counties ($P<0.0001$).

Conclusions: Gynecologic oncologists are unequally distributed in the United States, with the highest concentration in urban areas, where the ovarian cancer incidence rates are lowest. This inverse relationship may underlie existing treatment disparities for some groups of patients. Further exploration into additional barriers that affect availability and access to care for patients with ovarian cancer is needed.

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Biologic roles of tumor and endothelial delta-like ligand 4 in ovarian cancer

W. Hu[1], C. Lu[1], R. Stone[1], J. Bottsford-Miller[1], A. Nick[1], M. Shahzad[2], K. Matsuo[3], R. Coleman[1], A. Sood[1]
[1]University of Texas M.D. Anderson Cancer Center, Houston, TX, [2]University of Wisconsin, Madison, WI, [3]University of Southern California, Los Angeles, CA

Objective: The Notch/Delta-like ligand 4 (Dll4) pathway is emerging as an important target for new anti-angiogenesis approaches. The significance of Dll4/Notch signaling in ovarian cancer is not fully understood, and was examined in the current study.

Dll4 expression was examined in 108 epithelial ovarian cancer samples (24 from patients with recurrent ovarian cancer treated with an anti-VEGF agent (aflibercept or bevacizumab)). The biologic importance of Dll4 was further investigated by in vitro and in vivo studies with Dll4 gene silencing.

Results: Dll4 was overexpressed in 72% of tumors and was an independent predictor of poor survival. Among patients treated with aflibercept or bevacizuamb in combination with chemotherapy, the responders (complete response + partial response) had lower levels of Dll4 than those with stable or progressive disease ($P<0.001$). In our orthotopic ovarian cancer model, VEGF increased Dll4 expression in tumor vasculature under hypoxic conditions. Immobilized Dll4 downregulated VEGFR2 expression in endothelial cells directly through methylation of the VEGFR2 promoter. Silencing Dll4 in tumor and tumor-associated endothelial cells resulted in inhibition of ovarian cancer growth and deregulation of angiogenesis (microvessel density and pericyte coverage), accompanied by induction of hypoxia in the tumor microenvironment. Furthermore, the combination of mouse and human Dll4 siRNA plus bevacizumab resulted in the greatest inhibition of tumor growth, reducing tumor size by 98 and 87% compared with controls, and by 93 and 46% compared with treatment with bevacizumab alone, in the SKOV3ip1 and A2780 murine ovarian cancer models, respectively.

Conclusions: Dll4 plays a functionally important role in both the tumor and endothelial compartments of ovarian cancer, and targeting Dll4 in combination with anti-VEGF treatment might hold promise for anti-angiogenesis approaches.

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Impact of beta blockers on epithelial ovarian cancer survival

E. Diaz, B. Karlan, I. Cass, C. Walsh, A. Li
Cedars–Sinai Medical Center, Los Angeles, CA

Objective: Chronic stress may promote ovarian cancer progression through autonomic nervous system mediators such as norepinephrine and epinephrine. Beta blockers, commonly used to manage hypertension, block the production of these adrenergic hormones and may prolong survival in breast and prostate cancers. We sought to determine the association between use of beta blockers and epithelial ovarian cancer (EOC) disease progression and survival.

After institutional review board approval, we performed a retrospective review of all patients with EOC treated between 1996 and 2006 at our institution. All patients underwent cytoreductive surgery followed by platinum-based chemotherapy. Women were considered beta blocker users if these medications were documented on at least two records more than six months apart. Statistical tests included Fisher's exact, Kaplan–Meier, and Cox regression analyses.

Results: Two hundred forty-six patients met criteria for inclusion. Sixty-eight patients were on antihypertensive medications, 23 of whom (9% of the entire cohort) were on beta blockers. Mean ages of hypertensive patients were the same as those on beta-blockers compared with those on other antihypertensive medications (67 years), but were statistically greater compared with ages of non-hypertensive patients (58 years, $P<0.0001$). We did not observe differences in the incidence of diabetes or coronary artery disease between the groups. In the entire cohort, 26 (11%) were suboptimally cytoreduced and beta blocker use did not correlate with debulking status. Median progression-free survival for beta blocker users was 27 months, compared with 17 months for non-users ($P=0.05$). Similarly, overall disease-specific survival was longer for beta blocker users (56 months) compared with non-users (48 months, $P=0.02$, HR = 0.56). Multivariate analysis identified beta blocker use as an independent positive prognostic factor, after controlling for age, stage, grade and cytoreduction status ($P=0.03$). In a separate analysis, overall survival remained longer for patients using beta blockers (56 months) when compared with hypertensive patients on other medications (34 months) and patients without hypertension (51 months) ($P=0.007$).

Conclusions: In this cohort of patients with EOC, beta blocker use reduced the chance of death by 56% compared with that of non-users. A potential suppressive impact of beta blockers on tumor biology should be confirmed in larger prospective trials and correlative translational studies.

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Long-term survival of patients with epithelial ovarian cancer detected by sonographic screening

R. Miller, C. DeSimone, F. Ueland, L. Seamon, I. Podzielinski, S. Goodrich, J. Elder, E. Pavlik, J. van Nagell
University of Kentucky Medical Center/Markey Cancer Center, Lexington, KY

Objective: The purpose of this study was to determine the long-term survival of women whose ovarian cancers were detected by sonographic screening.

Eligibility for this trial included all asymptomatic women ≥ 50 years of age and women ≥ 25 years of age with a documented family history of ovarian cancer. From 1987 to 2010, 36,136 asymptomatic women received annual sonographic screening. Women with persisting abnormal screens underwent tumor morphology indexing, serum biomarker analysis and surgery. Patients with ovarian cancers underwent complete FIGO surgical staging and maximal tumor cytoreduction. Postoperatively, patients were treated with six courses of carboplatin/paclitaxel chemotherapy and were followed with periodic serum CA-125 determinations and CT scans. Overall survival was estimated by the Kaplan–Meier method.

Results: Forty-six invasive epithelial ovarian cancers, 13 epithelial ovarian tumors of low malignant potential (LMP), and five ovarian granulosa cell tumors were detected. The stage distribution of these cases was as follows: stage I, 39 (61%); stage II, 10 (16%); stage III, 15 (23%). All patients with LMP tumors and granulosa cell tumors are alive and well, and none have experienced recurrent disease. Patients with invasive epithelial ovarian cancer were treated with maximal surgical cytoreduction followed by six courses of carboplatin and paclitaxel chemotherapy. Duration of follow-up varied from six months to 23 years (mean = 5.1 years). Optimal tumor debulking was achieved in 86% of patients with stage IIIC disease and 100% of all other patients. The five-year survival of patients with invasive epithelial ovarian cancer detected by screening was: $86.8 \pm 8.9\%$ for stage I, $77.1 \pm 14.4\%$ for stage II, and $71.9 \pm 14.3\%$ for stage III. The five-year survival of all patients with invasive epithelial ovarian cancer detected by screening was $80.2 \pm 6.8\%$.

Conclusions: Annual sonographic screening of at-risk asymptomatic women resulted in (one) a decrease in stage at detection and (two) an increase in five-year survival when compared with women with ovarian cancer treated at the same institution during the same period who did not have screening.

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MicroRNA 101 inhibits ovarian cancer xenografts by relieving the chromatin-mediated transcriptional repression of p21waf1/cip1

A. Semaan[1], A. Qazi[2], S. Seward[1], R. Ali-Fehmi[1], R. Morris[1], A. Munkarah[3], V. Dhulipala[2], C. Steffes[1], D. Weaver[1], B. Ramesh[2]
[1]Wayne State University, Detroit, MI, [2]Karmanos Cancer Institute, Detroit, MI, [3]Henry Ford Health System, Detroit, MI

Objective: Enhancer of zeste homolog 2 (EzH2) is broadly overexpressed in several solid tumors and has oncogene-like properties. In addition, the genomic loss of microRNA 101 (miR-101) in cancer leads to the overexpression of EzH2 and concomitant dysregulation of epigenetic pathways, resulting in cancer progression. Here we explore the role of miR-101 in epithelial ovarian cancer (EOC) both in vitro and in vivo.

MDAH-2774, SkOV-3, and TOV-21G cell lines were transfected with miR-101 expression plasmid (miR-101 sequence: 5' UAC AGU ACU GUG AUA ACU GAA G 3'). Standard protocols were followed for Western blot analysis of EzH2 levels after EzH2 knockdown with miR-101 plasmid transfection. Triplicate growth curves were generated using the cell counting Kit CCK-8 (Dojindo, Gaithersburg, MD). Chromatin immunoprecipitation assay (ChIP) using EzH2 antibody was performed (Upstate, Temecula, CA). The following sequences were used for amplification of the p21waf1/cip1 promoter from chromatin immunoprecipitates: 5' GGT GTC TAG GTG CTC CAG GT 3'

(forward primer), 5' GCA CTC TCC AGG AGG ACA CA 3' (reverse primer). Eight-week-old CB17/ICr-SCID mice were injected with 3×106 MDAH-2774 cells that were transfected with miR-101 plasmid.

Results: MicroRNA 101 achieved more than 70% knockdown of the EzH2 protein 48 hours after transfection in both MDAH-2774 and SKOV-3 cell lines, demonstrating efficient inhibition of EzH2. Furthermore, MDAH-2774 cells transfected with miR-101 showed 15% less growth than the control on day three after transfection, versus 48% for SKOV3 cells. ChIP assays revealed that the expression of miR-101 resulted in a reduction in the interaction of EzH2 protein with the p21waf1/cip1 promoter. An increase in the expression of p21waf1/cip1 in miR-101 transfected cells was confirmed by Western blot analysis. Forced expression of miR-101 in CB17/ICr-SCID mice was associated with a marked reduction in palpable tumor generation by MDAH-2774 cells, indicating its inhibitory potential in the growth of MDAH-2774 cells in vivo.

Conclusions: Silencing of EzH2 expression by miR-101 led to a decrease in in vitro cell growth as well as significant reduction of in vivo xenographic tumor growth. In addition, miR-101 expression relieved EzH2-mediated chromatin repression, resulting in the expression of the tumor suppressor p21waf1/cip1. We believe that EzH2 knockdown followed by p21waf1/cip1 reexpression by miR-101 may constitute a potential therapeutic intervention in EOC.

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Pressure to respond: Hypertension predicts clinical benefit from bevacizumab in recurrent ovarian cancer

A. Nick, R. Stone, P. Soliman, A. Sood, D. Gershenson, R. Coleman, P. Ramirez
University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: The concept that development of hypertension (HTN) denotes successful inhibition of the VEGF pathway led us to examine the relationship between HTN and outcome among patients with recurrent ovarian cancer undergoing therapy with bevacizumab (BEV).

We identified patients with recurrent ovarian cancer who underwent treatment with BEV alone or in combination with cytotoxic chemotherapy or anticancer hormonal therapy at a single institution between February 2005 and April 2010. HTN was graded according to CTCAE Version 3.0. Patients were classified as responders if BEV was continued after the initial assessment of response. Logistic regression was used to estimate the association between the incidence of HTN and clinical benefit.

Results: One hundred thirty-five patients received BEV for treatment of recurrent ovarian carcinoma. The median age of patients was 54 years (range: 16–82). The majority had high-grade tumors (78%) with serous histology (64%) and underwent optimal cytoreduction (74%). The median number of BEV cycles was 3.5 (range: 0.5–23). Excluding the six patients taken off therapy for HTN-related toxicity prior to assessment of response, the incidence of any-grade HTN with BEV across the entire cohort was 46% (59/129). Among the patients who developed HTN, 75% (44/59) had HTN prior to administration of cycle 4. There was a higher rate of elevated blood pressure with BEV therapy among patients classified as responders than among nonresponders (57% vs 33%, $P=0.007$). The median overall survival among patients classified as responders to BEV was significantly longer than that of patients classified as nonresponders (1.17 years, 95% CI = 0.95–1.63, vs 0.53 years, 95% CI = 0.33–0.87, $P<0.001$). There was no significant difference in the prevalence of a diagnosis of preexisting HTN (35% vs 43%, $P=0.3$), stage of disease, or degree of cytoreduction between responders to BEV and nonresponders. Individuals who developed HTN on therapy had a 2.75 increased odds of responding to BEV compared with individuals with normal blood pressure (95% CI = 124–5.66, $P=0.006$), and this increased likelihood of response persisted when controlling for tumor grade, stage, histology, degree of cytoreduction and number of prior therapies (OR = 2.50, 95% CI = 1.17–5.32, $P=0.02$).

Conclusions: Patients with BEV-related HTN had a higher likelihood of responding to therapy compared with those who did not develop elevated blood pressures. Thus, treatment-related HTN may predict outcome to antiangiogenic treatment.

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Prognostic impact of lymphadenectomy in clinically early-stage ovarian malignant germ cell tumor

H. Mahdi[1], R. Hanna[2], S. Seward[3], R. Swensen[1], H. Tamimi[1], R. Morris[3], A. Munkarah[4]
[1]University of Washington, Seattle, WA, [2]University of North Carolina, Chapel Hill, NC, [3]Wayne State University, Detroit, MI, [4]Henry Ford Health System, Detroit, MI

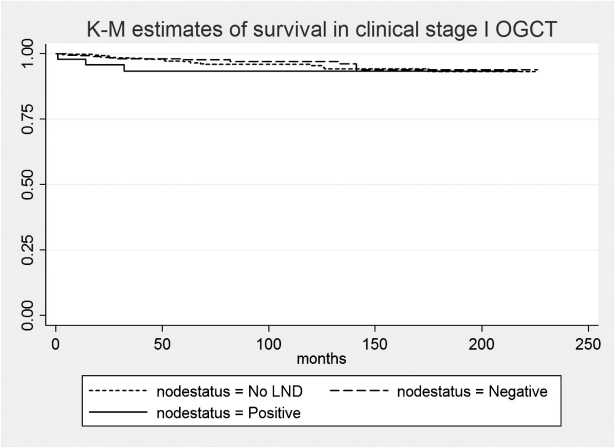
Objective: The goal of this study was to examine the prognostic impact of staging lymphadenectomy on survival of patients with clinical stage I ovarian germ cell tumor (OGCT).

Patients with a diagnosis of clinical stage I OGCT were identified from the Surveillance, Epidemiology and End Results Program (SEER) for the period 1988 to 2006, and were divided into three groups: Patients with clinical stage I and no lymphadenectomy (LND-1), patients with lymphadenectomy and histologically negative nodes (LND + 1) and patients with lymphadenectomy and histologically positive nodes (LND + 3C). Histological types were grouped into dysgerminoma (D), malignant teratoma (MT) and mixed germ cell tumors with pure nondysgerminoma cell tumors (MGCT/PNDCT). The Wilcoxon rank sum test, Kaplan–Meier survival methods, and Cox regression proportional hazards were used for statistical analysis.

Results: One thousand eighty-three patients met the inclusion criteria: 590 (54.48%) were clinical stage I and had no lymphadenectomy (LND-1), and 493 (45.52%) were clinical stage I and had lymphadenectomy. Of 493 patients who had lymphadenectomy, 441 (89.5%) were FIGO surgical stage I (LND + 1) and 52 (10.5%) were upstaged to FIGO stage IIIC because of nodal metastasis (LND + 3C). Patients with dysgerminomas were more likely to undergo lymphadenectomy than those with malignant teratoma or MGCT/PNDCT (62.4% vs 34.5% vs 44.1% respectively, $P<0.001$). Lymphadenectomy was performed more frequently in Caucasian patients than in African-American patients (47% vs 35.1, $P<0.05$). Patients with bilateral ovarian involvement were 1.4 times more likely to have lymphadenectomy than those with unilateral ovarian involvement ($P<0.04$). Overall five-year survival was 96.9% for LND-1, 97.7% for LND + 1, and 93.4% for LND + 3C ($P=0.6$). Within histology and stage subgroups, lymphadenectomy had no effect on survival. In multivariate analysis, lymphadenectomy was not an independent predictor of survival when controlling for age, histology and race (HR = 1.2, 95% CI = 0.62–2.58, $P=0.5$). Moreover, the presence of lymph node metastasis had no significant effect on survival (HR = 2.7, 95% CI = 0.67–10.96, $P=0.21$) (see figure).

Conclusions: Neither lymphadenectomy nor lymph node metastasis was an independent predictor of survival in patients with clinical stage I OGCT. This probably reflects the highly chemosensitive nature of these tumors. This study suggests that although lymphadenectomy

is important for directing chemotherapy in OGCT, it does not carry an independent prognostic significance.



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Longitudinal evaluation of cancer-associated biomarkers before and after weight loss in RENEW study participants: Implications for cancer risk reduction

F. Linkov[1], D. Bovbjerg[1], J. Delany[1], B. Goodpaster[2], J. Jakicic[1], D. Lenzner[1], Y. Lin[1], G. Maxwell[3], A. Felix[1], A. Lokshin[1]
[1]University of Pittsburgh Cancer Institute, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]Walter Reed Army Medical Center, Washington, DC

Objective: Obesity is a major risk factor for the development of endometrial cancer (EC). An improved understanding of biologic mechanisms associated with weight loss may guide development of preventive strategies for EC. Thus, we hypothesized that intentional weight loss would reduce EC risk through modification of biomarkers related to inflammation, hormonal balance and cancer antigens. In this study, we explored longitudinal biomarker changes in women who lost weight by participating in the Re-Energize With Nutrition, Exercise and Weight Loss (RENEW) study.

Serum samples from 88 participants with class II and class III obesity (BMI = 42.7 ± 5.2 kg/m^2) were obtained from the RENEW study. Twenty bead-based xMAP immunoassays were used in this study: cancer-associated antigens 125 and 15-3; carcinoembryonic antigen (CEA); interleukin (IL)-2, -6, -7, -8, and -10; tumor necrosis factor α (TNF-α); insulin-like growth factor-binding proteins (IGFBPs) 1 and 2; VEGF; eotaxin; soluble E-selectin; thyroid-stimulating hormone (TSH); prolactin; growth hormone (GH); resistin; adiponectin; and epidermal growth factor (EGF). Samples were analyzed using Luminex. A one-way repeated-measures ANOVA was used to evaluate changes in biomarker expression levels over time (baseline, six months, and 12 months). A linear mixed effect model was used to examine biomarker expression as a function of age, race, time period and BMI.

Results: Through participation in the RENEW study, participants lost an average of 12.8 kg from baseline to the 12-month assessment, with the largest change occurring in the first six months of the intervention. Expression of VEGF, soluble E-selectin, GH, adiponectin, IL-6, IL-7, CA-125, and IGFBP-1 differed significantly between baseline, six months, and 12 months. After adjustment for age, race and time period, we found that BMI had significant positive associations with soluble E-selectin and IL-6 and significant negative associations with GH, adiponectin, and IGFBP-1. In separate analyses looking at change scores for both BMI and biomarkers, significant relationships were seen for soluble E-selectin, GH, adiponectin, IL-6 and IGFBP-1.

Conclusions: This is one of the first efforts to explore changes in cancer-associated biomarkers in weight loss research participants at high risk for endometrial cancer development. This work adds to the current literature in several fields including endometrial cancer biomarkers and weight loss, and has significant potential implications for endometrial cancer prevention.

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Performance of implementing guideline-driven cervical cancer screening Measures in an Inner-City Hospital System

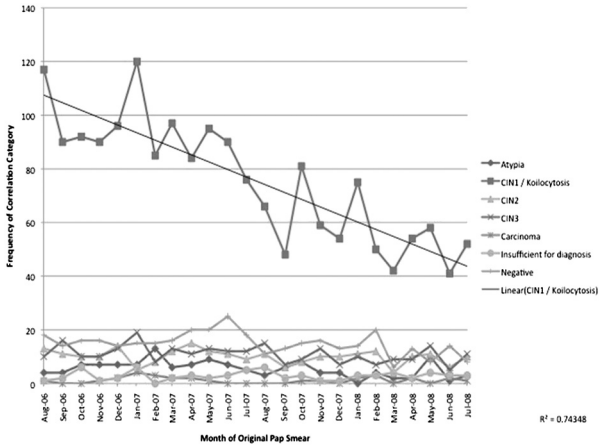
E. Wu, D. Wieland, L. Reimers, E. Burton, T. Gruenberg, M. Abadi, M. Einstein
Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

Objective: In 2006, the American Society for Colposcopy and Cervical Pathology (ASCCP) updated evidence-based guidelines recommending screening intervals for women with abnormal cervical cytology. In our low-income inner-city population, we sought to improve performance by uniformly applying the guidelines to all patients, regardless of prior practice of providers. We report the prospective evaluation of the performance of a comprehensive tracking, reminder, and a strictly evidence-based, algorithm-driven call-back and appointment scheduling system for cervical cancer screening in a resource-limited inner-city population.

Outreach efforts were formalized with algorithm-based protocols for triage to colposcopy, with strict adherence to evidence-based guidelines. During implementation from August 2006 through July 2008, we prospectively tracked performance using the electronic medical record with administrative and pathology reports to determine performance variables such as total numbers of Pap tests and colposcopy visits and the type and distribution of abnormal cytology and histology results, including all cervical intraepithelial neoplasia (CIN) 2+ diagnoses.

Results: Overall, 86,257 gynecologic visits and 41,527 Pap tests were performed systemwide during this period of widespread and uniform implementation of standard cervical cancer screening guidelines. The number of Pap tests performed per month varied little. The incidence of CIN 1 significantly decreased from 117/171 (68.4%) the first tracked month to 52/95 (54.7%) ($P = 0.04$) (see Fig. 1). The monthly incidence rate of CIN 2+, including incident cervical cancers, did not change. However, the total number of colposcopy visits declined dramatically, resulting in a 50% decrease in costs for colpsoscopy with biopsy services and approximately a 12% decrease in costs related to excisional biopsies.

Conclusions: By prospectively tracking implementation of guideline-driven cervical cancer screening guidelines in an inner-city hospital system, the number of unnecessary colposcopies was dramatically reduced without increasing numbers of potentially missed CIN 2+, including cervical cancer. Uniform implementation of administration-based performance initiatives for cervical cancer screening minimizes differences in provider practices and maximizes performance of screening while containing screening-related costs.



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Significant endometrial pathology detected during a transvaginal ultrasound screening trial for ovarian cancer

R. Woolas[1], A. Talaat[1], M. Anderson[1], D. Brinkmann[1], F. Gardner[1], A. Gentry-Maharaj[2], A. Ryan[2], A. Rosenthal[3], U. Menon[2], I. Jacobs[2]
[1]*Queen Alexandra Hospital, Portsmouth, United Kingdom,*
[2]*UCL EGA Institute for Women's Health, London, United Kingdom,*
[3]*St. Bartholomew's Hospital, London, United Kingdom*

Objective: Few data on the performance of prevention or screening strategies for endometrial cancer exist. To determine the potential of transvaginal sonogram (TVS) measurement of endometrial thickness (ET) ≥10 mm to facilitate the early diagnosis of significant endometrial pathology, a prospective study was conducted among women 50–80 years of age.

Three thousand six hundred forty-six asymptomatic women with an intact uterus were recruited to undergo annual pelvic ultrasound examination in a screening trial for ovarian cancer. Individuals found to have an ET≥10 mm were offered further investigation. All women were followed up for at least pne year after their last scan to determine whether endometrial cancer was subsequently diagnosed.

Results: Over eight years, 19,866 scans were performed, a mean of 5.5 per subject. Two hundred fifty individual women had at least one reading of ET≥10 mm. Fifty-two percent of the abnormalities detected in this group were associated with endometrial polyps. Nineteen of these women (7.5%) were diagnosed with invasive cancer (18) or severe atypical hyperplasia (1). Ten (55%) of these cancers occurred or were diagnosed after the first (prevalence) screen. Subsequently, nine primary endometrial tumors were detected on incidence screening and all were FIGO stage Ia. Follow-up revealed seven additional women who also developed invasive uterine cancer (five) or simple atypical hyperplasia (two) after TVS of <10 mm. Only two of these cases presented clinically with postmenopausal bleeding; the other five were identified through a screening process. One had an abnormal glandular smear, another a <10-mm polyp in association with a clear discharge, and three more were identified in association with adnexal masses, including one stage Ia ovarian cancer. To date no woman in this cohort has died from endometrial cancer.

Conclusions: TVS with a cutoff ≥10 mm can detect asymptomatic endometrial cancer. The positive predictive value of serious progressive pathology at hysteroscopy was 7.5%. The observed to expected ratio, distribution among annual screens, and staging of the screen-detected tumors suggest a lead time on the order of two years was obtained at the time of clinical presentation. Further support for this finding is that among this cohort undergoing nearly 20,000 women-years of screening, approximately 10 endometrial cancers would be expected to present. Twice this number were diagnosed. These data suggest that such early detection may prevent mortality and can reduce the dilemmas surrounding use of radiotherapy as an adjuvant treatment for endometrial cancer.

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Women with invasive gynecologic malignancies are more than 12 times as likely to commit suicide as are women in the general population

K. Ward[1], A. Roncancio[2], S. Plaxe[1]
[1]*UCSD–Kaiser San Diego, La Jolla, CA,* [2]*University of Texas School of Public Health Center for Health Promotion and Prevention Research, Houston, TX*

Objective: The purpose of this study was to evaluate the risk of suicide among women with invasive gynecologic malignancies (GMs) and to characterize the population of women with GMs who committed suicide.

The SEER Program's 17 registries and U.S. population data from 1973 to 2007 were queried to find women whose death certificate recorded suicide as the cause of death. The incidence rate per 100,000 (IR) of suicide for women with GMs was compared with the IR of suicide in women in the general population and with the IR in women with non-GMs during the study period. Relative risk (RR) of suicide and 95% CI were calculated. The temporal relation of suicide to diagnosis and the population characteristics of women with GMs who committed suicide were analyzed.

Results: During the study period, the IR of suicide among women in the United States was five (95% CI=5–5). In the same period, 219 suicides were reported among 350,962 women with GMs; the IR of suicide among women with GMs was 62 (95% CI=54–71). The RR of suicide in women with GMs compared with women in the general population was 12.5 (95% CI=10.9–14.2), indicating that women with GMs were more than 12 times as likely to commit suicide than were other women. The IR among women with non-GMs was 49 (95% CI=46–52) during the same period. Women with GMs were 30% more likely to commit suicide than were women with non-GMs (RR=1.3, 95% CI=1.1–1.5). Among women with GMs who committed suicide, mean age was 56 years, 90% were white, 56% were married, 55% had localized disease, 75% had surgery, and 31% had radiation. Primary tumor sites were: 94 uterine (43%), 64 ovarian (29%), 50 cervical (23%), seven vulvar (3%), and four vaginal/other (2%). In the population with GMs, 23% of suicides occurred during the first year after diagnosis, 12% occurred in the second year, and 11% in the third.

Conclusions: Women with GMs are at a greatly increased risk of suicide compared with both the general population and women with non-GMs. Suicide risk appears greatest near the time of diagnosis and diminishes thereafter. Reasons for the elevated risk cannot be determined by the present study. As many women with GMs see health care providers frequently, they may be a particularly suitable population for targeted suicide prevention efforts. Better understanding of the descriptive epidemiology of suicide among women with GMs could lead to improved risk assessment, screening for severe depression and prevention of this potentially avoidable cause of death.

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Additional data from a study of lymphatic mapping and sentinel node identification in early-stage cervical cancer

L. Rob, M. Halaska, M. Komar, M. Pluta, H. Robova, P. Skapa
Faculty Hospital Motol/Charles University, Prague, Czech Republic

Objective: The aim of this study was to present the results of sentinel lymph node (SLN) mapping in early cervical cancer using a combination of ^{99m}Tc and blue dye in an ultrashort protocol.

From February 2002 to June 2010 we included 385 women with early-stage cervical carcinoma. Thirteen patients were excluded for evident extrauterine spread. ^{99m}Tc followed by blue dye was injected under general anesthesia after visualization of the pelvis (laparotomy or laparoscopy). Women were subdivided by tumor volume into three groups (IB1 <20 mm, IB1 >20 mm, and IB2 after neoadjuvant chemotherapy [NAC]). We evaluated detection rate (DR), specific side detection rate (SSDR) and distribution of lymph nodes.

Results: We evaluated 1120 SLNs from 372 women (77 positive nodes from 59 women). One hundred eighty-two women were in group IB1 <20 mm, in whom DR was 98.4% and SSDR 95.6%. Ninety-two women were in group IB1 >20 mm, in whom DR was 94.6% and SSDR 91.3%. Ninety-eight women were in group IB2 NAC, in whom DR was 90.8% and SSDR 86.7%. The 1120 SLNs were distributed as follows: 43.6% in the external iliac artery and vein, 42.6% in the supraobturator, 4.9% in the bifurcation and common iliac artery and vein, 4.8% in the presacral area, and 4.0% in the medial part of the lateral parametrium. The 77 positive SLNs were distributed as follows: 40.3% in the external illiac artery and vein, 42.9% in the supraobturator, 6.5% in the bifurcation and common iliac artery and vein, 5.2% in the presacral area and 5.2% in the medial part of the lateral parametrium. One false-negative SLN was located in the presacral area.

Conclusions: Sentinel lymph node biopsy in early cervical cancer is a sensitive method for detection of lymph node metastases and should be part of individually tailored surgery.

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Secondary cytoreductive surgery: A key tool in the management of recurrent ovarian sex cord–stromal tumors

D. Namaky[1], P. Ramirez[2], M. Munsell[2], A. Nick[2],
D. Gershenson[2], J. Brown[2]
[1]Good Samaritan Hospital, Cincinnati, OH, [2]University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: Therapeutic options for patients with recurrent malignant ovarian sex cord–stromal tumors (SCSTs) are limited. Secondary cytoreductive surgery (CS) has been shown to provide a survival advantage in select patients with epithelial ovarian cancer. We evaluated the role of secondary CS in patients with SCSTs of the ovary.

We identified patients with recurrent ovarian SCSTs who underwent secondary CS at a single institution between 1985 and 2009. Clinical and pathologic factors were identified. Survival analyses were performed using the Kaplan–Meier method and compared using the log-rank test.

Results: We identified 105 eligible patients who met inclusion criteria. The median progression-free survival (PFS) after secondary CS was 33.1 months. The median overall survival after secondary CS was 169.8 months, and median follow-up was 61.9 months (range: 1.1 months to 21.8 years). Of 55 cases with sufficient information to determine residual disease, secondary CS was considered optimal, defined as <1 cm residual disease, in 41 patients (75%) and suboptimal in 14 patients (25%), but median PFS was no different ($P=0.604$). Patients who underwent secondary CS for a single site of disease ($n=37$ patients) had a median PFS of 46.5 months, whereas patients with multifocal disease ($n=68$ patients) had a median PFS of 31.5 months ($P=0.095$). Sixty-seven patients (63.2%) received adjuvant chemotherapy after secondary CS. The median PFS after secondary CS was 32.8 months for patients who received chemotherapy ($n=67$ patients) and 40.1 months for patients who did not receive adjuvant chemotherapy ($n=37$ patients, $P=0.57$). Age was not associated with PFS. Seventy-six patients (71.7%) recurred again after secondary CS with a median time to recurrence of 16.9 months. Of the 76 patients who had multiple recurrences, 47 (66.2%) had multiple cytoreductive surgeries; the median PFS after each successive surgery progressively declined. The site of recurrence was distant in 15% of patients at the time of first recurrence but was distant in 24% of patients at the time of second recurrence ($P=0.169$).

Conclusions: Most patients with recurrent ovarian SCSTs can be optimally cytoreduced. Secondary cytoreductive surgery should be considered as a treatment option for selected patients with recurrent disease.

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Sentinel lymph node mapping in patients with endometrial cancer undergoing robot-assisted or standard laparoscopic procedures

M. Leitao, F. Khoury Collado, G. Gardner, E. Jewell, C. Brown,
Y. Sonoda, D. Levine, R. Barakat, N. Abu-Rustum
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The goal of this study was to determine the feasibility of incorporating sentinel lymph node (SLN) mapping into robot-assisted laparoscopic (RBT) and standard transperitoneal laparoscopic (LSC) procedures in patients with newly diagnosed endometrial cancer.

All cases with a preoperative endometrial cancer diagnosis who underwent attempted SLN mapping during an RBT or LSC procedure without requiring conversion to laparotomy from September 25, 2005 to August 25, 2010 were identified. Various clinicopathologic data were abstracted. Time to complete the SLN mapping was captured during RBTs but not during LSCs. Appropriate statistical tests were used.

Results: We identified 270 total cases (119 RBTs and 151 LSCs). SLN mapping was performed using only blue dye in 223 cases (83%). Isosulfan blue dye was used in 249 cases (92%). The site of dye injection was the cervix only in 248 cases (92%). SLNs were identified in 224 cases (83%). The nodal basin distribution of the identified SLNs was: right pelvis only ($n=51$, 23%), left pelvis only ($n=32$, 14%), bilateral pelvis ($n=133$, 59%), pelvis and aortic ($n=6$, 3%), and aortic only ($n=2$, 1%). SLNs were identified in 136 of 151 (90%) LSCs compared with 88 of 119 (74%) RBTs ($P<0.001$). SLN mapping in all RBT cases was done usiing only cervical injections of blue dye. The median time to perform SLN mapping robotically was 20 minutes (range: 5–65). Successful SLN identification was based on surgeon experience with SLN mapping ($P<0.001$), and the most experienced surgeon performed LSC exclusively. The nodal basin distribution of identified SLNs was similar for RBT and LSC ($P=0.4$). The median body mass index was 32.6 kg/m^2 (range: 18.2–66) for the failed mapping cases compared with 28.3 kg/m^2 (range: 18.3–49.7) for the

successfully mapped cases ($P=0.003$) irrespective of surgical approach. Identification of SLNs was not associated with uterine weight, tumor histology, tumor grade or use of preoperative lymphoscintigraphy.

Conclusions: Sentinel lymph node mapping is feasible and can be easily incorporated into the management of patients with endometrial cancer undergoing both RBT and LSC procedures. SLN mapping can be performed in a reasonable amount of time. The use of preoperative planar lymphoscintigraphy does not appear to be necessary. Improvement in SLN identification, accuracy of SLN mapping, and long-term outcomes in this cohort of patients will require further study.

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Short- and long-term morbidity and outcomes after robotic surgery for endometrial cancer staging

F. Backes[1], L. Brudie[2], M. Farrell[1], S. Ahmad[2], N. Finkler[2], G. Bigsby[2], D. O'Malley[1], D. Cohn[1], R. Holloway[2], J. Fowler[1]
[1]Ohio State University, Columbus, OH, [2]Florida Hospital Cancer Institute, Orlando, FL

Objective: Minimally invasive surgery (MIS) for endometrial cancer (EMCA) staging has increased with the introduction of robotic surgery. Although intraoperative and immediate postoperative complications are low, little is known about long-term outcomes. We set out to assess short- and long-term morbidities.

All patients who underwent robotic staging for EMCA between 2006 and 2009 from two separate institutions were identified. Patient charts were retrospectively reviewed for complications and morbidities. Statistical comparisons were made with $\chi 2$ tests and logistic regression, between the periods 2006/2007 and 2008/2009, and for the entire cohort after institutional differences were excluded.

Results: Five hundred three patients were identified. No differences in complication rates were found between the two time periods, even though the median BMI increased from 29.9 (range: 19–52) to 32 (range: 17–70) ($P=0.03$). Median length of stay was one day (range: 1–46). No cystotomies, two enterotomies, one ureteric injury, and four vessel injuries occurred; 4.4% required an extension of the umbilical port to remove the uterus; and 7% of cases were converted to laparotomy. A postoperative pelvic abscess was found in 2% of patients, and 3.3% developed a wound infection. The total venous thromboembolism rate for robotic cases was 1.7%; six were diagnosed with a pulmonary embolus (1.3%), and all had undergone robotic lymphadenectomy. Five patients (1%) were diagnosed with a deep vein thromboembolism. The incidence of deep vein thromboembolisms was higher in cases converted to laparotomy (3/31, 9.7%, vs 2/472, 0.4%) ($P<0.01$). Workup for vaginal drainage occurred in 5%, and no fistulas were found. (Partial) cuff dehiscence was the most likely cause of drainage and occurred in 11 (2.2%); 13.4% of patients who had robotic staging developed lymphedema, compared with 3.2% if robotic surgery was converted to laparotomy (NS). Number of nodes and BMI did not contribute to the difference. Lymphocyst formation was similar at 5.4%. One death occurred in the 30-day postoperative period. Three (0.5%) patients developed a port site recurrence. Trends in operative times will be reported.

Conclusions: Robotic surgery for EMCA can be performed safely with a low rate of complications or long-term morbidities. Although vaginal drainage is a frequent complaint, fistulas are extremely rare. There seems to be a trend toward increased lymphedema after robotic lymphadenectomy, However, prospective studies will have to further evaluate this observation.

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Poster Area 1
Basic Science/Translational Research, Hereditary Cancers and the Role of Genetics: Abstracts 94–140
Sunday, 6 – Tuesday, March 8, 2011
Exhibit Hall–Bonnet Creek Ballroom

Basic/Translational Research

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7-Methyl indole ethyl isothiocyanate: A novel cytotoxic agent for endometrial cancer

K. Kristjansdottir, R. Singh, K. Kim, T. Lange, L. Brard
Women & Infants Hospital/Brown University, Providence, RI

Objective: 7-Methyl indole ethyl isothiocyanate (7Me-IEITC) is a novel agent with antitumor activity in ovarian cancer cell lines and neuroblastoma cell lines. The objective of this study was to evaluate the antitumor effect of 7Me-IEITC in endometrial cancer cell lines.

Cell viability of endometrial cancer cell lines (KLE, ECC-1) in conjunction with an ovarian cancer cell line (IGROV-1) after treatment with 7Me-IEITC was determined using MTS assay. Morphologic and apoptotic responses of KLE cells were studied by fluorescence microscopy (DAPI staining, TUNEL assay). Changes of the mitochondrial transmembrane potential, the effect of reactive oxygen species (ROS) production and cell cycle progression were studied by FACS analysis. To determine the molecular mechanism and role of ROS activation in 7Me-IEITC induced cytotoxicity, cells were pretreated with ascorbic acid in the presence or absence of drug. Expression profiles of MAP kinases, prosurvival factors and cell cycle regulators and the activation of PARP-1 and caspases were studied by Western blotting.

Results: 7Me-IEITC reduced the cell viability of KLE cells and ECC-1 cells (IC_{50} values ~20 μM). At subcytotoxic concentration (8 μM), 7Me-IEITC caused rapid loss of the mitochondrial transmembrane potential and strong apoptosis in KLE cells. There was downregulation of prosurvival kinases and upregulation of proapoptotic BCL2 family members along with activation of caspases. 7Me-IEITC acted as an antiproliferative agent and arrested cell cycle progression of KLE cells in S phase. Pretreatment with ascorbic acid abrogated caspase 3/7, SAPK/JNK activation, and cleavage of PARP-1, suggesting that 7Me-IEITC mediated its cytotoxicity in these endometrial cancer cell lines primarily by ROS production.

Conclusions: 7Me-IEITC has antitumor effects in endometrial cancer cell lines and may be developed as a potential therapeutic drug for endometrial cancer.

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A novel hedgehog pathway smoothened inhibitor (BMS-833923) demonstrates in vitro synergy with carboplatin in ovarian cancer cells

R. Rocconi, E. Meng, L. Shevde, M. Finan, E. Reed
University of South Alabama Mitchell Cancer Institute, Mobile, AL

Objective: Normally dormant, the hedgehog (Hh) signaling pathway has shown enhanced activity in numerous malignancies including

ovarian cancer. Activated Hh is represented by the translocation of GLI1 to the nucleus which is initiated by the cell surface protein, smoothened (SMOH). We describe the effectiveness of a novel SMOH inhibitor, BMS-833923, when given in combination with chemotherapy in an in vitro assay for ovarian cancer.

Western blot was used to determine the presence of Hh signaling proteins (PTCH, SMOH, GLI1) in several ovarian cancer cell lines (SKOV3, OV90, TOV112D, ES2) as well as normal ovarian epithelial cells (IOSE80). To assess the effects of inhibition of SMOH by BMS-833923, levels of GLI1 and PTCH were measured by quantitative RT-PCR, and localization of GLI1 was studied by immunocytochemistry. The MTS in vitro assay was performed using chemotherapy agents commonly used for ovarian cancer (carboplatin, paclitaxel, gemcitabine, topotecan and liposomal doxorubicin) ± BMS-833923. With a cross-diagonal multidrug treatment design, the combination index (CI) was calculated to determine mathematical synergy using the median effect method per Calcusyn software.

Results: All ovarian cell lines showed varying levels of Hh-associated proteins. Compared with IOSE80, all ovarian cancer cell lines demonstrated increased intranuclear GLI1 expression indicating an activated Hh pathway. BMS-833923 treatment resulted in a significant downregulation of GLI1 (fivefold) and PTCH (threefold) proteins compared with untreated controls. Further, immunofluorescence staining of GLI1 showed near-complete exclusion of intranuclear GLI1 with nuclear shadowing and vacuolization. In MTS cell survival assays, the combination of chemotherapy and BMS-833923 was universally more effective than chemotherapy or BMS-833923 alone. Specifically, significant cell death was demonstrated with the combination of BMS-833923 and carboplatin (8% cell survival). Calcusyn CI calculations determined that multiple dosage combinations resulted in synergy with a CI range of 0.3 to 0.49 (synergy defined as $CI < 1$).

Conclusions: The addition of a novel SMOH inhibitor, BMS-833923 demonstrates significant activity when combined with chemotherapy. Specifically, the combination of carboplatin and BMS-833923 results in significant synergy across multiple dosages. The mathematical synergy demonstrated when using this novel therapeutic is promising and warrants further investigation.

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Ab-IL2 fusion proteins mediate NK cell immune synapse formation in epithelial ovarian cancer by polarizing CD25 to the target cell–effector cell interface

J. Connor[1], I. Buhtoiarov[1], S. Gillies[2], J. Gubbels[3], J. Hank[1], P. Sondel[1], A. Kapur[1], M. Patankar[1]
[1]University of Wisconsin, Madison, WI, [2]Provenance Biopharmaceuticals Corporation, Waltham, MA, [3]Augustana College, Sioux Falls, SD

Objective: The huKS-IL2 immunocytokine (IC) consists of interleukin (IL)-2 fused to a monoclonal antibody against the epithelial cell adhesion molecule (EpCAM), whereas the hu14.18-IL2 IC recognizes the GD2 disialoganglioside. They are under evaluation for treatment of EpCAM+ (i.e., ovarian) and GD2+ (neuroblastoma, melanoma and some uterine sarcoma) malignancies because of their proven ability to enhance tumor cell killing by antibody-dependent cell-mediated cytotoxicity (ADCC) and by inducing antitumor cytotoxic T cells. Here, we demonstrate that huKS-IL2 and hu14.18-IL2 bind to tumor cells via their antibody components and increase adhesion and activating immune synapse (AIS) formation with NK cells by engaging the immune cells' IL-2 receptors (IL2R).

NK cells isolated from peripheral blood and peritoneal fluid of patients with ovarian cancer were analyzed for binding to the IC by flow cytometry. Inhibition of IC-binding NK cells was measured in the presence of the anti-IL2R blocking antibody. Immune synapses between NK cells and tumor targets were examined by monitoring the polarization of LFA-1, actin, IL2R and IC at the site of contact between NK cells and tumor targets. Flow cytometry-based cell adhesion assays were performed to quantify the interaction between NK cells and tumor cells occurring on the addition of the IC.

Results: The high-affinity IL2R-expressing NK leukemia cell line NKL shows a fivefold increase in binding to tumor targets when treated with IC compared with matching controls. This increase in binding is effectively inhibited by blocking antibodies against CD25, the α chain of the IL2R. NK cells isolated from the peritoneal environment of ovarian cancer patients, known to be impaired in mediating ADCC, bind to huKS-IL2 via CD25. The increased binding between tumor and effector cells via ICs is due to the formation of AIS that are characterized by the simultaneous polarization of LFA-1 or CD2 and F-actin at the cellular interface. AIS formation is inhibited by anti-CD25 blocking antibody and is 50–200% higher with IC versus the parent antibody.

Conclusions: These findings demonstrate that the IL-2 component of the IC allows IL2Rs to function not only as receptors for this cytokine, but also as facilitators of NK cell–target cell binding.

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Activating PIK3CA and RAS mutations identified exclusively in carcinosarcomas of uterine origin

W. Growdon, L. Garrett, B. Rousel, V. Scialabba, L. Ellisen, D. Dias-Santagata, R. Foster, R. Tambouret, B. Rueda, D. Borger
Massachusetts General Hospital/Harvard University, Boston, MA

Objective: Carcinosarcomas are aggressive and uncommon malignancies that arise throughout the female reproductive tract. Although surgical resection and adjuvant chemotherapy with radiation therapy are treatment standards, recurrent, refractory disease is a common challenge that requires more effective treatment approaches. This study was undertaken to identify susceptible molecular alterations in carcinosarcoma across gynecologic sites of origin that would provide a rationale for evaluating molecularly targeted therapies in the treatment of this disease.

With institutional review board approval, a cohort consisting of 52 primary gynecologic carcinosarcomas arising from the uterus ($n = 31$), ovary ($n = 18$), fallopian tube ($n = 2$), and vagina ($n = 1$) were obtained from patients who were initially treated and followed at our institution from 1993 to 2009. Nucleic acids were extracted from the intermixed tumor region, isolated carcinomatous element and isolated sarcomatous element of diagnostic tissue specimens. Genotyping was performed using a broad-based platform that simultaneously queried >120 common mutations across 14 cancer genes. Mutational status was correlated with clinical variables using logistic regression and Kaplan–Meier survival estimates.

Results: Cancer gene mutations were identified in 46% of the 52 patient cohort, including TP53 (23%), PIK3CA (19%), KRAS (15%), CTNNB1 (4%), and NRAS (2%). Mutation in a single gene was observed in 31% of patient samples, whereas synchronous mutations involving two and three genes were noted in 13 and 2% of samples, respectively. Comparative evaluation of the carcinomatous and sarcomatous elements within a tumor demonstrated a similar mutation signature. Mutations in PIK3CA, KRAS and NRAS were exclusive to tumors of uterine origin. Age-adjusted Cox proportional hazards modeling

associated advanced age, stage, and TP53 mutations with decreased survival in the uterine subset.

Conclusions: Although carcinosarcomas across gynecologic disease sites are histologically similar, therapeutically relevant mutations in the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways predominated in carcinosarcomas arising in the uterus. These data suggest that novel therapeutics that selectively target these pathways could be valuable for a significant proportion of carcinosarcomas of uterine origin.

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AMPK activation mimics glucose deprivation and induces cytotoxicity in ovarian cancer cells

J. Liu[1], A. Priebe[2], L. Tan[1], H. Wahl[1], A. Opipari[1], R. Kwok[1]
[1]*University of Michigan, Ann Arbor, MI,* [2]*Sanford Women's Health Gynecologic Oncology, Sioux Falls, SD*

Objective: Upregulation of glycolysis has been demonstrated in multiple tumor types and is believed to originate as an adaptive response to the selective pressure of the tumor microenvironment. Clinically, small-volume ovarian tumors can be visualized using [^{18}F] fluorodeoxyglucose PET (FDG-PET), suggesting that ovarian cancer cells are highly glycolytic. We have previously demonstrated that glucose deprivation results in diminished intracellular ATP in ovarian cancer cells. AMPK is activated during energy deficiency to restore ATP levels, and AMPK activation has been shown to induce cytotoxicity in malignant cells in vitro as well as in vivo. We sought to determine whether glucose deprivation could induce cytotoxicity in ovarian cancer cells through activation of AMPK, and whether AMPK activators could mimic glucose deprivation-induced cytotoxicity.

Ovarian cancer cells and ovarian surface epithelial cells (OSE) were incubated with normal mediim, glucose-free medium, medium containing 2-deoxyglucose (2-DG), or the AMPK activators metformin and AICAR. Cellular growth rate, growth inhibition under experimental conditions, and rate of glucose uptake were determined. Expression of pAMPK and pAkt was determined by immunoblotting.

Results: Ovarian cancer cells were sensitive to glucose deprivation as compared with OSE. Sensitivity to glucose deprivation was independent of growth rate and rate of glucose uptake, and appeared to be dependent on constitutive activation of Akt. Glucose deprivation resulted in activation of AMPK and inhibition of Akt phosphorylation. Similarly, treatment with AMPK activators resulted in AMPK activation, Akt inhibition and induced cell death.

Conclusions: Ovarian cancer cells are glycolytic as compared with normal, untransformed cells and are sensitive to glucose deprivation. Ovarian cancer cells are sensitive to glucose withdrawal in the presence or absence of constitutive Akt activity. Because ovarian cancer cells are dependent on glucose for growth and survival, treatment with AMPK activators that mimic glucose deprivation may result in broad clinical benefits to patients with ovarian cancer.

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Antiproliferative activity of a phenolic extract from a native Chilean Amaranthaceae plant in drug-resistant ovarian cancer cell lines

J. Brouwer-Visser[1], M. Cossio[1], N. Urzùa[2], G. Montenegro[2], S. Horwitz[1], R. Moreno[2], G. Huang[1]
[1]*Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY,* [2]*Pontificia Universidad Católica de Chile, Santiago, Chile*

Objective: There remains a dire need to develop effective treatments for drug-resistant ovarian cancer. In our natural product screening program, we identified for investigation a partially purified phenolic extract (APE1) from a native Chilean plant of the Amaranthaceae family. The purpose of this study was to evaluate the activity of APE1 in drug-resistant ovarian cancer cell lines.

Using the sulforhodamine B assay, the effect of APE1 on cellular proliferation was assessed in three parental ovarian cell lines (A2780, HEY, OVCAR8); five drug-resistant cell lines selected by six–12 months of exposure of the parental cells to increasing concentrations of the microtubule stabilizing agent taxol, ixabepilone, or discodermolide; and an immortalized, nontumorigenic cell line (HOSE2) derived from normal human ovarian surface epithelial cells. Propidium iodide staining and flow cytometric analysis were performed to detect alterations in cell cycle distribution following APE1 treatment. To determine the effect of APE1 on AKT activity, Western blot analysis was done using antibodies specific for phosphorylated AKT (Ser473 and Thr308) and total AKT.

Results: APE1 demonstrated similar antiproliferative activity in all of the parental and drug-resistant ovarian cell lines, with 50% growth inhibition (IC_{50}) at mean concentrations of 3.8 μg/mL in the parental cell lines and 4.3 μg/mL in the resistant cell lines. In the nontumorigenic HOSE2 cells, the IC_{50} was approximately two-fold higher (8.9 μg/mL). Cell cycle analysis of A2780 cells treated with APE1 (2 μg/mL) demonstrated accumulation of hypodiploid (sub-G_1) cells, quantified at 29.4% sub-G_1 at six hours and 47.7% sub-G_1 at 24 hours, consistent with rapid induction of cell death. Western blot analysis in A2780 cells showed a two-fold decrease in Ser473 and 4.5-fold decrease in Thr308 phosphorylation of AKT following APE1 treatment (2 μg/mL × 24 hours), consistent with suppression of AKT activity.

Conclusions: APE1 demonstrates broad antiproliferative activity in drug-sensitive and drug-resistant ovarian cancer cell lines, induces rapid accumulation of cells in sub-G_1 and decreases AKT activity. In addition, its selective potency in ovarian cancer cell lines compared with nontumorigenic ovarian cells could provide a therapeutic advantage in the potential treatment of patients with ovarian cancer.

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Association between global DNA hypomethylation in leukocytes and risk of ovarian cancer

S. Akers, K. Moysich, W. Zhang, P. Link, A. Miller, S. Lele, K. Odunsi, A. Karpf
Roswell Park Cancer Institute, Buffalo, NY

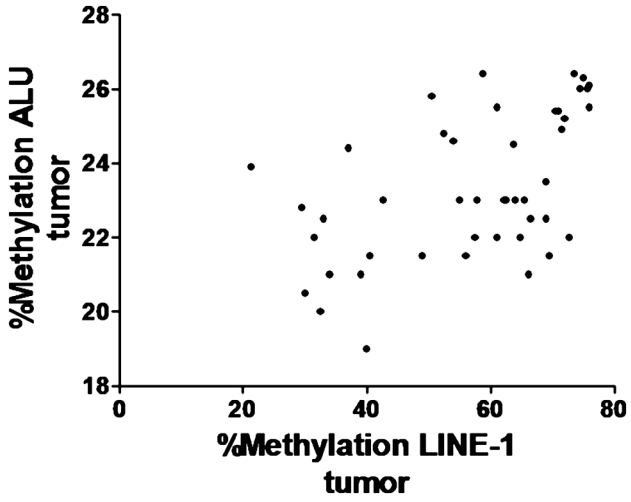
Objective: DNA hypomethylation was the first recognized epigenetic defect in human cancer. Leukocytes from patients with breast cancer show a significant reduction in global DNA methylation as compared with controls ($P < 0.001$). Systemic alterations in DNA methylation could provide a novel means for early cancer detection, particularly in asymptomatic cancers such as ovarian cancer. In the current study, we examined global DNA methylation in leukocytes from patients with ovarian cancer.

Data and samples (blood and tissue) were obtained from patients with a diagnosis of ovarian cancer and healthy controls. DNA was extracted from the blood and tumor, and the DNA underwent sodium bisulfite conversion and subsequent amplification with PCR. The PCR products were processed to yield single-stranded DNA with annealed

sequencing primer. Methylation levels were then quantified for LINE-1 and Alu.

Results: Ovarian cancer patient leukocytes show global DNA hypermethylation, as assessed by quantitative LINE-1 bisulfite pyrosequencing, as compared with controls ($P<0.001$). Quantitative Alu bisulfite pyrosequencing showed global DNA hypomethylation ($P=0.0002$). LINE-1 methylation in tumor did correlate with Alu methylation in tumor ($P=0.0002$) (see figure), but LINE-1 methylation of leukocytes did not correlate with Alu methylation. There was no correlation between LINE-1 methylation in leukocytes and LINE-1 methylation in tumor tissues from matched ovarian cancer patients ($P=0.58$). We analyzed LINE-1 methylation in different histologic subtypes of ovarian cancer and found a difference between clear cell and controls ($P<0.05$). Cases with endometrioid histology showed a significant difference in methylation as compared with serous cases ($P<0.05$).

Conclusions: Our study reveals that LINE-1 sequences are hypermethylated in leukocytes from ovarian cancer patients, and that alterations of LINE-1 methylation in leukocytes compared with controls may be linked to particular ovarian cancer disease subtypes. Clear cell histology and stage IV disease were associated with LINE-1 hypermethylation. Alu sequences showed hypomethylation in the leukocytes and tumors of ovarian cancer patients. However, there was no correlation between the leukocytes and tumor. Alu methylation changes were not associated with any specific histologic subtype, stage, grade or survival. Our data demonstrating that leukocyte DNA hypomethylation occurs in ovarian cancer patients should be exploited to develop novel diagnostics for this malignancy.



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Cisplatin, carboplatin, and paclitaxel: Unique and common pathways that underlie ovarian cancer response

E. Bicaku, Y. Xiong, D. Marchion, X. Stickles, J. Gonzalez-Bosquet, R. Wenham, J. Lancaster
H. Lee Moffitt Cancer Center, Tampa, FL

Objective: Cisplatin and carboplatin have been shown to have similar therapeutic efficacy against ovarian cancer (OVCA), but different toxicity profiles, either alone or in combination with paclitaxel. The molecular basis of OVCA response to each drug, either as single agents or in combination, remains to be fully delineated. In the current study, we adopted a genomic approach to characterize unique and common pathways that underlie ovarian cancer response to these agents.

A panel of ovarian cancer cell lines ($n=36$) were treated with increasing doses of carboplatin (CARBO), cisplatin (CIS), paclitaxel (PTX), or carboplatin plus paclitaxel (CPTX), and the dose–response effects quantified using MTS cell proliferation assays. IC_{50} values were calculated. In parallel, pretreatment Affymetrix custom gene expression microarray analysis was performed on each cell line. Gene expression and chemosensitivity data were evaluated for each drug, and Pearson correlation coefficients were calculated for expression data and drug IC_{50} values. Genes demonstrating expression/IC_{50} correlations ($P<0.01$) were subjected to biologic pathway analysis.

Results: OVCA cell line sensitivity to CARBO, CIS, PTX, and CPTX was associated with the expression of 1201, 454, 1025, and 1049 genes, respectively. Genes associated with OVCA sensitivity included representation of 77 (CARBO), 68 (CIS), 64 (PTX) and 25 (CPTX) biologic pathways ($P<0.01$). OVCA cell sensitivity to Carbo and CIS was associated with 359 common genes, including 23 common pathways. Similarly, sensitivity to CARBO and CIS was associated with 54 and 45 unique pathways, respectively. Comparison of the sensitivity of combination CPTX with the sensitivity to each individual agent identified three (CIS), eight (CARBO), and two (PTX) represented pathways common to sensitivity to both the combination and single-agent treatment. Three pathways (BAD apoptosis and survival, APC and cell cycle regulation, and transcription of CREB) were represented in common between CARBO/CIS, CIS/CPTX and CARBO/CPTX.

Conclusions: We have integrated OVCA cell line chemosensitivity data with genomewide expression to provide insights into the biologic basis of OVCA response to agents used in primary therapy. Our findings identify pathways that may be common determinants of response to single-agent platinum and also platinum/taxane combination therapies, and that may aid rational selection of targeted agents that enhance cytotoxic response in the future.

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Clinical significance of vascular cell adhesion molecule 1 in the ovarian cancer microenvironment

J. Scalici[1], C. Harrer[1], K. Atkins[2], A. Jazaeri[2], L. Duska[2], J. Slack-Davis[1]
[1]University of Virginia, Charlottesville, VA, [2]University of Virginia Health System, Charlottesville, VA

Objective: Study of the ovarian cancer microenvironment has revealed an active role for vascular cell adhesion molecule 1 (VCAM-1) in the metastatic process. VCAM-1 is a mediator of peritoneal invasion: Its blockade significantly reduced tumor cell invasion through a mesothelial cell layer in vitro and significantly reduced tumor burden in an animal model. Soluble VCAM-1 has been found in a biomarker panel to be a sensitive and specific indicator of increasing disease burden in late-stage disease. We therefore hypothesized that mesothelial VCAM-1 expression increases with peritoneal disease burden. We aimed to evaluate its expression as well as its ligand $\alpha4\beta1$ integrin (VLA-4) on diseased peritoneum and ovary, respectively. We also questioned whether VCAM-1, a regulator of tumor cell invasion, could predict the likelihood of acheiving an optimal cytoreduction.

We identified paraffin blocks containing mesothelium from epithelial ovarian cancer patients from 1998 to 2010 and their medical records. Immunohistochemical staining for VCAM-1 was performed with scoring by a single pathologist. Fresh ovarian tissue was evaluated for expression of VLA-4. Flow cytometry was used to assess expression of VLA-4 on ovarian tissue.

Results: Mesothelial VCAM-1 expression significantly increased with disease stage (0% stage I vs 60% stage III/IV, $P=0.002$). Expression in the setting of peritoneal invasion was increased versus no invasion. (60% vs 0%, $P=0.0003$). There was a trend toward reduced expression in patients who received neoadjuvant chemotherapy versus upfront surgery (25% vs 100%, $P=0.047$). Examination of VLA-4 expression revealed no distinction between benign and malignant ovarian tissue as all expressed the VCAM-1 ligand. Peritoneal VCAM-1 expression did not significantly correlate with optimal cytoreduction or the need for radical surgery in our series.

Conclusions: VCAM-1 expression is an important component in the ovarian cancer microenvironment as it regulates invasion and is differentially expressed in advanced disease. Additionally, its co-receptor appears native to ovarian tissue. Mesothelial VCAM-1 expression directly correlates with invasive disease burden, and there is a trend toward decreased expression after exposure to chemotherapy. This suggests that VCAM-1 may serve as a molecular marker of chemoresponsiveness. More importantly, because the tumor microenvironment is genetically stable, VCAM-1 may provide a unique and valid therapeutic target for the treatment of drug-resistant disease.

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Combined erbB/VEGFR blockade has improved anticancer activity over single-pathway inhibition in ovarian cancer in vivo

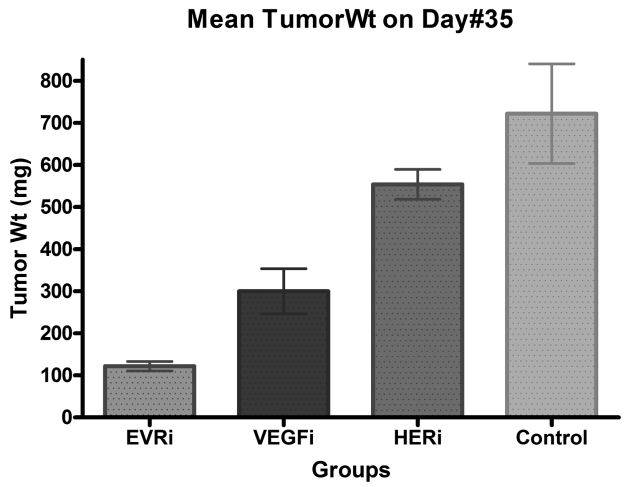
T. Farzan, S. Harrington, J. Krempski, S. Weroha, X. Hou, K. Kalli, P. Haluska
Mayo Clinic, Rochester, MN

Objective: Ovarian cancer still claims the highest mortality among gynecologic cancers. Better understanding of pathways critical for ovarian cancer growth and survival has led to the development of specific inhibitors that target key components. The human epidermal growth factor receptor (ErbB/HER) and vascular endothelial growth factor (VEGF) pathways have demonstrated evidence of dysregulation that is important in ovarian cancer progression. Clinical evaluations targeting either the erbB or VEGF pathway are active areas of investigation. We hypothesized that co-targeting both pathways would be more effective than blocking either of these pathways alone. To test this, we determined the efficacy of HER and VEGFR blockade alone and in combination in vivo.

We developed a luciferase-expressing ovarian cancer model (Skov3.ip1.luc) that allowed us to monitor intraperitoneal tumor burden serially using a noninvasive in vivo imaging system. Skov3.ip.luc cells were injected intraperitoneally into nude mice, which were randomized to three treatment groups and one control group (15 mice/group). The treatment groups were as follows: Pan HER inhibitor group (HERi, AC480); VEGFR inhibitor group (VEGFRi, cediranib); and ErbB/VEGFR inhibitor group (EVRi, BMS-690514). Starting on day four, the mice were treated by oral gavage at the MTD of each agent for three cycles, each cycle consisting of five days of treatment followed by two days of drug-free interval. Tumor burden was calculated twice weekly by intraperitoneal administration of luciferase substrate (D-luciferin) and measurement of whole-animal bioluminescence with the IVIS 200 Bioluminescence Imaging System (Xenogen). On day 35, the animals were sacrificed and the tumors were harvested and weighed. Results were analyzed by paired *t* test and Mann–Whitney test.

Results: The VEGFRi and EVRi groups had lower tumor weights and light emission compared with the control group. The VEGFRi group had significantly lower tumor weights and light emission than the HERi group ($P=0.0014$ and 0.0065). The EVRi group had significantly lower tumor weights and light emission than both the HERi and the VEGFi groups ($P=0.0001$ and 0.0207).

Conclusions: Co-targeting the HER and VEGF pathways has improved antitumor activity over blocking either pathway alone. The use of noninvasive imaging allowed serial monitoring of tumor burden and correlated with tumor volume. Clinical investigations with a combined erbB/VEGFR inhibitor may be an attractive area of development in the treatment of ovarian cancer.



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Comparison of mTOR and HIF pathway alterations in the clear cell carcinoma variant of kidney, ovary and endometrium

Z. Al-Wahab[1], R. Morris[1], A. Semaan[1], L. Solomon[1], S. Munns[1], S. Seward[1], R. Ali-Fehmi[1], A. Munkarah[1,2]
[1]Wayne State University, Detroit, MI, [2]Henry Ford Health System, Detroit, MI

Objective: The inhibitors of mTOR and HIF pathway molecules have been approved to treat advanced clear cell renal cell carcinoma (RCC). Ovarian clear cell carcinoma (OCC) and endometrial clear cell carcinoma (ECC) exhibit similar morphology and have been reported to share overlapping gene expression profiles with clear cell RCC. Our objective was to study the expression of HIF and mTOR pathway markers in OCC and ECC, and to compare the patterns with those present in clear cell RCC as a rationale for investigating potentially similar treatment approaches for OCC and ECC.

Immunohistochemical staining using antibodies against mTOR pathway markers PTEN, phospho-S (p-S6),and phosphor-4E binding protein 1(p-4E BP1) and HIF pathway marker Glut1 was performed on tissue microarrays constructed from 39 clear cell RCCs, 33 OCCs, and 29 ECCs. Nuclear and/or cytoplasmic expression was evaluated for p-S6, p-4E BP1, and Glut1 markers based on the intensity of staining (graded 0–3) and the percentage of positive cells. PTEN immunostain was assessed as expressed or not.

Results: Comparing clear cell RCC with OCC and ECC, we found a high expression of p-4E BP1 in all three tumor systems. However, OCC and ECC revealed a significantly higher expression of p-S6 ($P=0.04$ for OCC and 0.0008 for ECC) and Glut1 ($P=0.006$ for OCC and 0.0006 for ECC) than in clear cell RCC, whereas lack of PTEN expression was significantly higher in clear cell RCC than in OCC and ECC ($P=0.0006$ for OCC and 0.0008 for ECC).

Conclusions: The overexpression of p-4E BP1 mTOR pathway effector in OCC and ECC is similar to that seen in clear cell RCC. These data suggest a potential role for this effector in the oncogenesis of OCC and ECC. They also support a possible therapeutic utility of inhibiting this effector in a strategy similar to that adopted for clear cell RCC.

Immunohistochemical staining results.

	Clear cell RCC	OCC	ECC
p-4E BP1 high expression	71% ($n=38$)	76% ($n=17$)	79% ($n=28$)
p-S6 high expression	54% ($n=37$)	78% ($n=32$)	93% ($n=27$)
PTEN lack of expression	82% ($n=39$)	42% ($n=33$)	37.5% ($n=24$)
Glut1 high expression	49% ($n=39$)	82% ($n=33$)	90% ($n=29$)

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Concordant gene expression profiles in matched primary and recurrent serous ovarian cancers predict platinum response

G. Sfakianos[1], J. Yan[2], R. Whitaker[1], S. Murphy[1], A. Berchuck[1]
[1]*Duke University Medical Center, Durham, NC,* [2]*Cancer Guide Diagnostics, Durham, NC*

Objective: Primary therapy for ovarian cancer involves debulking surgery and platinum-based chemotherapy. Most patients develop recurrent disease and undergo additional therapy. Our group and others have sought to develop genomic predictors that would guide therapies. These predictors have been developed using frozen tumor samples from primary surgery, because it is more difficult to obtain tumor at the time of recurrence. The objective of this study was to compare gene expression between primary and recurrent ovarian cancers to determine whether samples obtained at primary surgery can guide therapies throughout the course of disease.

Gene expression profiles were generated using Affymetrix U133A + 2.0 arrays in 21 pairs of high-grade serous ovarian cancers collected from the same patients at initial surgery and at a second surgery later in the course of disease. Quality controls, raw *Q*, background, and mean PM intensity, as well as percentage presence, were examined for each chip. Unsupervised clustering and principal component analysis were applied to group samples.

Results: All 21 patients had advanced-stage disease. Hierarchical clustering grouped matched tumors from the same patient together. The primary and recurrent tumors were compared using ANOVA. Although none of the genes passed multitest correction by FDR, 37 genes identified at $P<0.005$ were able to separate the primary tumors from the recurrent tumors. We tested the primary and recurrent tumor data sets for their response to platinum therapy by applying the top 100 genes from a previously developed platinum sensitivity signature. The sensitivity for this signature was 0.80 in both groups, and specificity was 0.42 for primary tumors and 0.58 for recurrent tumors. Overall, there was no significant difference between the primary and recurrent tumors when analyzed with hierarchical clustering, ANOVA, and a previously developed platinum sensitivity signature, demonstrating concordance in gene expression between matched primary and recurrent pairs.

Conclusions: These data provide evidence that gene expression profiles from primary ovarian cancers are retained in samples obtained at recurrence. Further analyses are needed to determine which specific genomic signatures remain consistent beyond platinum resistance. The ability to base genomic predictive tests on tumor samples from primary surgery would greatly facilitate the development of personalized approaches to the management of women with ovarian cancer.

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Cooperative regulation of hPygo2 biomarker expression in cervical dysplasia and cancer

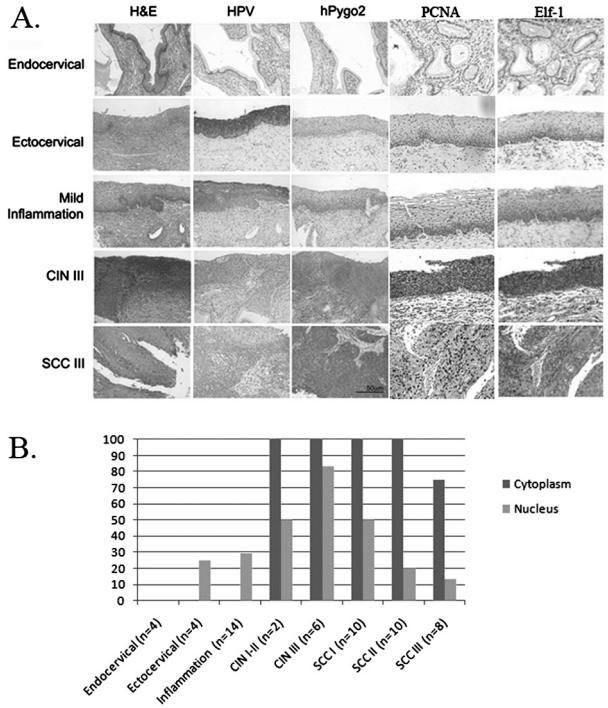
C. Popadiuk, K. Kao, Y. Tzenov
Memorial University, St. John's, NL, Canada

Objective: We previously demonstrated that the Wnt signaling component hPygo2 is overexpressed and required for cancer cell growth and that Elf-1, which is regulated by the retinoblastoma (Rb) tumor suppressor, activates hPygo2. Because HPV-E7 protein suppresses Rb, we hypothesized that hPygo2 would persist in cervical cells transformed by human papillomavirus (HPV). The purpose of this study was therefore to determine the mechanism of overexpression of hPygo2 in human cervical dysplasia.

Expression analyses were performed using immunoblot, immunofluorescence, and immunohistochemistry for protein and quantitative PCR for mRNA. Gene expression assays were performed in vitro using expression and reporter plasmid transfection, and in vivo transcription factor complex binding by chromatin immunoprecipitation (ChIP) assays.

Results: Expression of hPygo2 mRNA and protein was significantly higher in HPV-transformed endocervical cells and cervical cancer cell lines relative to primary endocervical cells (HEN). Immunohistochemical analysis of hPygo2 protein expression in a tissue microarray of cervical cancer progression showed weak accumulation of hPygo2 in nuclei of parabasal cells of normal ectocervical epithelium. Cervical intraepithelial neoplasia (CIN) 2 and 3 staged dysplasias showed high levels of expression in cytoplasm, and the highest levels of expression were found in squamous cell carcinomas. HPV antibodies stained nuclei and cytoplasm of nonneoplastic tissues very strongly and, to a lesser extent, CIN 2, CIN 3 and squamous cell carcinomas. Transfection of mutant Rb tumor suppressor repressed Elf-1 activation of hPygo2 in HPV-transformed endo- and ectocervical cells, while Elf-1 itself amplified hPygo2 gene and protein expression. In vivo ChIP assays demonstrated that both Elf-1 and Rb cooperated to regulate hPygo2 expression in HPV-transformed cervical cells.

Conclusions: Our findings revealed that hPygo2 protein accumulates in cervical cells as a result of HPV infection and increases with dysplasia leading to frank cancer. Deregulation of Rb protein by HPV resulted in de-repression of the Elf-1 oncogenic transcription factor, which in turn stimulated expression of hPygo2. These findings provide a mechanism to support the hypothesis that increased hPygo2 biomarker expression is a cellular response to HPV infection in cervical dysplasia and cancer.



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Detection of the tissue-derived biomarker peroxiredoxin 1 in serum of patients with ovarian cancer: A biomarker feasibility study

E. Hoskins[1], B. Hood[2], M. Sun[2], T. Krivak[1], T. Conrads[3], R. Edwards[1]
[1]Magee–Womens Hospital of UPMC, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA, [3]Women's Health Integrated Research Center at Inova Health System, Annadale, VA

Objective: Biomarker discovery is essential to the development of a screening test for epithelial ovarian cancer (EOC). We hypothesized that tumor-specific proteins located in the local tumor microenvironment, specifically tissue interstitial fluids, are potential biomarkers for detection in serum from patients with EOC.

Papillary serous ovarian cancer tumor tissue was collected at the time of surgery. Tissue sections (1–3 mm^3) were incubated in 1 mL phosphate-buffered saline at 37 °C for one hour. The resultant protein-rich solution was tissue interstitial fluid (TIF). Clarified TIF underwent a rigorous work flow, which included novel application of the Multiple Affinity Removal System (MARS), one-dimensional gel electrophoresis, trypsin digestion, peptide extraction and high-throughput analysis by nanoflow reversed-phase liquid chromatography (nanoRPLC)–tandem mass spectrometry (MS/MS). MS analysis provided protein sequences and relative protein quantification in TIF samples. Select amplified proteins––peroxiredoxin 1 (PRDX1), α-enolase (ENO1), and annexin II (AXA2)––were validated via Western blot. Ingenuity Pathways Analysis (IPA) aided in identifying potential serum biomarkers. A cytoplasmic protein, peroxiredoxin 1 (PDRX1), was selected for quantification in corresponding serum. Sera from a cohort of women with benign ovarian lesions were obtained for comparison with serum PDRX1 levels of patients with ovarian cancer.

Results: Four hundred seventy-four proteins were identified by two or more peptide sequences in all four TIF samples. We selected PRDX1 for serum validation because of its potential for being a cancer biomarker, as suggested by IPA, and its propensity to promote tumorigenesis in low-malignant-potential tumors of the ovary and in breast cancer. The presence of PRDX1 in serum was determined with a commercially available ELISA. The mean PRDX1 level in serum samples was 25.19 ± 19.9 ng/mL ($n = 4$) in study patients with ovarian cancer and 6.731 ± 5.46 ng/mL ($n = 4$) in benign controls.
Conclusions: We determined the presence of more than 400 potential biomarkers in TIF of papillary serous ovarian cancers. We validated the presence of select proteins via Western blot. This is the first published report of measured protein PRDX1 in serum. PRDX1 detection can now be evaluated for its performance as a biomarker as compared with other existing biomarkers.

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Differential gene expression in endometrium, abdominal wall adipose tissue and omentum in obese women with and without endometrial cancer

S. Modesitt, J. Hsu
University of Virginia, Charlottesville, VA

Objective: Endometrial carcinoma is the most common gynecologic cancer in the United States, and 40% of cases are obesity related. The study objectives were to analyze differential gene expression in endometrial, abdominal wall and omental tissue in obese women with and without endometrial cancer undergoing abdominal hysterectomy.

This is a subset analysis of a prior study on the impact of obesity and exercise in endometrial cancer in which obese women with and without cancer underwent abdominal hysterectomy and tissue was collected at surgery. For this analysis, eight women (four with endometrial cancer and four benign) were matched by age and body mass index. RNA was extracted from the tissue, and microarray analysis was performed using Affymetrix Human Genome U133 Plus 2.0 Array GeneChips. Probe signal output data were analyzed using a linear modeling technique and empirical Bayesian statistics and Bonferroni–Hochberg (BH) multiple sample adjustment of *P* values. Output was filtered by tissue type using a BH-adjusted *P*-value cutoff of 0.0001 and log 2-fold difference to identify probes that differed significantly between the cancer and control cohorts.
Results: The mean age was 52.6 years, and the mean body mass index was 44.5 kg/m^2. Women with and without cancer did not differ significantly with respect to serum levels of estradiol, estrone, androstenedione, testosterone, progesterone, sex hormone-binding globulin, adiponectin, insulin and leptin. Using the filtering criteria, 2373 probes in endometrium, 21 probes in abdominal adipose and 88 probes in omentum were identified as being differentially expressed between the two groups. No probes were found in all three tissue types, but endometrium and adipose shared two probes in common, adipose and omentum shared five, and endometrium and omentum shared three. When looking specifically at nine hormone/adipocyte factors previously measured, four related probes were differentially expressed in the endometrial tissue but none in the other tissue types. The first one was for the gene encoding 17β-hydroxysteroid dehydrogenase II, a crucial enzyme in estradiol synthesis that was upregulated in the cancer cohort. Also, three hormone receptors (androgen, insulin, and progesterone) were significantly downregulated in the cancer cohort.

Conclusions: Differential microarray gene expression between cancer and control groups of at-risk obese women indicate significant genetic or molecular factors potentially involved in endometrial pathogenesis that could become primary prevention targets.

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Differential microRNA expression in *cis*-platinum-resistant versus -sensitive ovarian cancer cell lines

A. Sherman[1], L. Hu[1], C. Melton[1], D. Kapp[2], J. Chan[1]
[1]*UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA,* [2]*Stanford University Medical Center, Stanford, CA*

Objective: The objective of this study was to determine the association of differential microRNA expression and *cis*-platinum-resistant versus -sensitive ovarian cancer.

MTT assays were used to determine drug resistance in *cis*-platinum-resistant (A2780-CP) versus -sensitive (A2780) ovarian cancer cell lines. MicroRNA microarray was performed to identify potential targets for reversing drug resistance. Microarray results were further validated via quantitative real-time PCR (qRT-PCR). To confirm our in vitro findings, we employed The Cancer Genomic Atlas (TCGA) data portal. Using the Agilent microRNA array platform, we evaluated data from 443 patients with corresponding genomic, chemotherapy, recurrence, and outcome data. We divided patients into two groups, those who were platinum sensitive (>24-month progression-free survival [PFS]) and those who were platinum resistant (<6-month PFS), and identified differential microRNA expression. Student's *t* test, Kaplan–Meier survival estimates, and Cox proportional hazards models were employed for statistical analyses. Targetscan and Pictar genomic sequence analyses were used to identify gene targets of microRNAs.

Results: The A2780-CP ovarian cancer cells had a 3.2-fold higher resistance to *cis*-platinum (IC_{50} 5.74 vs 1.80 μM, $P = 0.049$). MicroRNA microarray analysis identified differentially expressed (>2-fold) microRNAs including mir-181a, mir-10b, mir-27b, and mir-126. Specifically, mir-181a had a 3.4-fold overexpression in resistant compared with sensitive cancer cells, confirmed with qRT-PCR. Of 443 tumor specimens from TCGA data, a 1.25-fold higher expression of miR-181a was associated with a median recurrence-free survival of 23 months versus 59 months in those with lower miR-181a expression ($P = 0.013$). Additionally, a greater proportion of patients with high miR-181a expression recurred within 24 months (28.7% vs 18.8%, $P = 0.062$). Furthermore, miRanda algorithms for complementarity identified target genes associated with miR-181a and BCL2L11, a known facilitator of apoptosis.

Conclusions: Our data suggest that miR-181a may be implicated in platinum-resistant serous ovarian cancer. Targeting microRNA expression may have significant promise in the treatment of drug-resistant ovarian cancer.

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DNA methylation markers associated with serous ovarian cancer subtypes

U. Chandavarkar[1], M. Campan[1], S. Houshdaran[1], C. Pearce[1], H. Shen[1], M. Widschwendter[2], A. Berchuck[3], L. Roman[4], P. Laird[1]
[1]*University of Southern California, Los Angeles, CA,* [2]*University College, London, UK,* [3]*Duke University Medical Center, Durham, NC,* [4]*USC/LAC Medical Center Women and Children's Hospital, Los Angeles, CA*

Objective: Ovarian cancer is the most deadly of the gynecologic malignancies. Several clinicopathologic factors have been used to prognosticate clinical outcome and select therapy, but none has provided sufficient insight into the biology of the disease. Even within a single histology, there may be variability in outcome and exposure history. DNA methylation is an epigenetic modification that consists of the addition of a methyl group to a cytosine followed by a guanine (mCpG). DNA methylation is important for gene transcription and in cancer cells, DNA methylation patterns are altered and this may lead to transcriptional changes. The purpose of this study was to identify DNA methylation-based subtypes of a single histology (serous ovarian carcinoma) and to design sensitive and specific DNA methylation markers to be tested in paraffin-embedded tissues in order to correlate the subtypes with known clinical characteristics.

High-throughput quantitative DNA methylation analysis was performed using the Illumina Infinium platform for 389 serous ovarian cancer samples and 27,578 CpG dinucleotides spanning 14,495 genes. Statistical analyses identified the most biologically variant CpG sites. DNA methylation values from these selected probes and all samples were used to perform consensus *k*-means clustering, and cluster labels were assigned. We designed MethyLight reactions for six of the discriminant markers and tested them in 30 serous ovarian cancer samples.

Results: We uncovered three novel DNA methylation-based clusters within serous ovarian cancer best categorized by a panel of biologically variant CpG probes. MethyLight reactions for five of these markers identified DNA methylation differences in 30 serous ovarian cancers.

Conclusions: We have identified three unique serous ovarian cancer subtypes best distinguished by variant DNA methylation features. Further investigations will be aimed at testing the five designed MethyLight markers in tissues linked to clinical information. It is hoped that this work will provide a better understanding of the pathogenesis of serous ovarian cancer and will lead to a more individualized approach to care.

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Epithelial ovarian cancer tumor microenvironment is a favorable biomarker resource

E. Hoskins[1], B. Hood[2], M. Sun[2], T. Krivak[1], T. Conrads[3], R. Edwards[1]
[1]*Magee–Womens Hospital of UPMC, Pittsburgh, PA,* [2]*University of Pittsburgh, Pittsburgh, PA,* [3]*Women's Health Integrated Research Center at Inova Health System, Annadale, VA*

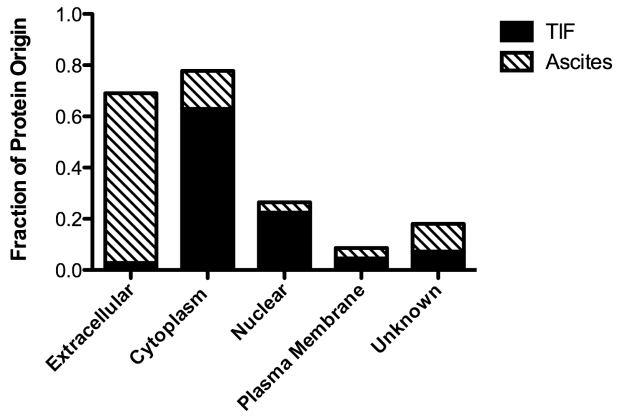
Objective: Serum proteomics for biomarker detection has limitations: the presence of highly abundant and nonspecific proteins, which preclude detection of specific ovarian cancer biomarkers. Ascites and tissue interstitial fluid (TIF) obtained from patients affected with epithelial ovarian cancer (EOC) are an alternative source of biomarkers for ovarian cancer screening test development. We hypothesized that TIF is a superior protein-rich medium that contains ovarian cancer-specific proteins for biomarker discovery compared with ascitic fluid.

EOC tumor and ascites were collected within 30 minutes of removal at the time of debulking surgery. Samples used were from four chemotherapy-naïve patients with pathologically proven papillary serous EOC. For TIF collection, we implemented a standardized sampling strategy, involving incubation of tumor tissue in saline for 1 hour at 37 °C immediately following resection. In parallel, TIF and ascitic fluid were clarified of cellular debris at 1200 rpm for 20 minutes. The supernantants of both fluids were placed at −80 °C until analysis. TIF and ascites underwent a rigorous work flow including application of the Multiple Affinity Removal System, protein quantification, one-dimensional gel

electrophoresis, trypsin digestion, peptide extraction, and high-throughput analysis by nanoflow reversed-phase liquid chromatography (nanoRPLC)–tandem mass spectrometry (MS/MS). MS analysis provided protein sequence and relative protein quantification in TIF and ascites samples, respectively. Proteins identified by two or more peptide sequences in all patient samples for each respective medium were included in the analysis.

Results: Four hundred fifty-nine proteins were exclusively identified in TIF in all patient samples, and 74 proteins were contained in all four ascitic fluid samples. Proteins from these two tumor environments had contrasting function and location. Sixty-six percent of ascitic fluid proteins were extracellular, similar to serum composition. TIF proteins were largely subcellular, 63% cytoplasmic and 22% nuclear in origin (see the figure).

Conclusions: We developed a standardized work flow for ovarian cancer biomarker detection in EOC biofluids. TIF contained largely subcellular proteins, which were of lower abundance and ovarian cancer specific, whereas ascitic fluid had a serum-like proteomic profile, with mostly nonspecific extracellular proteins. The distinguished proteome profile favors TIF as an optimal biomarker source for ovarian cancer screening test development.



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EZH2 expression correlates with increased angiogenesis in ovarian carcinoma

R. Ali-Fehmi[1], Z. Al-Wahab[1], A. Semaan[1], S. Seward[1], R. Morris[1], A. Munkarah[1,2], A. Sood[3]

[1]Wayne State University, Detroit, MI, [2]Henry Ford Health System, Detroit, MI, [3]University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: We recently discovered EZH2, a polycomb repressor, to have substantially increased expression in tumor endothelial cells. In this study, we examined the clinical and functional significance of EZH2 and its correlation with VEGF and angiogenesis in ovarian carcinoma.

Mouse ovarian endothelial cells (MOEC) were transfected with the Renilla luciferase plasmid either with or without the EZH2 promoter construct. Cells were then treated with VEGF (conditioned medium from SKOV3 ovarian cancer cells [SKOV3-CM]). EZH2 mRNA was quantified using real-time RT-PCR. EZH2 protein levels were evaluated with Western blot. One hundred eighty paraffin-embedded epithelial ovarian cancer specimens (collected between 1985 and 2004) with available clinical outcome data were identified. Immunohistochemistry (IHC) for EZH2, CD34, and VEGF was performed. For EZH2 and VEGF, the stained slides were scored based on intensity and percentage of cells stained and categorized as high and low expressors. Microvessel density (MVD) was quantified as the number of blood vessels staining positive for CD34 in 10 high-power fields, and the mean was calculated. Clinical parameters and survival data were obtained from the clinical information system and SEER registry.

Results: In MOEC, there was a significant increase in EZH2 promoter activity and EZH2 mRNA expression levels in response to VEGF (SKOV3-CM). This increase in EZH2 promoter activity and mRNA was blocked by the VEGFR2-specific antibody DC101. The increase in EZH2 protein levels in response to VEGF was blocked by the anti-VEGFR2 antibody. Using IHC, EZH2 expression was evaluated in 180 cases in both tumor and endothelial compartments (EZH2-T and EZH2-E). Sixty-six and sixty-seven percent of the samples showed high EZH-2 expression in the tumor and endothelial compartments, respectively. High expression of EZH2-T and EZH2-E was significantly associated with high-stage ($P<0.001$) and high-grade ($P<0.05$) disease. High EZH2-T and EZH2-E expression was also significantly associated with decreased overall survival (median: 2.5 years vs 7.33 years, $P<0.001$, for EZH2-T; 2.33 vs 8.33 years, $P<0.001$, for EZH2-E). Tumors with high VEGF expression were significantly correlated with high EZH2-E expression ($P<0.001$). Moreover, tumors with high EZH2-E expression also had significantly greater MVD ($P<0.001$).

Conclusions: These findings suggest that EZH2 may be a regulator of tumor angiogenesis and support the possibility of its being a therapeutic target in ovarian carcinoma.

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Identification and characterization of CD44+/CD24–ovarian cancer stem cell properties and their correlation with survival

E. Meng, L. Shevde, B. Long, P. Sullivan, S. McClellan, M. Finan, E. Reed, R. Rocconi

University of South Alabama Mitchell Cancer Institute, Mobile, AL

Objective: Cancer stem cells are considered to be primarily responsible for cancer self-renewal, invasion, and resistance to therapy. We describe a subpopulation of ovarian cancer cells with the surface marker profile CD44+/CD24– that exhibits the cancer stem cell properties of enhanced differentiation, invasion, resistance to therapy and correlation with survival.

Fluorescence-activated cell sorting (FACS) was used to sort ovarian cancer cell lines (TOV112D, OV90, SKOV3, ES2) into two phenotypically distinct populations: OCSC (CD44+/CD24–) and non-OCSC (all other phenotypes). Each phenotype was evaluated in a serial differentiation experiment to determine the level of differentiation at 24, 48, and 72 hours. Invasion properties were measured using the Matrigel invasion assay. Cells were treated with carboplatin, paclitaxel and paclitaxel + carboplatin and evaluated with the MTS cell survival assay to determine relative resistance to chemotherapy. Ascites derived from 20 patients with advanced-stage ovarian cancer was obtained and evaluated for the proportion of CD44+/CD24– cells and its correlation with survival.

Results: The proportion of CD44+/CD24– cells corresponded to the clinical aggressiveness of each ovarian cancer cell line histologic subtype: in order of increasing aggressiveness, endometrioid, TOV112D––0.5%; papillary serous, SKOV3––66% and OV90––77%; and clear cell, ES2––99%. OCSC demonstrated enhanced progressive

differentiation for OCSC with 93, 87, and 77% at 24, 48 and 72 hours, respectively. Compared with non-OCSC, OCSC showed a 60-fold increase in Matrigel invasion in both SKOV3 and OV90 cell lines ($P<0.001$ each). OCSC demonstrated significant resistance to all chemotherapy agents used in all cell lines, with a 71–93% increase in resistance compared with baseline. After confirmation by CK7 immunofluorescence staining, ovarian cancer cells obtained from ascites were evaluated for the proportion of CD44+/CD24– cells (range: 3.7–97.7%). Using a threshold of 25% CD44+/CD24– cells, patients with >25% OCSC were significantly more likely to recur (83% vs 14%, $P=0.003$) and had shorter median progression-free survival (six months vs 18 months, $P = 0.01$).

Conclusions: We have identified a phenotype of ovarian cancer stem cells that demonstrate the properties of enhanced differentiation, invasion, and resistance to chemotherapy. This CD44+/CD24– phenotype correlates with in vitro aggressiveness as well as prognosis with increased risk of recurrence and shorter progression-free survival in patients with ovarian cancer.

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Induction of apoptosis in cisplatin-resistant ovarian cancer cells by G-1, a specific agonist of the G-protein-coupled estrogen receptor GPR30

T. Nguyen[1], E. Ariazi[1], E. Brailoiu[2], G. Brailoiu[2], J. Taylor[1], J. Boyd[1]
[1]*Women's Cancer Program, Fox Chase Cancer Center, Philadelphia, PA,* [2]*Temple University School of Medicine, Philadelphia, PA*

Objective: Most patients with ovarian cancer given adjuvant platinum-based chemotherapy relapse with platinum-resistant disease. High expression of G-protein-coupled estrogen receptor GPR30 has been associated with poor prognosis in ovarian cancer. We recently showed that the synthetic GPR30 agonist G-1, which does not bind classic estrogen receptors, greatly inhibits MCF-7 breast cancer cell growth due to high and sustained cytoplasmic calcium (Ca^{2+}) levels. Here, we test whether G-1 also displays therapeutic potential against isogenic platinum-sensitive and -resistant ovarian cancer cell lines.

The A2780 ovarian cancer cell line was derived from a platinum-naïve patient. A series of cisplatin-resistant subclones were previously derived by exposure to increasing concentrations of cisplatin and termed CP70 (10- to 50-fold resistant), C30 (50- to 100-fold resistant) and C200 (300- to >1000-fold resistant). The effects of G-1 on cell proliferation and apoptosis, regulation of GPR30 mRNA expression, Ca^{2+} mobilization and apoptotic markers were examined using standard assays.

Results: At 500 nM, G-1 significantly inhibited A2780 cell growth by 55%, and growth of platinum-resistant CP70, C30, and C200 cells by 26, 74 and 54%, respectively. At 2.5 μM, G-1 blocked growth by ≥85% in all cell lines, and caused apoptosis/death in 76, 42, 40 and 32% of A2780, CP70, C30, and C200 cells, respectively. A2780 and C30 cells were further examined using G-1 at 2.5 μM. G-1 repressed GPR30 mRNA levels by 72% in A2780 cells and 47% in C30 cells. Within five–10 minutes of G-1 stimulation, cytoplasmic Ca^{2+} levels increased by 203 nM in A2780 and by 1017 nM in C30 cells. Antiapoptotic Bcl-2 protein was overexpressed in C30 cells relative to A2780 cells, possibly explaining why higher Ca^{2+} levels in C30 cells were necessary to induce apoptosis versus A2780 cells. G-1 induced p53 protein expression and cleavage of caspase-9, caspase-3, and PARP in both cell lines.

Conclusions: G-1 dramatically blocked growth and induced apoptosis in both platinum-sensitive and -resistant ovarian cancer cells. The underlying mechanism likely involves calcium overload, possibly leading to mitochondrial Ca^{2+} uptake and membrane disruption and, then, cleavage of caspase-9, caspase-3, and PARP. G-1 has been observed to have low toxicity in animal models. Thus, G-1 shows great potential for therapeutic use in platinum-sensitive and -resistant ovarian cancer.

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Insulin promotes proliferation and carcinogenesis of normal endometrial cells

E. Bishop, S. Lightfoot, D. Benbrook
University of Oklahoma, Oklahoma City, OK

Objective: Diabetes and insulin resistance are strong risk factors for type 1 endometrial cancer. The mitogenic actions of insulin are well described, but less is known about the role insulin may play in carcinogenesis. Key pathways within the insulin signaling cascade, such as Ras-MAPK and PI 3-K-mTOR, are also involved in the formation and progression of many cancers. The goal of this study was to determine if insulin exerted direct effects on normal endometrial cell proliferation and carcinogenesis.

The effects of varying doses of insulin on endometrial cells collected from human menstrual blood from healthy volunteers were measured using a standard MTS cytotoxicity assay. These cells were also grown in 3-D organotypic culture for two weeks and exposed to a known carcinogen, 7,12-dimethylbenz[α]anthracene (DMBA), insulin and the combination of both agents. Effects of insulin were evaluated by histologic evaluation and quantified with anchorage-independent growth assays.

Results: Insulin increased proliferation of endometrial cells in a dose-dependent fashion. In the organotypic model, insulin caused the development of malignant features such as nuclear pleomorphism, hyperchromasia, and mitosis as a single agent and enhanced these malignant features in the DMBA-treated cultures. Consistent with these findings, soft agar colony-forming assays demonstrated significantly greater numbers of anchorage-independent colonies in cultures treated with insulin plus DMBA in comparison to cultures treated with DMBA alone.

Conclusions: Insulin exerts direct effects on endometrial cells by increasing their proliferation and enhancing their susceptibility to carcinogenesis. This work justifies further investigation into the mechanisms of these effects.

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MicroRNA and messenger RNA pathways associated with ovarian cancer cell sensitivity to topotecan, gemcitabine and doxorubicin

X. Stickles, E. Bicaku, D. Marchion, N. Chen, Y. Xiong,
J. Gonzalez Bosquet, R. Wenham, S. Apte, J. Lancaster
H. Lee Moffitt Cancer Center, Tampa, FL

Objective: Chemosensitivity is a major determinant of clinical outcome for patients with ovarian cancer (OVCA). However, the molecular basis to chemoresponse remains to be fully characterized. We have previously reported that microRNAs (miRNAs), which influence messenger RNA (mRNA) posttranscriptional control and contribute to human carcinogenesis, may also influence cancer cell response to chemotherapy. In the current study, we sought to identify those miRNAs associated with ovarian cancer cell response to topotecan, gemcitabine and doxorubicin.

The expression of 335 unique miRNAs was measured in 36 OVCA cell lines using custom-printed arrays. In parallel, the sensitivity

(IC_{50}) of these cell lines to topotecan, gemcitabine, and doxorubicin was determined with the CT-Blue cell proliferation assay. Pearson correlation identified miRNAs associated with OVCA cell line drug sensitivity. Predicted mRNA targets of identified miRNAs were subject to functional biologic pathway analyses.

Results: Pearson correlation identified three miRNAs (miR_144, miR_219, miR_496) associated with doxorubicin sensitivity ($P<0.01$), five miRNAs (miR_196, miR_410, miR_501, miR_9, miR_30-a_3p) associated with topotecan sensitivity ($P<0.01$), and six miRNAs (miR_183, miR_296, miR_512_3p, miR_518e, miR_515_5p, miR_302a) associated with gemcitabine sensitivity ($P<0.05$). Predicted mRNA targets of these miRNAs included representation of 24 pathways that were associated with doxorubicin resistance ($P<0.001$), five pathways with gemcitabine resistance ($P<0.01$), and 10 pathways with topotecan resistance ($P<0.01$). Two pathways (calcium signal transduction and dopamine 2 receptor transactivation of PDGFR) were associated with responsiveness to all three agents.

Conclusions: We have identified miRNAs and their predicted target mRNAs associated with ovarian cancer cell response to three widely used chemotherapeutic agents. Integration of miRNA and mRNA data may aid in the characterization of important molecular pathways associated with OVCA chemoresponse.

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Molecular profiling of patients with curatively treated advanced serous ovarian carcinoma from The Cancer Genome Atlas

D. Levine
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: Ovarian cancer mostly presents at an advanced stage and has a low overall survival rate. However, there is a subgroup of patients who present with advanced-stage disease, receive standard initial therapy, and are seemingly cured. Understanding the molecular composition of these patients' tumors may help us to improve the treatment of those who do suffer recurrence. We hypothesized that molecular profiles of survivors who are seemingly cured by initial treatment would differ from those of survivors who have had recurrences.

Patients from The Cancer Genome Atlas (TCGA) with stage IIIC or IV, high-grade serous ovarian carcinoma who have survived more than five years without recurrent disease constituted the curative group. Similar TCGA patients who recurred but still survived more than five years constituted the recurrent group. Fresh-frozen tumor tissues were collected at the time of initial surgery, and nucleic acids were extracted at the TCGA Biospecimen Core Repository. Gene expression profiling was performed on three transcriptome microarrays and one microRNA array. Unsupervised clustering and supervised class comparison were performed. Pathway analyses were performed using Ingenuity Pathways Analysis (IPA).

Results: Sixteen curative and 42 recurrent patients were identified from the TCGA data using the criteria outlined. Ninety-four percent of patients had platinum-sensitive disease and 64% were optimally cytoreduced, with no significant differences between the two groups. Unsupervised cluster analysis of both RNA and miRNA data identified three main clades, with no segregation between the curative and recurrent groups. Class comparison of the RNA data using the 7180 most variable probe sets identified 19 differentially expressed probes between the two groups at a relatively stringent *P* of 0.001, more than the seven expected by chance alone. At a more relaxed *P* of 0.01, pathway analyses with 158 probes identified overrepresented networks that included NFkB transcription, ERK signaling, and MYC oncogenesis. Class comparison of the miRNA data using all 723 genes identified only four differentially expressed microRNAs between the two groups at a *P* of 0.01.

Conclusions: The data identify active transcriptional regulation in patients with ovarian cancer likely to be cured with initial surgical cytoreduction and adjuvant chemotherapy. MicroRNA expression does not appear to affect recurrence potential in these long-term survivors. Knowledge of the molecular features associated with curative treatment may help to target pathways for new therapeutic approaches.

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Neuropilin-1 blockade in the tumor microenvironment reduces tumor growth

A. Nick[1], R. Stone[1], J. Bottsford-Miller[1], W. Spannuth[2], N. Jennings[1], A. Bagri[3], R. Coleman[1], A. Sood[1]
[1]*University of Texas M.D. Anderson Cancer Center, Houston, TX,* [2]*Medical University of South Carolina, Charleston, SC,* [3]*Genentech, Inc., San Francisco, CA*

Objective: Neuropilin-1 (NRP1) is a VEGF co-receptor expressed on tumor and endothelial cells. On the basis of the known role of pericytes in the tumor vasculature, we examined the functional and biologic significance of targeting NRP1 in ovarian cancer using a novel monoclonal antibody.

Neuropilin-1 expression was examined in ovarian cancer, endothelial and pericyte-like cell lines. In vivo effects of NRP1 blockade (anti-NRP1B antibody) with or without a VEGF-targeted antibody were examined. To isolate the impact of blocking NRP1 in the tumor microenvironment, we chose a NRP1-null cancer cell line for in vivo experiments. To determine mechanisms associated with NRP1 blockade, staining for CD31, ki67 and TUNEL was performed on tumors obtained from in vivo experiments. To determine the role of perivascular cells in NRP1 blockade, a sandwich ELISA was performed using PDGF-BB, a known pericyte regulator.

Results: Blockage of NRP1 using anti-NRP1B antibody reduced tumor growth in the NRP1-null model by 70%. The anti-NRP1B antibody plus anti-VEGF antibody group demonstrated the greatest reduction in tumor growth (96% reduction compared with controls, $P=0.01$). In vivo NRP1 blockade resulted in a 71% decrease in microvessel density (MVD) ($P<0.001$) and no change in tumor cell proliferation or apoptosis. Combined NRP1 and VEGF blockade yielded a 67% decrease in MVD ($P<0.001$) and a 25% decrease in tumor cell proliferation ($P=0.007$). Sandwich ELISA revealed PDGF-BB direct binding to NRP1 at 1 nM. Furthermore, anti-NRP1B yielded a 63% reduction in PDGF-BB-stimulated pericyte-like cell migration ($P<0.001$) and a 46% reduction in VEGF-stimulated tumor cell migration ($P<0.05$).

Conclusions: Neuropilin-1 is overexpressed in both ovarian cancer cells and the tumor vaculature. Targeting NRP1 in the tumor microenvironment reduces vascular maturation and sensitizes the vasculature to anti-VEGF therapy. As such, NRP1 represents an attractive therapeutic target for further development.

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Ovarian cancer lymph node metastases express unique cellular structure and adhesion genes

M. Spillman, N. Manning, W. Dye, K. Horwitz
University of Colorado Anschutz Medical Campus, Aurora, CO

Objective: Lymph node metastases (LNM) of ovarian cancer outside the peritoneal cavity occur in approximately 30% of cases. These nodal metastases are generally viewed as a poor prognostic feature. In this study, we sought to identify the gene expression pattern targeting ovarian cancer cells to lymph nodes and to contrast the LNM pattern with the gene expression pattern of abdominal ovarian cancer cells (ABT).

Ovariectomized athymic nude mice received fluorescent xenografts of ER+ PEO4 human ovarian cancer cells. Estrogen replacement therapy was given by subcutaneous 17β-estradiol Silastic pellet for 11 weeks. Growth of ABT was followed by external fluorescence, and identification of LNM at time of necropsy was assisted by fluorescence. Intraperitoneal abdominal ovarian tumors and mediastinal LNM were harvested from the same mouse and flash-frozen. Laser capture was used to isolate tumor cells from surrounding mouse tissues, and RNA was made. Four ABT and paired LNM cDNAs were hybridized to Affymetrix U133 Plus 2 gene chip microarrays. Significant expression differences were defined by a paired *t*-test P value < 0.05 and expression difference > 1.5-fold.

Results: Two distinctly different gene expression patterns were defined. The top 30 genes upregulated in LNM (↑LNM) as compared with paired ABT were concentrated in cellular structure and adhesion. This group included neuronal cell adhesion molecule (NRCAM), keratin 13 (KRT13) and kallikrein-related peptidase 10 (KLK10). Significantly, the α2,6-sialytransferase (ST6GALNAC5), which has been previously defined as a breast cancer brain metastatic factor, was upregulated in ovarian LNMs. KLK10 overexpression has been previously shown to be a poor prognostic factor in late-stage ovarian cancer. Genes associated with growth in the native peritoneal site (↑ABT) were growth factor-associated proteins such as cellular retinoic acid-binding protein 1 (CRABP1), fibroblast growth factor receptor 1 (FGFR1), inhibin beta-A (INHBA), and neuropilin 2 (vascular endothelial growth factor-165 receptor 2). A different complement of cellular adhesion factors were upregulated, including gap junction protein gamma1 (GJC1), collagen type IIIα (COL3A1), tubulin beta 2B (TUBB2), and layilin (LAYN).

Conclusions: A switch in the cadre of cellular structure and adhesion molecules expressed in ovarian cancer cells may promote LNM. Targeting of these molecules could provide selective therapy for ovarian cancer cells in lymph node sanctuary sites.

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Overexpression of fibroblast growth factor 1 and fibroblast growth factor receptor 4 in high-grade serous ovarian carcinoma: Correlation with survival and implications for therapeutic targeting

T. Zaid[1], M. Thompson[1], K. Wong[1], T. Yeung[1], Z. Yeung[1], S. Kwan[1], C. Co[1], R. Schmandt[1], M. Birrer[2], S. Mok[1]
[1]*University of Texas M.D. Anderson Cancer Center, Houston, TX,* [2]*Massachusetts General Hospital/Harvard University, Boston, MA*

Objective: The purpose of this study was to correlate expression of fibroblast growth factor receptor 4 (FGFR4) to overall survival (OS) in advanced-stage high-grade serous ovarian carcinoma (HGSC) and to evaluate pathways involved in the fibroblast growth factor 1 (FGF1)/FGFR4 HGSC signal axis and the feasibility of therapeutic targeting.

FGF1 and FGFR4 DNA copy numbers were determined by quantitative PCR in 52 HGSC samples. OS was correlated with FGFR4 expression quantified by immunohistochemistry in 188 HGSC cases. Western blotting (WB) was used to quantify FGFR4 expression in HGSC cell lines and HOSE. ELISA was used to quantify FGF1 in conditioned medium from HGSC cell lines. The effects of FGF1 on proliferation, migration, invasion and chemoresistance of HGSC in vitro were quantified; experiments were repeated with FGFR4 knockdown and a FGFR4 trap. FGF1-activated signaling pathways in HGSC were identified by treating HGSC cell lines expressing transcription response elements linked to luciferase with FGF1. Reverse-phase protein array (RPPA) was used to screen for changes in protein expression and phosphorylation after treatment with FGF1 with WB confirmation. The FGFR4 kinase domain was sequenced in 43 HGSC samples.

Results: FGFR4 was amplified and overexpressed in all HGSC cell lines compared with HOSE. FGFR4 and FGF1 DNA copy numbers were significantly correlated ($r = 0.4$, $P = 0.04$). FGFR4 staining intensity correlated with poor OS in HGSC patients (28 months vs 55 months, $P < 0.001$). FGF1 significantly increased proliferation only in high FGFR4-expressing HGSC cells (20–60%, $P < 0.001$). This effect was abolished by silencing FGFR4 or by treatment with a FGFR4 trap. Migration and invasion of HGSC cell lines expressing FGFR4 in collagen matrix were increased significantly by FGF1 (10%, $P = 0.04$). FGF1 had no effect on chemoresistance in vitro. RPPA and the luciferase reporter assay demonstrated activation of multiple pathways (MAPK, PI3K, WNT, and NFKB) in response to FGF1. Pathway activation was successfully inhibited by silencing FGFR4 or FGFR4 trap treatment. Sequencing of the FGFR4 kinase domain did not reveal any mutations.

Conclusions: Our work suggests that concurrent amplification and overexpression of FGF1 and FGFR4 located on 5q31–35 is associated with poor survival in advanced-stage HGSC. Our in vitro data provide evidence that FGF1 binding to FGFR4 activates multiple cellular pathways leading to a more aggressive cancer phenotype. Inhibition of FGF1 effects by the FGFR4 trap in vitro suggests that targeting patients with an activated FGF1/FGFR4 axis in their tumors using trap proteins may be a therapeutic strategy with potential for improving survival in advanced-stage HGSC.

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Phosphatase and tensin homolog (PTEN) pseudogene expression in endometrial cancer: A conserved regulatory mechanism important in tumorigenesis?

Y. Ioffe[1], K. Chiappinelli[2], P. Pollock[3], M. Powell[2], I. Zighelboim[2], P. Thaker[2], D. Mutch[2], P. Goodfellow[2]
[1]*Washington University, St. Louis, MO,* [2]*Washington University School of Medicine, St. Louis, MO,* [3]*Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, Australia*

Objective: The PTEN pseudogene PTENP1 was recently shown to play a role in cell proliferation in prostate cancer. PTENP1 acts as a "decoy" for microRNAs (miRNAs) that target the PTEN tumor suppressor. The 3' UTRs of PTEN and PTENP1 share common binding sites for eight microRNAs. In a prostate cancer cell line model, miRNA binding to the overexpressed PTENP1 modulated PTEN levels and led to cell growth inhibition. As a first step toward determining if PTENP1 might also play a role in endometrial tumorigenesis, we sought to determine whether PTENP1 is expressed in endometrioid endometrial cancer (EMCA) cell lines and primary tumors along with miRNAs that are predicted to regulate PTEN and PTENP1 levels.

RNA was prepared from six EMCA cell lines (AN3CA, HEC1A, KLE, Ishikawa, MFE296, RL952), two prostate cancer cell lines (PC3 and DU145), and 50 primary tumors. PTEN and PTENP1 transcript levels were evaluated using semiquantitative RT-PCR. TaqMan RT-PCR was used to quantitate expression of PTEN and PTENP1 transcripts. We then compared the levels of the two transcripts in EMCA cell lines. MicroRNA profiling was undertaken using NanoString technology to quantitate the expression of 749 miRNAs in EMCA cell lines and primary tumors.

Results: All six EMCA cell lines expressed PTEN. Among those, PTENP1 was expressed at modest levels in KLE and MFE296 and at much lower levels in Ishikawa and RL952, and was not expressed in the AN3CA and HEC1A cell lines. MicroRNA profiling of the KLE and AN3CA cell lines revealed that all eight miRNAs predicted to bind to PTEN and PTENP1 3' UTR (miR-20a, miR-19b, miR-21, miR-26a, miR-17, miR-216, miR-214 and miR-217) are expressed at high levels. In KLE, miR-21 was the 3rd most abundant miRNA, miR-19b was the 9th, and miR-26a was the 16th most abundant miRNA. In AN3CA, miR-749 was the 14th most abundant miRNA, miR-19b was 18th, and miR-26a ranked 19th. Twenty-eight of 50 primary EMCA tumors expressed PTENP1. MicroRNA profiling in primary tumor specimens is currently underway.

Conclusions: The pseudogene PTENP1 is expressed in EMCA cell lines and tumors, along with PTEN/PTENP1 targeting microRNAs. The PTEN/PTENP1/miRNA mediated growth regulation in which PTENP1 interacts with miRNAs is likely to be conserved in endometrial cancer. Functional studies in EMCA cell lines and tumors are required to assess the impact of PTENP1 on PTEN expression and tumor-associated phenotypes.

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Proteasome inhibition increases death receptors and decreases major histocompatibility complex I expression: Pathways to exploit in natural killer cell immunotherapy

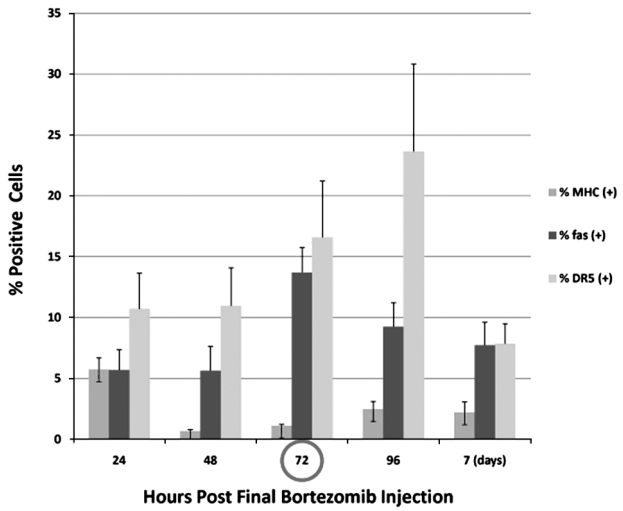
M. Geller, L. Priby, L. Rogers, J. Miller
University of Minnesota, Minneapolis, MN

Objective: Natural killer (NK) cells play a role in tumor suppression and are an attractive candidate for immune-based cellular therapy. The proteasome inhibitor bortezomib has been shown in other tumors to upregulate tumor death receptors for Fas ligand (FasL) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) as well as downregulate major histocompatibility complex I (MHCI), making target cells more susceptible to NK cell killing. We sought to determine if pretreatment of ovarian tumor in a xenograft model with intraperitoneal bortezomib could increase death receptors for FasL and TRAIL (DR5) and downregulate MHCI.

Forty-four T cell-, B cell-, NK cell- and dendritic cell-deficient mice (NOD/SCID/λcnull) mice were inoculated intraperitoneally with MA148 tumor cells. NK cell product was prepared by CD3 and CD19 depletion of a single leukapheresis collection from a healthy human donor. Following tumor establishment, mice were randomized into the following intraperitoneal arms: bortezomib alone given one day prior to the NK cells; activated NK cells (activated ex vivo with 1000 U/mL interleukin [IL]-2) alone, activated NK cells + extended IL-2 injection at 25,000 U/day x seven days, and bortezomib + activated NK cells + extended IL-2 × 7 days. Mice were euthanized eight and 14 days following NK cell infusion. Primary and metastatic tumor was collected for flow cytometry analysis of Fas and MHC I. The timing of maximum upregulation of Fas and DR5 receptors and downregulation of MHC I was performed in a separate experiment following sacrifice of mice 24, 48, 72, and 96 hours and seven days following two bortezomib doses (1 mg/kg IP) given four days apart.

Results: Mice tolerated NK cell therapy alone and in combination with bortezomib and IL-2. Fas receptor expression was nine-fold greater in primary and metastatic tumor over control for bortezomib treatment arms eight days following NK cell injection. A 10-fold decrease in MHCI was observed in both primary and metastatic tumor in the bortezomib-treated arms. Fourteen days following NK injection, these trends reverted to baseline. Maximum upregulation of Fas and DR5 receptors and downregulation of MHCI occurred 72 hours after bortezomib dosing (see figure).

Conclusions: Our in vivo findings indicate bortezomib may play a key role in sensitizing ovarian cancer to NK cell killing by upregulating the death receptor for Fas ligand and TRAIL and downregulating MHCI in MA-148 cells. These findings suggest that pretreatment of ovarian cancer with bortezomib 72 hours prior to administering donor NK cells may be a pathway to exploit in NK cell immunotherapy.



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Proteomic analysis demonstrates that BRCA1-deficient epithelial ovarian cancer cell lines activate alternative pathways following exposure to cisplatin

J. Lesnock[1], B. Hood[1], M. Sun[1], B. Teng[1], B. Rungruang[1], M. Flint[1], T. Krivak[1], T. Conrads[2]
[1]Magee–Womens Hospital of UPMC, Pittsburgh, PA, [2]Women's Health Integrated Research Center, Anova Hospital, Fairfax, VA

Objective: Epithelial ovarian cancer (EOC) associated with BRCA1 mutations is particularly susceptible to platinum agents due to defective DNA damage repair. Although several studies have attempted to define genetic mechanisms underlying this deficiency, no studies at the level of the proteome have been done. Toward this end, we have conducted a global, relatively quantitative proteomic investigation to identify dysregulated protein pathways in BRCA1-deficient EOC cell lines challenged with cisplatin.

A cell line derived from a patient with papillary serous EOC with a known mutation in BRCA1 (UWB1.289) and its isogenic partner with BRCA1 function restored (UWB1.289 + BRCA) were exposed to cisplatin at their respective IC_{50} concentrations for 72 hours. A global, quantitative proteomic analysis was performed on the treated and

untreated cells from each using high-resolution mass spectrometry. Raw mass spectrometric data were processed and analyzed for variations in the spectral counts of peptides between sample sets and bioinformatics was accomplished using Ingenuity Pathways Analysis (IPA).

Results: The total numbers of proteins and peptides identified are listed in the table. Cisplatin-treated UWB1.289 cells had 458 upregulated and 748 downregulated proteins compared with untreated cells, with a spectral count difference ≥2. A group of molecules associated with an oxidative stress response pathway were noted to be significantly upgraded compared with the untreated line. This pathway includes nine molecules involved in cellular defense responses to oxidative stress, and two molecules in this pathway are inhibited by cisplatin. It is not significantly upregulated within the BRCA1-restored cell line after treatment. Following cisplatin treatment of the UWB1.289 + BRCA cell line, there was a significant upregulation of caspase signaling factors, which are involved in apoptosis and cleavage of DNA damage sensors. This pathway is downregulated in UWB1.289-treated cells.

Conclusions: BRCA1 dysfunction is an important factor in the response to treatment with platinum for patients with EOC. Our results indicate that a number of auxiliary protein signaling pathways are activated in BRCA1-deficient EOC cell lines in response to cisplatin exposure. Specifically, upregulation of oxidative stress pathway molecules and inhibition of caspase-induced cleavage of DNA damage sensors within the BRCA1-deficient cell line may represent mechanisms of compensation for inadequate DNA repair.

	UWB1.289 No treatment	UWB1.289 Cisplatin	UWB1.289 + BRCA1 No treatment	UWB1.289 + BRCA1 Cisplatin
Proteins	2,482	2,221	2,438	2,160
Peptides	23,964	21,980	22,395	21,199

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Quantitative PCR array identification of microRNA clusters associated with epithelial ovarian cancer chemoresistance

D. Fishman, F. Wang, A. DiFeo, G. Narla
Mt. Sinai School of Medicine, New York, NY

Objective: Despite improved chemotherapy regimens, chemoresistance remains a challenge for the treatment of epithelial ovarian cancer (EOC). Meanwhile, effective biomarkers to predict an individual's response to a distinct therapy are lacking. In the present study, we aimed to identify chemoresistant EOC-associated microRNA (miRNA) signature and explore the possibility of developing a miRNA-based novel therapeutic strategy to overcome chemoresistance.

The expression profile of 88 cancer-related miRNAs was determined using a 96-well plate cancer RT2 miRNA PCR array from SA Biosciences in an in vitro cell culture model composed of ovarian cancer cell line A2780 (sensitive) and its cisplatin-resistant variants CP20 (moderately resistant) and CP70 (resistant) (Fig. A). Total RNA was extracted using the TRIzol reagent (Invitrogen) and reverse transcribed using the RT2 miRNA First Strand Kit from SA Biosciences.The resulting cDNA was then diluted, mixed with 2× RT2 SYBR Green PCR Master Mix (SA Biosciences), and loaded into the wells of a PCR array plate to allow real-time PCR amplification and detection. Data analysis was performed with the Web-based software package for the miRNA PCR array system. Cells undergoing apoptosis were measured by FACS on cisplatin treatment to determine the apoptotic index.

Results: Among the 88 miRNAs profiled, 15 were significantly overexpressed in CP70 cells and 7 were significantly downregulated in CP70 cells as compared with A2780 (absolute fold change >5, $P<0.05$). Hierarchical clustergram analysis was performed to show the cluster of those miRNAs (Fig. B). Correlation analysis of the expression of those miRNAs with the apoptotic index of A2780, and its resistant variants, CP20 and CP70, revealed a panel of miRNAs associated with cisplatin response. Of those miRNAs that are overexpressed in cisplatin-resistant cell lines (CP20 and CP70) as compared with A2780, 7 showed a positive linear correlation with cell resistance (Fig. C) ($R^2>0.9$). Of the 7 miRNAs that were significantly downregulated in CP70 cells, 5 (miR-17, -18a, -19a, -20a, and -125b) showed a negative linear correlation with chemoresistance (Fig. D) ($R^2>0.9$), among which miR-17 displayed a perfect correlation ($R^2=0.9999$).

Conclusions: Our results suggest the complexity of miRNA regulation in chemoresistance, and the miRNA panels identified in our preliminary study open a new avenue for the study of miRNA biology and function evaluation in chemoresistance.

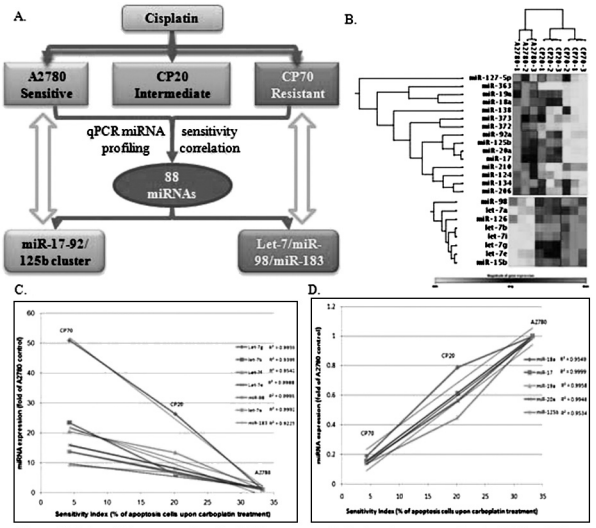

Figure 1. Eighty-eight cancer-related miRNAs were profiled using the cancer-related miRNA qPCR array from SA bioscience. **A.** Schematic view of our *in vitro* model for miRNA profiling in OvCa cell lines of varied response to cisplatin. **B.** Clustergram view of representative miRNAs identified to be differentially expressed in sensitive OvCa cells and its resistant variants. Note, miR-17-92 cluster miR-125b and let-7/miR-98 are shown clustered together. **C.** miRNAs that are positively correlated with EOC resistant phenotype to cisplatin. **D.** miRNAs that are negatively correlated with EOC resistant phenotype to cisplatin. The miRNA expression in **C. and D.** was presented as fold of that in A2780 (y-axis) against the sensitivity of each cell line (x-axis).

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Stop and smell the volatile organic compounds: A novel breath-based bioassay for detection of ovarian cancer

A. Nick, R. Stone, J. Bottsford-Miller, P. Ramirez, C. Tung, G. Armaiz-Pena, E. Felix, A. Sood
University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: The high mortality rate of ovarian carcinoma is attributed in part to the lack of an adequately sensitive screening modality. Breath analysis offers a painless, noninvasive technique of separating and identifying volatile hydrocarbons using gas chromatography/

mass spectroscopy (GC/MS). The aim of the current work was to determine the feasibility of using exhaled volatile organic compounds to identify ovarian cancer.

Preclinical breath samples were concentrated using a solid-phase microextraction (SPME) fiber and thermally desorbed within a GC inlet, and detected volatile organic peaks in the breath were identified with MS using the NIST library. Based on our preclinical findings, we designed a prospective clinical study powered to detect statistically significant differences between patients with and without pathologically confirmed ovarian carcinoma using the breath-based bioassay.

Results: Using an orthotopic preclinical model, breath was collected when animals had palpable tumor. Comparisons of total ion chromatograms of tumor- and non-tumor-bearing mice revealed a differentially expressed peak that was identified as butyrolactone (on average 2.5-fold higher in abundance among tumor-bearing mice). To date, we have successfully collected breath samples from 12 and 19 noncancer and cancer patients, respectively. Among patients with a pathologic diagnosis of benign pelvic mass, 53% had endometriosis. Nine of 19 patients (47%) with a pathologically confirmed malignancy had high-grade serous carcinoma; the remaining patients had endometrioid, clear cell or low-grade serous carcinoma. All but one patient had advanced-stage (III or IV) disease, and only one patient had known pulmonary metastases (malignant pleural effusion). To date, there is reproducibility of chromatograms between patients and healthy controls with identification of two differentially expressed peaks between cancer and noncancer patients (oxime-methoxy-phenyl, 7-fold vs 9-fold, and 1-hexanol-2-ethyl, 8-fold vs 10.5-fold, respectively).

Conclusions: We demonstrate that exhaled breath collection among patients with ovarian carcinoma is feasible and well tolerated, highlighting a novel technique for detection of ovarian carcinoma.

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Stress and the metastatic switch in epithelial ovarian carcinoma

M. Shahzad[1], J. Arevalo[2], R. Stone[3], G. Armaiz-Pena[3], J. Bottsford-Miller[3], A. Nick[3], S. Lutgendorf[4], G. Lopez-Berestein[3], S. Cole[2], A. Sood[3]

[1]University of Wisconsin School of Medicine and Public Health, Madison, WI, [2]UCLA School of Medicine, Los Angeles, CA, [3]University of Texas M.D. Anderson Cancer Center, Houston, TX, [4]University of Iowa Hospitals and Clinics, Iowa City, IA

Objective: Studies are now starting to link neurobehavioral stress to accelerated tumor growth and metastasis due to sustained sympathetic nervous system (SNS) activation. However, the exact mechanism of stress-induced metastasis is currently unknown. Here we examine the molecular and biologic significance of interleukin (IL)-8 in stress-induced tumor metastasis.

Interleukin-8 expression was determined by real-time RT-PCR and ELISA. IL-8 promoter activity was assessed using luciferase reporter constructs. Activation of specific AP1 family components (c-fos, FosB, Fra1, cJun, JunB, and JunD) by norepinephrine was examined by detecting nuclear accumulation of individual proteins using ELISA. In vivo effects of chronic stress were determined using several metastasis-specific orthotopic ovarian cancer models (SKOV3ip1 and HeyA8), and gene silencing (IL-8 and AP1 complex components) was achieved with siRNA incorporated into liposomal-DOPC.

Results: Norepinephrine treatment of ovarian cancer cells resulted in a 250–300% increase in IL-8 protein and 240–320% increase in its mRNA levels. Epinephrine treatment resulted in similar increases. Moreover, norepinephrine treatment resulted in a 3.5- to 4-fold increase in IL-8 promoter activity. These effects were blocked by propranolol. Promoter deletion constructs identified the AP1 complex as being responsible for the catecholamine-mediated increases in IL-8. Among the AP1 complex members, FosB was the pivotal component that was responsible for IL-8 regulation. In vivo daily restraint stress increased tumor growth by 235% (HeyA8, $P<0.008$) and 221% (SKOV3ip1, $P<0.001$). This enhanced tumor growth was completely prevented by IL-8 or FosB gene silencing. Similar effects were seen on tumor metastasis. In a metastasis-specific orthotopic ovarian cancer mouse model (SKOV3), daily restraint stress resulted in significantly higher (63%, $P<0.04$) tumor nodule counts and distant metastatic spread compared with control siRNA-DOPC. Concomitant treatment with IL-8 siRNA-DOPC or propranolol completely abrogated the stimulatory effects of daily restraint stress on tumor metastasis. In the setting of chronic stress, IL-8 and FosB silencing reduced microvessel density by 2.5- and 3.5-fold, respectively ($P<0.001$) and completely blocked the stimulatory effects of stress on tumoral protein levels of IL-8, MMP-2, and MMP-9.

Conclusions: Our findings suggest that chronic stress results in significant induction of FosB-driven increases in interleukin-8, leading to excessive tumor growth and metastasis.

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Targeting the hedgehog pathway reverses taxane resistance in ovarian cancer

A. Ziebarth[1], A. Steg[1], K. Bevis[1], A. Katre[1], R. Alvarez[2], C. Landen[1]

[1]UAB Comprehensive Cancer Center, Birmingham, AL, [2]University of Alabama, Birmingham, AL

Objective: Hedgehog (Hh) signaling pathways have been implicated in stem cell biology and chemotherapeutic resistance of several solid tumors, including breast cancer, hepatocellular carcinoma, and melanoma. Our objective was to explore the effects of targeting the Hh pathway as a means of reversing taxane resistance in ovarian cancer.

Ovarian cancer cell lines A2780ip2, SKOV3ip2, Hey A8, and their taxol-resistant derivatives A2780cp20 (also platinum resistant), SKTRip3 and HeyA8MDR were analyzed for expression of Hh pathway proteins (Smo, Gli 1) by Western blot and quantitative PCR. Cell lines were treated with three different Smo inhibitors: cyclopamine, LDE225 (Novartis) or CUR199691 (CUR, Genentech), alone and combined with paclitaxel. Knockdown of Smo, Gli1 and Gli2 was performed with siRNA. Cell viability was assessed by MTT assay and apoptosis by PARP cleavage. In vivo, SKTRip2 orthotopic xenografts were treated with vehicle, LDE225, paclitaxel or combination therapy for five weeks, and intraperitoneal tumor weights measured and compared using Student's t test.

Results: Smo was strongly expressed in the A2780ip2/A2780cp20 and SKOV3ip1/SKTRip3 cell lines, but low expression was noted in HeyA8/HeyA8MDR. Gli1 expression was high in A2780ip2/A2780cp20, moderate in SKOV3ip1/SKOV3TRip3 and absent in HeyA8/HeyA8MDR. Cyclopamine, LDE225, and CUR all inhibited growth in vitro with IC_{50} values in the range 7 to 20 μM for all cell lines. All agents also significantly sensitized all three taxane-resistant cell lines to paclitaxel, five- to 45-fold, even in the Smo[low] and Gli1 [neg] HeyA8MDR cell line. With specific siRNA-mediated targeting, sensitization to paclitaxel was noted with Smo, Gli1, and Gli2

knockdown only in the A2780cp20 cell line (three- to seven-fold increased sensitivity, no effect noted on platinum sensitivity). In vivo, mice with SKOV3TRip3 xenografts treated with LDE225 or paclitaxel alone had slightly less tumor burden than the control group (reduction in size by 28.1% [$P=0.42$] and 32.0% [$P=0.40$], respectively). However, those treated with combined LDE225 and paclitaxel had significantly less tumor burden than those treated with vehicle (70.5% reduction, $P=0.015$).

Conclusions: Targeting the hedgehog pathway induces significant antitumor activity in both taxane-sensitive and -resistant preclinical models of ovarian cancer. Further development of hedgehog pathway inhibitors in this disease context appears to be warranted.

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The cytoskeletal gateway for tumor aggressiveness in ovarian cancer is driven by class III β-tubulin

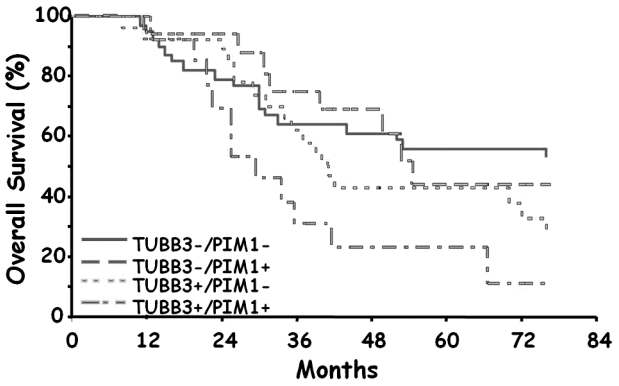
C. Ferlini[1], M. Mariani[2], S. Shahabi[2]
[1]*Danbury Hospital Research Institute, Danbury, CT,* [2]*Danbury Hospital, Danbury, CT*

Objective: Class III β-tublin (TUBB3) is a potent prognostic biomarker for ovarian cancer and other solid tumors. In this study we discovered a novel role for TUBB3 as gateway for cytoskeletal prosurvival signals.

Through genomic screening of a cell line made resistant to a drug whose activity is TUBB3 dependent, we identified two GTPases (GBP1 and GNAI1) whose expression is strictly related to TUBB3 expression. Using the technique of Far Western Blotting, we demonstrated that these GTPases physically interact with TUBB3. At variance with TUBB3, the two GTPAses can be overexpressed in vitro. Therefore, they serve as prey in a high-density protein microarray to identify protein kinases capable of interacting with them.

Results: Expression of two GTPases (GBP1 and GNAI1) was found to be directly related to TUBB3. With the use of transient overexpression, the functional roles of the two GTPases were ascertained: GBP1 is capable of activating the TUBB3 pathway, and GNAI1 inhibits this pathway. The physical interaction between the two GTPases and cytoskeletal proteins was confirmed with Far Western Blotting. At variance with TUBB3, the two GTPases can be expressed as recombinant proteins. In consideration of this fact, the two proteins served as prey in a high-density protein array. At least 18 protein kinases were capabe of interacting with both GTPases. Among these kinases, we focused our attention on PIM1. In fact, the occurrence of this interaction was proven in ovarian cancer cell lines, both sensitive and resistant to chemotherapeutics, using co-immunoprecipiation and, again, Far Western Blotting. For the first time, we discovered that PIM1 is expressed in the microtubules and its expression is directly related to resistance to paclitaxel and cisplatin, but not to epothilone-B. Finally, to analyze the translational value of our findings, we performed immunohistochemical analysis of TUBB3 and PIM1 expression in a clinical subset of 98 ovarian cancer patients. This approach revealed that patients who are double negative (TUBB3 and PIM1) have an overall survival (median = 76 months) better than that of patients who are double positive (median = 29 months).

Conclusions: TUBB3 is commonly believed to be a simple mechanism of paclitaxel resistance. This work demonstrated that TUBB3 is a non-drug-specific gateway into cytoskeleton for prosurvival signals like PIM1, and patients with ovarian cancer expressing both TUBB3 and PIM1 exhibit drug resistance and extremely short survival.



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The pattern of H3K56 acetylation expression in ovarian cancer

A. Liu[1], A. Wilson[1], T. Edwards[1], M. Williams[1], E. Holson[2], S. Bhaskara[1], S. Hiebert[1], J. Slaughter[1], O. Fadare[1], D. Khabele[1]
[1]*Vanderbilt University, Nashville, TN,* [2]*The Broad Institute, Cambridge, MA*

Objective: The histone marker H3K56 acetylation (H3K56ac)––newly recognized in mammals––is implicated in tumorigenesis and co-localizes with DNA damage response proteins in response to double-strand DNA breaks (DSBs). Histone deacetylase inhibitors (HDACi) sensitize cells to cisplatin, which is known to induce DSBs. Our objective was to evaluate the pattern of H3K56ac expression in ovarian cancer.

Expression levels of H3K56ac were examined by immunohistochemical (IHC) staining of tissue microarrays constructed from 210 specimens from patients treated for ovarian cancer at our institution from 1994 to 2004. The median age of the patients was 56.7. One hundred forty-four (69%) tumors were stages III and IV, and 148 (70%) had serous histology. IHC scores were based on staining intensity and distribution for a maximum score of 12. Induction of H3K56ac was measured in vitro by immunofluorescence (IF) and Western blot after treating SKOV-3 cells with HDACi compounds alone and in combination with cisplatin. The effects of the HDACi and cisplatin were evaluated by cell proliferation assays, IF, and Western blot.

Results: H3K56ac was elevated in proliferating, epithelial ovarian cancers and co-localized with mib-1 (a proliferation marker) and pan-keratin (an epithelial marker) in the tissue samples. High expression of H3K56ac (score >6) was observed in 174 (83%) tumors. In ovarian cancer cells exposed to HDACi compounds, H3K56ac activation was robust and prolonged. Similarly known markers of DNA damage response, gamma-pH2AX and RAD51, were activated by the HDACi. Induction of H3K56ac by the HDACi compounds was positively correlated with cell growth inhibition and apoptosis. Although the levels of H3K56ac decreased slightly in the presence of cisplatin alone, H3K56ac remained elevated in the presence of synergistic combinations of HDACi and cisplatin.

Conclusions: Elevated expression levels of H3K56ac were observed in the majority of epithelial ovarian tumors examined. Furthermore, the robust and prolonged activation of H3K56ac treated with HDACi suggests that H3K56ac may contribute in part to the

antitumor and chemosensitizing properties of HDACi compounds in ovarian cancers.

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The tumor suppressor KLF6, lost in a majority of ovarian cancer cases, represses VEGF expression levels

W. Bradley[1], P. Dottino[2], J. Rahaman[2], A. DiFeo[2], J. Martignetti[2]
[1]*Medical College of Wisconsin, Milwaukee, WI,* [2]*Mt. Sinai School of Medicine, New York, NY*

Objective: Vascular endothelial growth factor (VEGF) is required for both physiologic angiogenesis and tumor neo-angiogenesis. As recently demonstrated by the phase III Gynecologic Oncology Group (GOG) 0218 study of bevacizumab, VEGF inhibition represents a therapeutic target for improving progression-free survival (PFS). We previously demonstrated that the tumor suppressor KLF6, a member of the Kruppel-like zinc finger transcription factor family, is functionally inactivated in a majority of ovarian cancer cases. Targeted reduction of KLF6 in ovarian cancer cell lines resulted in marked increases in cell proliferation, tumor growth, angiogenesis and intraperitoneal dissemination. We therefore sought to investigate the role of KLF6 overexpression in the regulation of VEGF expression in ovarian carcinoma.

SKOV3, OVCAR3 and 53S ovarian carcinoma cells were cultured and transiently transfected with a blank vector (neo), KLF6 and KLF6-SV1, an oncogenic splice variant of KLF6. Cells were cultured under normoxic and hypoxic conditions. Efficiency of transfection was determined with Western blot and quantitative real-time PCR. Secreted VEGF levels were measured in cell culture supernatants using ELISA and Western blot. Luciferase assays determined the effect of KLF6 at the VEGF promoter site. KLF6 was co-transfected with the histone deacetylase, HDAC-3, which has previously been shown to augment the effect of transfected KLF6. Student's *t* test was used for comparison of continuous variables.

Results: Increased expression of KLF6 led to a 40% decrease in secreted levels of VEGF. Transfection and culture under hypoxic conditions augmented this reduction to a 60% decrease compared with non-KLF6-transfected cells. Furthermore, co-transfection of KLF6 with HDAC-3 led to an almost 60% reduction in secreted VEGF under normoxic conditions. Promoter assays demonstrated a significant decrease in activity at the VEGF promoter site in the KLF6-transfected cell lines.

Conclusions: Elevated expression of KLF6 results in decreased expression of secreted VEGF. Decreased promoter activity in KLF6-transfected cells indicates this may be the source of reduced protein expression. The decreased expression of VEGF is augmented by exposure to hypoxia, as well as with the co-transfection of HDAC-3 and KLF6. KLF6 inactivation may represent an important pathway for increased VEGF tumor expression and a possible target for modulating tumor angiogenesis.

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Thinking outside of the tumor: Targeting the ovarian cancer microenvironment

J. Scalici[1], C. Harrer[1], K. Atkins[2], K. McLachlan[3],
L. Duska[2], J. Slack-Davis[1]
[1]*University of Virginia, Charlottesville, VA,* [2]*University of Virginia Health System, Charlottesville, VA,* [3]*Biogen, San Diego, CA*

Objective: Vascular cell adhesion molecule 1 (VCAM-1)/very late antigen 4 (VLA-4) interplay in epithelial ovarian cancer illustrates the importance of the tumor microenvironment to the metastatic potential of disease. In an in vitro model, VCAM-1/VLA4 binding mediates ovarian tumor cell invasion through a mesothelial cell layer, and inhibition of either co-receptor significantly halts this process. The aim of this preclinical study was to assess the in vivo efficacy of targeting this interaction within the ovarian cancer metastatic niche combined with standard chemotherapy.

A xenograft mouse model of widely disseminated ovarian cancer was created by intraperitoneal injection of luciferase-expressing carboplatin-resistant SKOV3ip1 cells (1×10^6) into female nude mice. Bioluminescence confirmed tumor presence prior to treatment. Mice were then randomly assigned to one of four groups: (1) IgG alone, (2) carboplatin + IgG, (3) anti-VLA4 antibody alone, (4) carboplatin + anti-VLA4 antibody. Carboplatin and antibody were administered on a weekly and twice weekly schedule, respectively. Following four weeks of treatment mice were imaged and sacrificed. The omentum was collected, weighed, and stained for VCAM-1 expression.

Results: Bioluminescence confirmed peritoneal tumor presence in all animals at week 0. Repeat imaging at week four prior to sacrifice revealed a significant reduction in tumor burden in the anti-VLA4 + carboplatin group compared with the three other treatment groups ($P<0.05$). Significant disease progression from baseline was noted in all treatment groups except that treated with anti-VLA4 + carboplatin. Omental weights corroborated these findings, reflecting significantly less tumor in the anti-VLA4 + carboplatin group ($P<0.05$).

Conclusions: The tumor/microenvironment interaction likely imparts molecular behavior to tumor cells that impacts their invasive and metastatic potential. We identified a molecule that is differentially expressed in metastatic ovarian cancer in VCAM-1. Additionally, its co-receptor VLA4 is natively expressed on ovarian tissue. Targeting this interaction between two cell surface adhesion molecules in vivo successfully reduced tumor burden compared with both control and standard therapy in platinum-resistant tumors. These results lend credence to directing therapy at tumor-induced alterations in host tissue and identify the VCAM-1/VLA4 interaction as a valid target in the setting of platinum resistance.

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True blood: Platelets as a biomarker of ovarian cancer recurrence

J. Bottsford-Miller[1], S. Lutgendorf[2], C. Pecot[1], R. Stone[1], A. Nick[1],
K. Matsuo[3], E. King[1], K. Ring[4], K. De Geest[2], A. Sood[1]
[1]*University of Texas M.D. Anderson Cancer Center, Houston, TX,* [2]*University of Iowa Hospitals and Clinics, Iowa City, IA,* [3]*University of Southern California, Los Angeles, CA,* [4]*University of Virginia, Charlottesville, VA*

Objective: Thrombocytosis (>450,000 platelets/μL) is well documented at the time of diagnosis of ovarian cancer, but the course of platelet levels over the course of disease, in particular the interval preceding recurrence of disease, is not known. Therefore, we considered whether platelet levels might serve as a biomarker for ovarian cancer recurrence.

Following institutional review board approval, we obtained clinical and pathologic data on 341 women with ovarian cancer. All patients were treated with platinum and taxane chemotherapy and either primary or interval cytoreductive surgery. Platelet and CA-125 data were obtained at diagnosis, at completion of first-line therapy, and at first recurrence. Using an established preclinical orthotpic

mouse model of thrombocytosis and ovarian cancer, we tracked platelet counts and tumor progression in nude mice inoculated with ovarian cancer.

Results: The average age at diagnosis was 60.7 years (range: 36–88). Ninety percent had advanced-stage (stage III or IV) and 89% had high-grade disease; 60% underwent optimal surgical cytoreduction (<1 cm residual). Thirty-two percent had thromobocytosis at diagnosis, with a mean platelet level of 409,000/μL (range: 134,000–1,122,000/μL). An elevated platelet count at diagnosis was associated with significantly worse overall survival (mean = 3.81 years vs 5.86 years, $P<0.01$) and progression-free survival (mean = 1.03 years vs 1.89 years, $P<0.001$). Following completion of primary therapy, 86% of patients had a CA-125 level <35 U/mL, and all patients had a platelet count <450,000/μL (mean = 206,000/μL). At recurrence, CA-125 was elevated in 75% of patients. For all patients, the mean platelet count at recurrence was 338,000/μL, representing a 64% increase compared with the platelet count following completion of primary therapy ($P<0.001$). Among patients with a normal CA-125 at the time of recurrence, platelets were increased by an average of 108,400/μL at the time of recurrence compared with the end of primary therapy (49% increase, $P<0.01$). In the mouse model, platelet levels increased in parallel with expanding tumor volume, suggesting a direct relationship between platelet levels and tumor volume.

Conclusions: Preclinical and clinical findings suggest that platelet counts may be useful as a biomarker for disease progression in ovarian cancer.

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Tumor expression of the type I insulin-like growth factor receptor is an independent prognostic factor in epithelial ovarian cancer

G. Huang[1], T. Hebert[1], C. Kim[2], J. Lin[1], H. Arias-Pulido[3], H. Smith[1]
[1]Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [2]Memorial Sloan–Kettering Cancer Center, New York, NY, [3]University of New Mexico, Albuquerque, NM

Objective: High levels of insulin-like growth factors (IGF1, IGF2) have been shown to correlate with disease progression in ovarian cancer. However, the impact of type I insulin-like growth factor receptor (IGF1R) has not been investigated. The purpose of this study was to determine whether the tumor expression level of IGF1R, a high-affinity receptor for IGF1 and IGF2, is a prognostic factor for patients with primary epithelial ovarian tumors.

Epithelial ovarian carcinoma (EOC) and low-malignant-potential (LMP) tumor tissues from a single institution underwent pathology review, and a tissue microarray was constructed; there were 117 patients. Clinical data were abstracted. Immunohistochemistry was done using a monoclonal antibody directed at IGF1R (Cell Signaling). An *H* score was calculated by multiplying staining intensity (0, negative; 1+, weak; 2+, moderate; 3+, strong) by the percentage of positive cells (0–100%). IGF1R expression was categorized as high or low using the median *H* score. $\chi 2$ or Fisher's exact test was used to assess its association with clinicopathologic variables. Survival analysis was done using Cox proportional hazards regression. Adjustment for age, grade, stage, extent of cytoreduction, performance status and chemotherapy was achieved by including these variables in the Cox models. The Wald test was used to measure the statistical significance of hazard ratios (HR). *P* values <0.05 were deemed significant.

Results: IGF1R expression was significantly associated with stage ($P=0.004$), histology ($P<0.0001$), and grade ($P=0.0009$), but not with age or race. On Cox regression, IGF1R expression (HR = 0.37, $P=0.003$), stage (HR = 9.14, $P<0.0001$), and grade (HR = 5.67, $P=0.008$) were independent prognostic factors for disease-free survival. For analysis of overall survival, stratification was done for EOC versus LMP tumors (as no deaths occurred in the LMP group). On Cox regression, IGF1R expression (HR = 0.248, $P=0.0003$), stage (HR = 9.12, $P=0.0004$), and chemotherapy (HR = 0.136, $P<0.0001$) were independent prognostic factors of overall survival.

Conclusions: In contrast to IGF1/IGF2, high tumor expression of IGF1R is an independent, favorable prognostic factor for progression-free and overall survival in patients with ovarian tumors. Based on these novel findings, further investigation of the interrelationships between IGF1R expression and activation by IGF1 versus IGF2 (and their effects on intracellular signaling cascades) holds promise for biologic intervention.

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Hereditary Cancers and the Role of Genetics

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Compliance with recommended genetic counseling for Lynch syndrome: Room for improvement

F. Backes, E. Mitchell, H. Hampel, D. Cohn
Ohio State University, Columbus, OH

Objective: Three percent of patients with endometrial cancer (EMCA) will have Lynch syndrome (LS). Immunohistochemistry (IHC) for mismatch repair (MMR) proteins in tumor samples is a quick and relatively inexpensive way of screening for LS. At our institution we have found that >20% of patients have abnormal IHC for MMR proteins and >10% qualify for genetic counseling (GC). However, compliance with recommended GC is poor. Therefore, we set out to analyze patients' perceptions of their cancer risks and reasons for this noncompliance.

All patients with EMCA between 2007 and 2009 were identified. Pathology records were reviewed for the presence or absence of prospectively tested MMR proteins by IHC. Using an algorithm aimed at identifying all patients with LS (combination of IHC, family history, and personal history), it was recommended that certain patients seek consultation with a genetic counselor.

Results: Of 383 patients with EMCA, 47 (12%) were referred for GC. Of these, 26 patients provided a response (55%), and serve as the basis of this study. Thirteen (50%) had a family history of LS-associated cancer. Twenty patients (77%) were referred by their physician for GC, of whom 11 made an appointment, nine saw a genetic counselor, and eight had genetic testing. The primary reasons given by the 11 patients for not seeking GC were no insurance coverage and cost of the visit (54%), followed by anxiety related to the potential results of germline testing. Secondary reasons included the fact that testing would not change the existing risk (33%) and that the patient or family did not want to know about genetic risk (33%). To improve compliance, the majority wanted to get more information from their physician. As compared with the general population 35% thought their risk of LS was higher, 12% thought it was the same, 15% lower, and 38% were unsure. Forty-six percent thought the risk of colon cancer was higher and 26% thought it was the same. The majority thought ovarian cancer risk was lower. Most patients (38%) estimated the risk of colon cancer and EMCA for family members as similar to that of the general population and were not aware of any potential interventions for prevention or screening.

Conclusions: Most patients underestimate their risk of inheritable cancer. Clinicians should be cognizant of this fact, and use family history and IHC to refer patients appropriately. In addition, this survey reveals that more verbal and written information may

empower patients to engage in methods of screening and prevention for LS-associated cancers.

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Does genetic counseling for women at high risk of harboring a deleterious BRCA mutation alter risk-reduction strategies and cancer surveillance behaviors?

M. Henretta, A. Askew, M. Smolkin, E. Guffey, S. Modesitt, W. Cohn, M. Ropka
University of Virginia Health System, Charlottesville, VA

Objective: We conducted a proof-of-principle comparative effectiveness research study targeting the clinical utility of referring high-risk women for genetic counseling (GC). Women were determined to be at high risk for harboring a deleterious BRCA mutation if diagnosed with breast cancer at age ≤45 years. Our objective was to evaluate the effectiveness of GC by examining subsequent patient uptake of risk-reduction strategies and cancer surveillance behaviors.

Institutional review board approval was obtained for this cohort study of patients treated at a single academic medical center. Women who were diagnosed with breast cancer at age ≤45 were identified from an institutional data repository. We abstracted the following data: demographics, medical history, CA-125 testing, transvaginal ultrasound and the occurrence of risk-reducing salpingo-oophorectomy (RRSO) and contralateral prophylactic mastectomy (CPM).

Results: Records were reviewed for 101 patients, of whom 74 did not and 27 did receive GC. Distributions of demographic data (stage, race, payer) and initial mode of disease detection were similar across groups. Median follow-up time was five years (maximum = 10.9). Of the 74 potentially high-risk women who did not receive GC, none obtained genetic testing, 40% received transvaginal ultrasound, 14% underwent CA-125 testing, 7% underwent RRSO, and 4% had CPM during the study period. Of the 27 who did receive GC, 48% obtained genetic testing ($P<0.001$), 59% underwent transvaginal ultrasound ($P=0.095$), 63% underwent CA-125 testing ($P=0.009$), 37% underwent RRSO, and 22% had CPM.

Conclusions: Potentially high-risk women who did not receive GC were less likely to adopt risk-reduction strategies and cancer surveillance behaviors than those who did receive GC. It is unclear whether this is a direct consequence of the GC intervention or the intrinsic nature of the patients themselves. However, this scenario could never be ethically studied in a randomized trial. Younger women with breast cancer have a lifetime of benefit to be gained from GC, risk-reduction strategies, and cancer surveillance behaviors. Collectively, these can lead to prevention and/or early cancer detection, with the potential to decrease morbidity and mortality. The clinical utility of GC is likely lower when the population that may benefit the most from cancer risk assessment and management is not identified. The importance of GC must be stressed in this population of young women often referred to gynecologic oncologists for RRSO.

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Hereditary breast and ovarian cancer syndrome based on family history alone and implications for patients with serous carcinoma

K. Long, E. Tanner, N. Kauff, L. Krill, M. Leitao, D. Levine, E. Jewell, R. Barakat, D. Chi
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The objective of this study was to evaluate the clinical course and outcomes of patients with serous carcinoma of the ovary, fallopian tube or peritoneum suspected as being a part of a hereditary breast and ovarian cancer (HBOC) kindred based on family history alone.

Demographics, surgical data and clinical outcomes were collected for all patients with advanced-stage ovarian, tubal or peritoneal serous carcinoma who underwent primary cytoreductive surgery (CRS) at our institution from December 2000 to December 2009. Patients were excluded if family history was not available. Modified ACOG criteria were used to identify patients with suspected HBOC (SHBOC): personal history of breast cancer, first- or second-degree relative with breast cancer before age 50 and/or ovarian cancer at any age, two or more first-degree relatives with breast cancer. Genetic testing results were not reviewed. Standard statistical analysis was used.

Results: We identified 423 evaluable patients, of whom 111 (26.2%) met criteria for SHBOC. Median age was 59.5 years (range: 30–84) in SHBOC patients versus 60.7 years (range: 23–95) in normal-risk (NR) patients ($P=0.03$). Stage distribution was similar in both groups ($P=0.61$). Grade 3 carcinoma was found in 96.4% of SHBOC patients versus 83.7% of NR patients ($P=0.01$). Optimal CRS (<1 cm residual disease) was achieved in 73% of SHBOC patients versus 76.3% of NR patients ($P=0.49$). Intraperitoneal chemotherapy was used in 26.1% of SHBOC patients versus 24.4% of NR patients ($P=0.75$). Consolidation therapy was used in 39.6% of SHBOC patients versus 28.5% of NR patients ($P=0.04$). Platinum sensitivity (platinum-free interval ≥6 months without progression) was noted in 81.1% of SHBOC patients versus 62.5% of NR patients ($P<0.01$). In patients with optimal CRS, median progression-free survival was 26.2 months (95% CI = 23.4–29) for SHBOC patients and 20.3 months (95% CI = 16.9–23.7) for NR patients ($P=0.014$), and median overall survival was 76 months (95% CI = 58.8–93.2) for SHBOC patients and 52.3 months (95% CI = 44.5–60.1) for NR patients ($P=0.011$). On multivariate analysis using accepted prognostic factors, HBOC retained independent significance for progression-free survival (HR = 1.33, 95% CI = 1.03–1.7) and overall survival (HR = 1.75, 95% CI = 1.3–2.4).

Conclusions: Family history suspicious for HBOC was associated with increased platinum sensitivity and improved outcomes in patients with serous ovarian, tubal or peritoneal carcinoma. This information may be useful in patient counseling, individualization of care and future trial design.

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Management and clinical outcomes of women with BRCA1/2 mutations found to have occult cancers at the time of risk-reducing salpingo-oophorectomy

D. Iglesias[1], C. Sun[1], C. Langstraat[2], J. Bakkum-Gamez[2], S. El-Nashar[2], E. Keeler[1], D. Gershenson[1], K. Lu[1]
[1]University of Texas M.D. Anderson Cancer Center, Houston, TX, [2]Mayo Clinic, Rochester, MN

Objective: Risk-reducing salpingo-oophorectomy (RRSO) is of proven benefit in reducing the risk of ovarian cancer in women carrying BRCA1/2 mutations. However, occult cancers are diagnosed in up to 12% of women undergoing RRSO. It is unclear whether additional staging or adjuvant chemotherapy is necessary in patients with occult cancers. The objective of this study was to report postoperative treatment, clinical outcomes and survival in women diagnosed with an occult cancer during RRSO.

A multicenter retrospective review of BRCA1/2 mutation carriers who underwent RRSO at two institutions between January

2000 and August 2010 was conducted. All patients were followed in a high-risk ovarian cancer screening clinic and underwent pelvic imaging and a CA-125 level assessment prior to surgery. Data collected included patient age, BRCA mutation status, parity, body mass index, preoperative CA-125 level, prior cancer history, surgical information, pathology reports and follow-up data including treatment course, recurrences, new cancer diagnoses and survival.

Results: A total of 174 women BRCA1/2 mutation carriers underwent RRSO, of whom eight (4.6%) were diagnosed with occult cancers. Malignancies included four high-grade serous carcinomas (HGSCs) arising in the fallopian tube (FT), one HGSC arising from the ovary, one primary peritoneal HGSC, and two serous ovarian tumors of low malignant potential. The mean age at RRSO was 55.5 (range: 40–73) years for women diagnosed with occult cancers. All eight patients carried a BRCA1 mutation. Mean preoperative CA-125 level was 11.7 U/mL (range: 3.4–34.7 U/mL). Three of the six (50%) patients with invasive cancer underwent a staging procedure after initial RRSO (two had stage IA FT cancer and one had stage IIC FT cancer). Four of six (60%) patients with invasive cancer received at least three cycles of chemotherapy postoperatively. Median follow-up was 32.5 months (range: 2–104 months). All six patients with invasive cancer are alive with no evidence of disease. There have been no recurrences.

Conclusions: Occult ovarian/FT/peritoneal cancers in BRCA1/2 mutation carriers undergoing RRSO are often early stage. Given high grade histology and surface involvement, most patients with occult cancers were given chemotherapy. Regardless of treatment, BRCA1/2 mutation carriers found to have occult ovarian/FT/peritoneal cancers have a good overall prognosis.

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RNASeq identifies germline and tumor-specific mutations in a hereditary cervical cancer syndrome: Successful proof-of-principle study for gynecologic cancer gene discovery

R. Mosig[1], E. Senturk[1], H. Shah[1], S. Cohen[1], R. Sachidanandam[1], C. Eliasen[1], M. Glucksman[2], M. Chee[3], P. Dottino[1], J. Martignetti[1]
[1]Mt. Sinai School of Medicine, New York, NY, [2]Rosalind Franklin University of Medicine and Science, Chicago, IL, [3]Prognosys Biosciences, Inc., La Jolla, CA

Objective: Whole-genome transcriptome sequencing allows the high-resolution study of genetically complex diseases to quantify both expression levels and allelic variation at the nucleotide level. As proof-of-principle, we applied RNASeq toward identifying tumorigenic sequence variants in a stage IV cervical cancer from a patient with a clinically suspected hereditary cancer syndrome. Peutz–Jeghers syndrome is an autosomal dominant disorder characterized by gastrointestinal hamartomatous polyps and higher risk of epithelial cancers caused by mutations in the tumor suppressor LKB1.

Patient samples of a well to poorly differentiated endocervical-type mucinous adenocarcinoma, adjacent cervical tissue, and blood were collected at surgery under institutional review board approval. The tumor transcriptome was prepared for paired end sequencing using the Illumina GAII platform, and transcripts were aligned to the reference genome using RNADashBoard. Direct DNA sequencing validated the allelic distribution of LKB1 mutations in tumor-derived cDNA and PBMC-derived DNA. Mutations were computer-modeled and immunohistochemical staining allowed downstream pathway analysis.

Results: Tumor transcriptome analysis identified two mutations in LKB1: 179insA predicts a Y60fsX truncation leading to loss of most of the protein, and C910T predicts an R304W amino acid change (Fig. A). Direct sequencing of LKB1 from PBMC DNA confirmed the C910T transition and tumor cDNA validated each mutation on separate alleles consistent with two hits in the LKB1 gene. Modeling against the structure of the LKB1–STRAD–MO25 complex revealed that 304W would destabilize LKB1 helices and formation of the complex (Fig. B). Pathway analysis suggested that loss of LKB1 caused increased mTOR/HIF1α signaling and upregulation of Glut1. Staining of the primary and recurrent tumors confirmed increased Glut1 expression compared with normal cervical epithelia (Figs. C–E).

Conclusions: This study is the first successful use of RNASeq for mutation and pathway analysis in a gynecologic cancer syndrome. Beyond validating our approach to identify cancer-associated mutations, we have also demonstrated overactivity of mTOR/HIF1α. This finding suggests the ability to monitor for recurrence using FDG-PET and the potential for directed treatment using an mTOR inhibitor. Taken together, and in this evolving era of personalized medicine, these findings serve as a proof-of-principle study and suggest the benefit of future mutational analysis of other tumors by RNASeq.

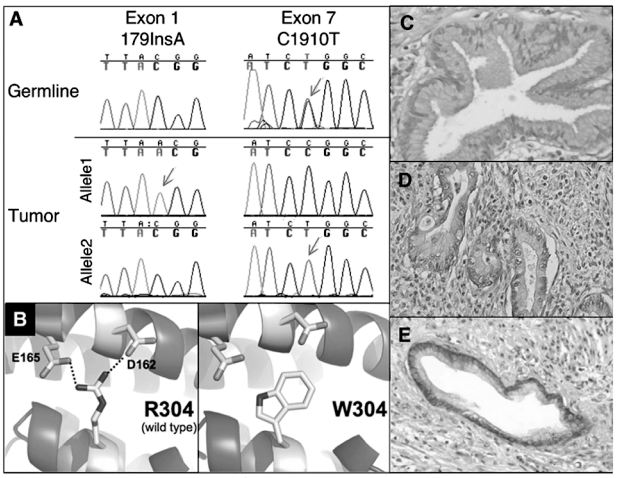

Figure 1. A) Direct sequencing of *STK11* from genomic DNA and tumor-derived cDNA with mutations highlighted. B) Molecular modeling of the R304W mutation.C) Absence of Glut1 staining in normal endocervical glandular cells unrelated control cervical specimen. D-E) Positive basal-membrane Glut1 staining in the primary (D) and recurrent tumor (E).

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The impact of BRCA testing on surgical treatment decisions for patients with breast cancer

K. Doll[1], W. Gradishar[1], J. Trosman[2], C. Weldon[2], J. Schink[1]
[1]Northwestern University/Prentice Women's Hospital, Chicago, IL, [2]Center for Business Models in Healthcare, Chicago, IL

Objective: Patients with breast cancer with a BRCA mutation have higher risks of ovarian cancer and breast cancer recurrence. These patients are more likely to view mastectomy as the best way to reduce future breast cancer recurrence while avoiding multiple surgeries and radiation (M.D. Schwartz et al., J Clin Oncol 2004;22:1823–9). Patients with breast cancer with a BRCA mutation who undergo salpingo-oophorectomy reduce their mortality risk (S. M. Domcheck et al., JAMA 2010;304(9)). The study goals were to better define how BRCA testing, prior to definitive surgery or after surgery, impacted rates of mastectomy versus conservative surgery and frequency of salpingo-oophorectomy.

This is a retrospective review of medical records and insurance claims for 228 patients with breast cancer who underwent BRCA testing and definitive surgery between July 1, 2007 and June 30, 2009. Following an institutional review board-approved protocol, we used

simple frequencies and Fisher's exact test to evaluate occurrences of BRCA testing relative to surgery and association with surgical decisions.

Results: The BRCA test was performed presurgery in 39% (90/228) and postsurgery in 61% (138/228) of this cohort. The majority of women, 68% (61/90), tested presurgery had a mastectomy compared with 38% (51/138) of women tested after surgery ($P=0.0001$) (see table). Of those choosing mastectomy, 57% (35/61) of the presurgery tested woman had bilateral mastectomy as compared with 28% (15/53) of the women tested after surgery ($P=0.0024$). Institution-specific data showed that only 5% (11/228) of the cohort had an oophorectomy.

Conclusions: Conducting BRCA mutation analysis prior to breast cancer surgery is associated with a more radical surgical approach. Unfortunately, more than half of patients with breast cancer did not have BRCA mutation information available for initial surgical planning. Data regarding oophorectomy rates in our study population were disappointing and point to a need for further education regarding ovarian cancer risk in survivors. Further research is needed to assess the feasibility and impact of genetic counseling and genetic testing within the preoperative workup for patients with breast cancer with familial/genetic risk.

Breast cancer patients' surgical decision: BRCA testin before versus after surgery

Surgery	BRCA before	BRCA after	Total
Mastectomy	61	53	114
Lumpectomy	29	85	114
Total	90	138	228

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Utility of symptom index in women at increased risk for ovarian cancer

D. Singh[1], K. Lowe[2], C. Colllins[1,3], L. Cohen[1,3], J. Dungan[1,3], L. Shulman[1,3], M. Andersen[4], B. Goff[4]
[1]Northwestern University, Chicago, IL, [2]Exponent Health Sciences, Bellevue, WA, [3]Prentice Women's Hospital, Chicago, IL, [4]University of Washington Medical Center, Seattle, WA

Objective: Developing a screening test for a low-prevalence cancer like ovarian cancer remains a challenge, and multimodal approaches that combine risk stratification, symptom index (SI), serum studies and transvaginal ultrasound (TVUS) have been proposed. In previous studies approximately 4% of average-risk and 10% of high-risk women had a positive SI. Our purpose was to evaluate the results of a multimodality screening program in women at increased risk for ovarian cancer and describe test results in both those with positive SI and those with a negative SI.

Women at elevated risk for ovarian cancer based on personal or family history were followed prospectively every six months with history, physical, SI, TVUS and serum studies. The women completed a detailed baseline questionnaire and underwent comprehensive genetics evaluation at initial visit, and information was updated at follow-up visits.

Results: Between April 2009 and April 2010, a total of 569 women (mean age = 51 years, range: 20–84) participated. The majority (89%) were Caucasian and 33% were nulliparous. Women were at increased risk because of inherited predisposition (12%), first-degree relative with ovarian cancer (42%) or personal history of breast cancer (27%). Of the total population, 25 (4%) had a positive SI, 25 (4%) had elevated CA-125, and 108 (18%) had a mass on TVUS, which met criteria for follow-up. TVUS was suspicious for malignancy in <1%. SI positivity did not differ among women with a positive CA-125 or with a mass on TVUS. However, women with a positive SI were less likely to have a benign ovarian lesion than those with a negative SI (8% vs 15%). The SI was significantly more likely to be positive in those older than 50 not using hormones compared with those using hormones (6% vs 1%). SI positivity did not vary by race, parity or risk category. SI positivity was significantly higher among women with a self-reported history of endometriosis (19% vs 4%), noncancerous cyst (9% vs 4%), or any ovarian condition (8% vs 4%), than among women who did not have these conditions. None of the screened patients developed ovarian cancer during the follow-up period.

Conclusions: In this population of women at increased risk for ovarian cancer, the rate of SI positivity was identical to that of the general population. The SI did not overlap with CA-125 or benign masses on TVUS and may identify a different subset of women who require evaluation for ovarian cancer. Our results confirm the potential utility of a SI as part of a multimodal program that includes risk stratification.

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Poster Area 2
Breast, Ovarian Cancer, Fallopian Tube/Peritoneal Cancer, Quality of Life and Ovarian Clinical Trials: Abstracts 141–193
Sunday, March 6 – Tuesday, March 8, 2011
Exhibit Hall - Bonnet Creek Ballroom

Breast Cancer

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EZH2 expression in triple-negative breast carcinoma

Z. Al-Wahab[1], A. Munkarah[1,2], S. Munns[1], S. Seward[1], A. Sood[3], R. Morris[1], R. Ali-Fehmi[1]
[1]Wayne State University, Detroit, MI, [2]Henry Ford Health System, Detroit, MI, [3]University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: The polycomb group protein EZH2 is a transcriptional repressor involved in cell cycle regulation. It has been linked to aggressive breast cancer and is being evaluated as a possible therapeutic target. Triple-negative (TN: ER-, PR- and Her-2- negative) breast carcinomas have aggressive clinical behavior. In this study, we investigated the expression of EZH2 in TN compared with non-TN breast carcinomas.

Tissue microarrays were constructed with 261 consecutive invasive breast carcinomas diagnosed at our institution over a three-year period with a median follow-up of 42 months. Immunohistochemistry for EZH2, CK5/6, EGFR and P53 was performed using standard procedures. EZH2 nuclear staining was scored based on intensity (0–3+) and was categorized into low and high expression. The results were correlated with clinicopathologic variables and patient outcome. Data were statistically analyzed using the χ^2 or Fisher's exact test, and survival was calculated with the Kaplan–Meier method.

Results: Among the 261 cases, 57 (21%) were categorized as TN, and 204 (79%) as non-TN. High expression of EZH2 was detected in 87 (33%) cases, and it was strongly associated with a TN phenotype ($P<0.0001$) compared with all other non-TN tumors. High EZH2 was noted in 41 of 57 (72%) TN versus 46 of 204 (22%) non-TN tumors. Increased EZH2 expression also significantly correlated with younger age (mean age = 54 years, $P=0.008$), higher grade ($P=0.04$), and high P53 expression ($P=0.006$). However, no correlation was

observed with race, tumor size, lymph node status and EGFR and CK5/6 expression. Survival analyses demonstrated that patients with high EZH2-expressing tumors exhibited a trend toward poorer overall survival compared with patients with low EZH2-expressing tumors (68% vs 80%, $P = 0.07$).

Conclusions: Our results show that high EZH2 expression is significantly associated with TN breast carcinoma and might be a potential therapeutic target for this aggressive subgroup of breast cancers, which warrants further investigations.

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Incidental gynecologic FDG-PET/CT findings in women with a history of breast cancer

T. Pua[1], A. Jewell[1], A. Novetsky[1], J. Lee[2], K. Friedman[1], J. Whyte[1], L. Boyd[1], B. Pothuri[1], J. Curtin[1], S. Blank[1]
[1]New York University School of Medicine, New York, NY, [2]UMDNJ-SOM Cooper University Medical Center, Camden, NJ

Objective: The goal of this study was to evaluate the incidental gynecologic findings among breast cancer patients undergoing radiographic surveillance with whole-body [^{18}F]fluorodeoxyglucose PET/CT (FDG-PET/CT).

The records of previously-treated breast cancer patients who were undergoing surveillance with FDG-PET/CT from 2005 to 2009 were reviewed. Charts of women whose FDG-PET/CT findings demonstrated FDG uptake in the ovaries or uterus were included and grouped as physiologic FDG uptake not requiring follow-up (H. Lerman et al., J Nucl Med 2004;45:266–71) or positive requiring workup with pelvic ultrasound. Pathology records for patients eventually undergoing surgery were reviewed. Comparative analysis was performed using Pearson's χ^2 test.

Results: Of 877 women who had breast cancer and underwent surveillance FDG-PET/CT, 110 (13%) had FDG-PET/CT findings of increased FDG uptake in the ovaries or uterus. Sixty-five (59%) of these 110 readings were, after evaluation by the oncologist ordering the study, deemed physiologic in nature, and these patients did not undergo further gynecologic workup because of their findings. Women with physiologic uptake on FDG-PET were younger than those undergoing follow-up, with a mean age of 44.6 ± 9.8 versus 49.6 ± 10.5 ($P = 0.01$). Pelvic sonography or further workup was recommended in 45 (41%) of the 110 women with positive scans. Among these cases, 12 (27%) had ultrasounds suspicious for malignancy; 21 (47%) had further sonography indicative of a benign process; and 12 (27%) did not have follow-up. Among the patients undergoing surgery, nine of 15 (60%) had malignancies: five metastatic breast cancer to the ovary, one uterine papillary serous carcinoma, and three primary ovarian cancers. Six of 15 had benign pathology. A predominant proportion of these malignancies (6/9) had a maximum SUV ≥ 6 ($P = 0.013$).

Conclusions: In this review of breast cancer patients undergoing surveillance FDG-PET/CT, 13% demonstrated FDG accumulation in the gynecologic organs, and of these, 41% were thought to require further assessment. Twenty percent (9/45) of women requiring subsequent evaluation ultimately underwent surgery and were found to have malignant etiology for their PET findings. Among women undergoing FDG-PET/CT for breast cancer surveillance, incidental gynecologic FDG avidity, once determined not to be physiologic by radiographic criteria, merits further evaluation.

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Ovarian/Fallopian Tube/Peritoneal Cancer

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Accuracy of frozen-section diagnosis of ovarian borderline tumor

K. Shih, K. Garg, R. Soslow, D. Chi, N. Abu-Rustum, R. Barakat
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The objective of this study was to determine the incidence of invasive cancer in ovarian masses diagnosed as borderline tumor (BT) at the time of frozen section.

We performed a retrospective review of all patients diagnosed with ovarian BT on frozen section at our institution from 2000 to 2010. Clinical and pathologic data, including histologic subtype, tumor size, age, preoperative CA-125 level and stage were extracted. Univariate analysis was performed using the χ^2 test, and multivariate analysis was performed using binary logistic regression.

Results: A total of 138 patients were identified, of whom 124 (89.1%) had BT on frozen section, which was confirmed on final pathology. In 14 (10.1%) patients, BT was diagnosed on frozen section but reclassified as invasive cancer on final pathology. Histologies included serous in 90 (65.2%), seromucinous in 12 (8.7%), mucinous in 29 (21.0%), endometrioid in 5 (3.6%), and clear cell in two (1.4%) patients. The incidence of reclassification to invasive cancer on final pathology was as follows: serous, 5.6%; seromucinous, 0%; mucinous, 13.8%; endometrioid, 80%; and clear cell, 50%. Reclassification of pathologic diagnosis was related to histologic subtype, but only for endometrioid and clear cell tumors ($P = 0.007$). Among serous tumors, those with a micropapillary pattern were more likely to be reclassified as invasive cancer on final pathology. The incidence of invasive cancer on final pathology for serous micropapillary tumors was 30% compared with 2.5% for serous non-micropapillary tumors ($P = 0.009$). Tumor size >8 cm was associated with an 18.2% incidence of invasive cancer on final pathology compared with 2.8% in tumors ≤ 8 cm ($P = 0.003$). Age and preoperative CA-125 level were not associated with a final diagnosis of invasive cancer. On multivariate analysis, endometrioid or clear cell histology (HR = 37, 95% CI = 4.9–250) and tumor size >8 cm (HR = 8.3; 95% CI = 1.5–46.5) were independently associated with reclassification to invasive cancer.

Conclusions: The accuracy of frozen-section diagnosis of ovarian BT is high, except in cases with endometrioid and clear cell histology. Micropapillary serous BT and tumor size >8 cm are also associated with reclassification to invasive cancer on final pathology. Comprehensive surgical staging can be considered in BTs >8 cm in diameter, as well as those with micropapillary serous, endometrioid and clear cell histology diagnosed at the time of frozen-section analysis.

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Advanced-stage ovarian cancer metastases to sigmoid colon mesenteric lymph nodes: Clinical consideration of tumor spread and biologic behavior

M. Peiretti, P. Rosenberg, G. Aletti, N. Colombo, L. Bocciolone, F. Landoni, V. Zanagnolo, A. Maggioni
European Institute of Oncology, Milan, Italy

Objective: The aim of the study was to analyze the incidence of mesenteric lymph node metastases in patients with advanced-stage ovarian carcinoma to understand the potential biologic behavior of tumor spread.

We retrospectively reviewed the medical records of all patients undergoing primary cytoreductive surgery and rectosigmoid resection for epithelial ovarian cancer from October 1997 through March

2010. Patients with pathologic documentation of mesenteric lymph nodes were selected for further review. χ^2 analysis was used to identify clinicopathologic factors associated with mesenteric lymphatic spread.

Results: We found a total of 120 patients in whom mesenteric lymph nodes were isolated by our pathologist. The median age of these patients was 57 years (range: 22–77). The median number of mesenteric nodes was eight (range: 1–37). Eighty-seven of 120 (72%) cases had one or more mesenteric lymph node metastases, whereas 33 of 120 (28%) were negative. Among patients with metastasis to mesenteric lymph nodes the only serosal or subserosal involvement was present in 31 of 87 (36%) patients; 31 of 87 (36%) had invasion into the muscolaris propria, 19 of 87 (22%) had invasion into the submucosa, and six of 87 (6%) presented with full-thickness invasion of the bowel wall. The increase in depth of invasion was not correlated with the risk of mesenteric lymph node involvement. Retroperitonal evaluation (pelvic and/or paraaortic lymph node dissection) was performed in 62% of the cases; 86% were positive and 83% of them showed mesenteric lymph node metastasis. In the 87 specimens analyzed, 59 (68%) had positive lymphovascular space invasion (LVSI), while in the other group, LVSI was observed in only 11 (33%) patients. Histologic grade did not correlate with the extent of bowel wall invasion or the presence of LVSI.

Conclusions: Our results showed that lymph nodes are commonly involved in the main basins draining from the different tumor locations. Therefore, when ovarian carcinoma involves the rectosigmoid colon, metastases to mesenteric lymph nodes are as common as those to the pelvic and paraaortic nodes. In patients with advanced disease, lymph node sites in addition to the pelvic and/or paraaortic should be considered, especially when optimal debulking is attempted.

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C-terminal binding protein 2: A potential marker for response to histone deacetylase inhibitors in epithelial ovarian cancer

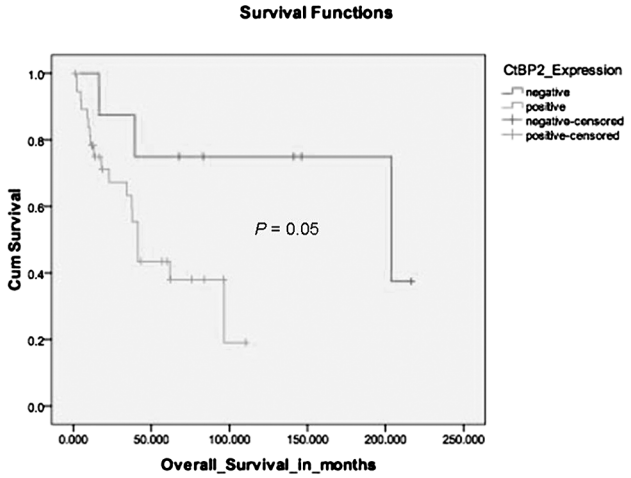
L. Barroilhet, J. Yang, K. Hasselblatt, J. Rauh-Hain, W. Welch, R. Berkowitz, S. Ng
Brigham & Women's Hospital, Boston, MA

Objective: The objective of this study was investigation of the expression pattern and functional roles of tumor antigen C-terminal binding protein 2 (CtBP2) in epithelial ovarian cancer.

CtBP2 expression was studied in 105 ovarian tumors by immunohistochemistry (IHC). Functional assays were performed with human ovarian cancer cell lines that integrated a CtBP2-targeting short-hairpin RNA (shRNA) construct. Protein expression in control and knockdown cell lines was examined by Western blotting. Cell proliferation was determined by seeding cells to 35-mm culture dishes and allowing growth to different time points. A CytoMatrix Screen kit from Millipore was used to evaluate cellular adhesion to specific components of the extracellular matrix. Cell migration assays were performed with a Boyden chamber-based assay. β-Catenin activity was measured using a TOPFLASH luciferase reporter assay and cellular sensitivity to HDAC inhibitors was measured using MTT assays. HDAC activity was measured using a colorimetric HDAC activity assay kit. CtBP2 expression was rescued in the knockdown cell lines with a full-length CtBP2 cDNA expression construct and empty vector. Overall survivals of patients with positive and negative CtBP2 expression were estimated using the Kaplan–Meier method, and compared with a log rank test.

Results: Our study shows that expression of the transcriptional co-repressor CtBP2 is elevated in human ovarian cancers. Downregulation of CtBP2 expression in ovarian cancer cell lines using short-hairpin RNA strategy suppressed the growth rate, adhesion, and migration of the resultant cancer cells. The knockdown cell lines also showed upregulation of HDAC activity and increased sensitivity to selected HDAC inhibitors. Introduction of a CtBP2 expression construct into the knockdown cell lines to reverse the CtBP2 expression was able to partially rescue cellular sensitivity to the HDAC inhibitors. The overall survival of patients with positive CtBP2 expression was found to be poorer (Fig. 1) compared with those patients with negative CtBP2 expression ($P = 0.05$), based on the Kaplan–Meier survival estimation.

Conclusions: We propose that CtBP2 is an ovarian cancer oncogene that regulates gene expression programs by modulating HDAC activity. CtBP2 expression may be a surrogate indicator of cellular sensitivity to HDAC inhibitors.



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CA-125 changes can predict optimal interval cytoreduction in patients with advanced-stage epithelial ovarian cancer treated with neoadjuvant chemotherapy

N. Rodriguez[1], J. Rauh-Hain[1,2], C. Feltmate[1], M. Del Carmen[2,3], R. Penson[2,3], A. Goodman[2,3], U. Matulonis[4], M. Muto[1], J. Schorge[2,3], N. Horowitz[1]
[1]Brigham & Women's Hospital, Boston, MA, [2]Massachusetts General Hospital, Boston, MA, [3]Harvard University, Boston, MA, [4]Dana–Farber Cancer Institute, Boston, MA

Objective: The purpose of this study was to evaluate the predictive power of CA-125 changes in the management of patients undergoing neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) for a new diagnosis of ovarian, fallopian tube or peritoneal cancer.

Using the Cancer Registry databases from our institutions, a retrospective review of patients with FIGO stage IIIC and IV epithelial disease who were treated with NACT-IDS between January 2006 and December 2009 was conducted. All patients received carboplatin (AUC 4 or 5) and paclitaxel (175 mg/m^2). The Mann–Whitney *U* test was used to compare data. Receiver operator characteristic curves were generated.

Results: Fifty-seven patients met study criteria. Median age was 66 years (range: 44–85). Median number of neoadjuvant cycles was 3

(range: 1–8). Optimal interval cytoreduction (defined as disease <1 cm) was achieved in 52 patients (91%). The median CA-125 level at diagnosis and before IDS was 545 U/mL (range: 38–10,150) and 63 U/mL (range: 5–2945), respectively. When patients with interval optimal cytoreduction were compared with patients with suboptimal cytoreduction, there was no statistical difference in the mean CA-125 level at diagnosis (1326 U/mL vs 589 U/mL, $P=0.3$) or before IDS (227 U/mL vs 570 U/mL, $P=0.1$). The mean percentage drop between the CA-125 obtained before NACT and the pre-IDS CA-125 differed significantly between patients who had optimal and those who had suboptimal cytoreduction (82% vs 41%, $P<0.001$). All patients ($n=33$) with a CA-125 drop greater than 80% by the third cycle of therapy had an optimal cytoreduction. In comparison, four of the five patients who had suboptimal cytoreduction had a CA-125 drop ≤50%. This ≤50% CA-125 drop was seen in only three of 52 patients with optimal cytoreduction. An 80% drop in CA-125 was able to predict optimal versus suboptimal cytoreduction with a sensitivity of 62%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 17%. The table outlines a comparison of the percentage drop between the CA-125 obtained before NACT and the pre-IDS CA-125.

Conclusions: Percentage change in CA-125 from the time of diagnosis to IDS is predictive of surgical outcome. In our study, patients who achieved a ≥80% drop in CA-125 by cycle 3 of NACT achieved optimal cytoreduction. A ≤50% drop was predictive of a suboptimal cytoreduction, but did not exclude optimal cytoreduction. If our findings are confirmed in a larger cohort, a <50% drop in CA-125 may encourage alternative management strategies.

Comparison of the sensitivity, specificity, PPV, and NPV at different percentage changes between the CA-125 obtained before the first cycle of chemotherapy and the preoperative CA-125 for prediction of optimal cytoreduction.

	Sensitivity	Specificity	PPV	NPV
50%	94	80	98	57
60%	90	80	98	44
70%	82	80	98	44
80%	62	100	100	17
90%	48	100	100	15

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CA-125 surveillance for women with ovarian, fallopian tube or primary peritoneal cancers: What do survivors think?

L. Boyd, S. Bedell, J. Curtin, R. Wallach, B. Pothuri, F. Muggia, A. Tiersten, S. Blank
New York University School of Medicine, New York, NY

Objective: Monitoring CA-125 levels is an expected part of patient care for women with ovarian, fallopian tube or primary peritoneal cancers. Recent evidence calls into question whether CA-125 levels should be monitored in surveillance in the absence of symptoms. We sought to determine if patients would accept no longer obtaining CA-125 levels as part of routine surveillance.

Institutional review board approval was obtained. With the use of billing codes, patients with ovarian, fallopian tube or primary peritoneal cancer were identified. From February 2010 to July 2010, an anonymous, self-administered survey was distributed to patients carrying one of these diagnoses. Descriptive statistics were performed and Fisher's exact test was applied to compare groups, with two-tailed $P<0.05$ considered significant.

Results: A total of 70 patients returned the survey. The average age of respondents was 61, and the majority were white (59/70) and non-Hispanic (66/70). The average time from diagnosis was 48 months, and 52 of 70 (74%) had stage III or IV disease. Thirty-one of 70 (44%) had received treatment for recurrent disease. When asked, "do you ask for your CA-125 results never, rarely, sometimes, most times or always," 63 of 70 (76%) responded "most times or always." Thirty-four of 70 (49%) responded that they were "most times" or "always" anxious about the results. Fifty-nine of 70 (84%) believed CA-125 can be used to detect cancer earlier, and 44 of 70 (63%) believed CA-125 can be used to start treatment earlier. Eighteen of 70 (26%) believed that CA-125 can be used to "decrease the treatment time needed," and 17 of 70 (24%) believed that CA-125 "can decrease the likelihood of dying from cancer." Fifty-one of 70 (73%) believed that CA-125 should be checked "every three to six months" or "more frequently than every three months." Only one of 70 (1%) believed that CA-125 should be checked "only with symptoms." Forty-one of 70 (59%) would "mildly" (3/70) or "strongly" (38/70) disagree if their physicians stopped checking CA-125 on a routine basis. Patients with advanced-stage disease were more likely to want frequent CA-125 testing ($P=0.03$).

Conclusions: The majority of ovarian cancer survivors are strongly interested in following their CA-125 results despite the fact that three-quarters have realistic expectations about its overall lack of effect on eventual outcome. A policy of testing CA-125 only when symptoms develop would likely have poor acceptance, particularly for patients with advanced-stage disease.

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Calretinin as a prognostic indicator in granulosa cell tumor

H. Arabi[1], R. Ali-Fehmi[2], L. Solomon[2], Z. Al-Wahab[2], A. Semaan[2], S. Bandyopadhyay[2], A. Munkarah[3], R. Morris[2]
[1]*Detroit Medical Center, Detroit, MI,* [2]*Karmanos Cancer Institute, Detroit, MI,* [3]*Henry Ford Health System, Detroit, MI*

Objective: Granulosa cell tumor (GCT) is a rare neoplasm hallmarked by an indolent clinical course and late recurrences. Although multiple clinical and pathologic parameters have been implicated as prognostic indicators for GCT, their predictive significance remains controversial. Calretinin is a calcium-binding protein primarily expressed by selected neurons in the peripheral and central nervous systems. Its expression in mesotheliomas has made it the primary confirmatory antibody in standard mesothelioma immunohistochemical panels. Recently, calretinin has been evaluated and studied as a novel diagnostic/prognostic marker of ovarian sex cord–stromal tumors including granulosa cell tumors. The aim of the study was to evaluate whether calretinin expression is correlated with the clinicopathologic parameters and prognosis in granulosa cell tumor.

Using our institutional database, we identified 51 patients diagnosed with GCT between 1975 and 2010 on whom archival tissue was available. Tumors were histologically classified into juvenile and adult subtypes. Follow-up data were obtained from our institutional record and the national SEER registry. Immunohistochemical staining for calretinin was performed on tissue microarray of all tumors. Immunoreactivity was semiquantitatively scored based on percentage of stained cells. Statistical correlation between immunostaining results, pathologic parameters, and survival was assessed using the *t* test.

Results: Of the 51 patients, five were diagnosed with juvenile GCT and 46 patients had the adult variant of the tumor. The median age at diagnosis was 51 years. Calretinin expression was low in 21 (41%) cases. Low expression of calretinin was significantly associated with larger tumor size. The mean size for tumors with low expression was 15.6 cm versus 9.4 cm for tumors with high expression ($P=0.009$). The recurrence rate was higher in the patients showing low expression (25% vs 6.7%). However, this was not statistically significant. Overall survival, however, was decreased in patients with low expression. Thirteen (57%) patients with low expression were alive compared with 23 (96%) patients with tumors exhibiting high expression of calretinin ($P=0.01$).

Conclusions: Our study shows that calretinin is not expressed or is underexpressed in GCTs with an aggressive clinical course. This result may justify larger studies to further evaluate the prognostic significance of calretinin in granulosa cell tumors.

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Carcinosarcoma of the ovary: A case–control study

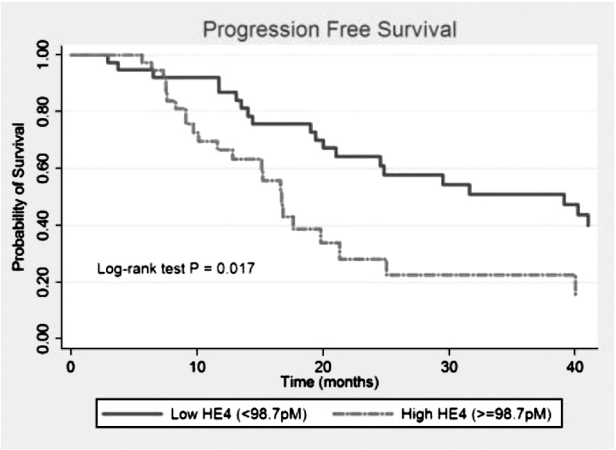
J. Rauh-Hain[1,2,3], W. Growdon[1,3], N. Rodriguez[2,3], A. Goodman[1,3], J. Schorge[1,3], D. Boruta[1,3], N. Horowitz[2,3], M. Del Carmen[1,3]
[1]*Massachusetts General Hospital, Boston, MA,* [2]*Brigham & Women's Hospital, Boston, MA,* [3]*Harvard Medical School, Boston, MA*

Objective: Carcinosarcoma of the ovary is a rare tumor with a grim prognosis. Chemotherapy for these tumors is chosen according to guidelines established for epithelial ovarian cancer (EOC). The purpose of this study was to compare response to chemotherapy and survival in patients with advanced-stage carcinosarcoma of the ovary and serous EOC.

From the Cancer Registry database at the two participating institutions we identified women with advanced carcinosarcoma of the ovary (FIGO stage III or IV) who underwent first-line platinum and taxane-based chemotherapy. Each case was matched to two women with serous EOC. Cases and controls were matched by age, stage, and year of diagnosis. Correlation between categorical variables was assessed with Fisher's exact test. The Kaplan–Meier method was used to generate overall survival data. Factors predictive of outcome were compared using the log-rank test and Cox proportional hazards model.

Results: Preliminary review identified 87 patients with histologically proven carcinosarcoma of the ovary treated between 1995 and 2007. Of these, 50 women had advanced carcinosarcoma of the ovary and were treated with first-line platinum and taxane-based chemotherapy and were selected as cases. These 50 cases were compared with 100 controls. No differences were seen in demographics and clinical characteristics. Optimal cytoreduction rate was similar in the cases and controls (78% vs 81%, $P=0.6$). The response rates to chemotherapy for cases and controls were 39 and 61% ($P=0.08$), respectively. Median progression-free survival was 11 months (95% CI = 8–14) versus 16 months (95% CI = 12–21) ($P=0.02$), and overall survival was 24 months (95% CI = 18–29) versus 41 months (95% CI = 33–49) ($P=0.002$) for cases and controls, respectively (see figure). A Cox proportional hazards model identified optimal cytoreduction (HR = 0.63, $P=0.05$) and serous histology (HR = 0.67, $P=0.04$) as independent predictors of overall survival.

Conclusions: Patients with advanced carcinosarcoma of the ovary appear to have a poorer response to platinum and taxane-based first-line chemotherapy and worse survival, compared with patients with serous EOC. Aggressive surgical treatment appears to play an important role. However, other alternative systemic therapeutic approaches should be sought for this group of patients.



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Changes in tumor blood flow as estimated by dynamic-contrast MRI may predict activity of single-agent bevacizumab in recurrent epithelial ovarian cancer and primary peritoneal cancer: An exploratory analysis of a Gynecologic Oncology Group phase II trial

D. Chase[1], M. Sill[2], M. Chambers[3], K. Darcy[2], E. Han[4], J. Fruehauf[1], B. Monk[5], B. Buening[6], J. Sorosky[7], R. Burger[8]
[1]*UC Irvine Medical Center, Orange, CA,* [2]*Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY,* [3]*VA Long Beach Healthcare System, Long Beach, CA,* [4]*City of Hope Medical Group, Duarte, CA,* [5]*St. Joseph's Hospital and Medical Center, Phoenix, AZ,* [6]*University of Washington Medical Center, Seattle, WA,* [7]*Hartford Hospital, Hartford, CT,* [8]*Fox Chase Cancer Center, Philadelphia, PA*

Objective: The purpose of this study was to assess the feasibility and utility of estimated tumor blood flow (ETBF) using a novel dynamic contrast MRI (DC-MRI) technique as a marker for antiangiogenic activity with exploratory analysis in women with recurrent epithelial ovarian cancer (EOC)/primary peritoneal cancer (PPC) treated with bevacizumab. Primary objectives addressed associations with progression-free survival (PFS) at six months and immunohistochemistry microvessel density (MVD).

In a phase II study, 63 enrolled patients were treated with bevacizumab (15 mg/kg IV every 21 days) until disease progression. DC-MRI was performed at baseline and at completion of three cycles of bevacizumab. Images were analyzed by a single-blinded radiologist. Exploratory analysis was performed to examine the association between ETBF and clinical measures including MVD, prior platinum sensitivity, tumor response and six-month PFS.

Results: Twenty-two percent (14/63) of patients had imaging that was available for analysis. Tumor and normal muscle contrast enhancement was measured by region of interest (ROI) signal intensity analysis within

the same DC-MR images. Flow rates through tumor and muscle tissue were obtained with linear models of the concentration of dye (or intensity of ROI) as a function of time. The ratio of flow rates in tumor to those in normal muscle provided the ETBF. Baseline ETBF differed little with respect to PFS status at six months (median ETBF = 2.8 and 2.6, IQR = 3.0, $P = 0.95$). The observed Spearman coefficient of correlation between ETBF and MVD was 0.49 ($P = 0.21$ and 0.10, two- and one-sided permutation tests, respectively; $n = 8$). Pre- and posttherapy ETBFs appeared to be correlated ($r = 0.84$). The results of the Wilcoxon test suggested an association between changes in ETBF and PFS status. The Hodges–Lehmann estimate of the shift parameter was 0.954 (95% marginal CI = 0.008–2.800). Patients who were progression free at six months tended to have increased ETBFs during therapy (median change = 0.3) compared with those who were not (median change = –0.3).

Conclusions: Use of functional imaging to estimate blood flow is a viable research endpoint and deserves further study. The positive correlation observed between ETBF and MVD may become statistically significant in larger studies. Additional studies will determine if increased ETBFs result from stabilization of the tumor vasculature. Consideration of additional imaging time points and monitoring specifically in target lesions may further improve the overall clinical utility of this DC-MRI endpoint.

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Comparing overall survival in patients with epithelial ovarian, primary peritoneal or fallopian tube cancer who received chemotherapy alone versus neoadjuvant chemotherapy followed by delayed primary debulking

R. Correa[1], S. Dunningan[2], T. Panzarella[2], S. Ferguson[2], K. Murphy[2], H. Mackay[2], M. Bernardini[2]
[1]*University Health Network, Toronto, ON, Canada,* [2]*Princess Margaret Hospital, Toronto, ON, Canada*

Objective: Neoadjuvant chemotherapy (NAC) is increasingly used for women with advanced-stage epithelial ovarian carcinoma (EOC). If delayed primary surgery occurs, it is usually after three or four cycles of platinum–taxane-based chemotherapy. The aim of this study was to evaluate the effect of surgery on women receiving NAC as opposed to those receiving NAC who did not undergo surgery. We compared the overall survival (OS) of women treated with NAC who underwent surgery and those in whom surgery was not attempted.

A retrospective chart review of 290 women in our database undergoing NAC between 1999 and 2008 was undertaken. Following exclusion for nonepithelial histology, primary radiation and loss to follow-up, 182 patients were eligible for analysis. All cases of women who did not undergo surgery ($n = 51$) but met the EORTC criteria for surgical intervention ($n = 31$), as per the recent randomized trial, were reviewed by three gynecologic oncologists. These patients were compared with the NAC patients who underwent delayed primary surgery ($n = 131$). OS was compared using log-rank or Wilcoxon statistics and adjusted for important covariates using a Cox proportional hazards model. A comparison between the two groups was also made based on initial response to chemotherapy, with good response defined as a >85% decrease in CA-125 of after three cycles of chemotherapy.

Results: Women who underwent surgery after NAC had a significantly improved OS when compared with those who underwent chemotherapy alone ($P = 0.0003$, HR = 2.18, 95% CI = 1.42–3.35). After adjustment for confounding variables including age at diagnosis, number of comorbidities and rate of decrease in CA-125, the survival advantage retained only borderline significance ($P = 0.052$, HR = 1.76, 95% CI = 0.996–3.1). Patients with a >85% reduction in CA-125 after three cycles of chemotherapy had a significantly better OS compared with those with a reduction ≤85% ($P = 0.029$) regardless of surgical intervention, and among women with a good response to chemotherapy, those who underwent surgery had no survival advantage over those treated with chemotherapy alone ($P = 0.48$).

Conclusions: Following EORTC criteria after NAC, women who undergo surgery have an improved OS compared with women treated with chemotherapy alone. However, the benefit appears to be lost in those women who had a high initial response to chemotherapy as measured by decrease in CA-125.

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Consolidation paclitaxel is more cost-effective than bevacizumab following upfront treatment of advanced ovarian cancer

J. Lesnock[1], C. Farris[2], T. Krivak[1], K. Smith[2], M. Markman[3]
[1]*Magee–Womens Hospital of UPMC, Pittsburgh, PA,* [2]*University of Pittsburgh, Pittsburgh, PA,* [3]*Cancer Treatment Centers of America, Eastern Regional Medical Center, Philadelphia, PA*

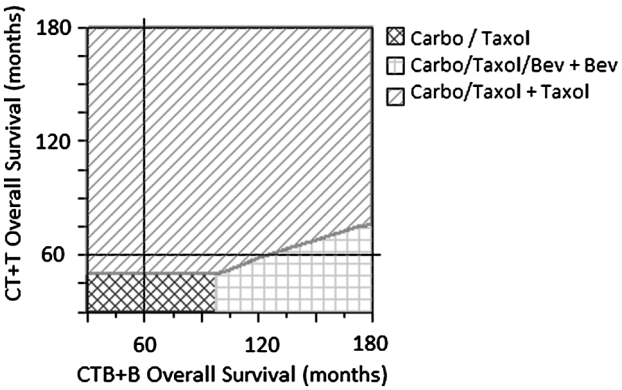
Objective: Standard therapy for advanced epithelial ovarian cancer (EOC) is surgical cytoreduction followed by six cycles of carboplatin and paclitaxel (CT). Randomized, phase III controlled studies have shown significant improvement in progression-free survival (PFS) with consolidation paclitaxel (T) and bevacizumab (B). We sought to evaluate the cost-effectiveness (C/E) of consolidation T versus B in the treatment of advanced EOC.

A decision model was developed to compare consolidation strategies. Arm 1 (reference) is six cycles of CT. Arm 2 is six cycles of CT followed by 12 cycles of T (CT + T). Arm 3 is one cycle of CT, five cycles of CTB, and 16 cycles of B (CTB + B). These are based on Gynecologic Oncology Group (GOG) protocols 178 and 218. Parameters include PFS and overall survival (OS), cost, and quality-of-life utility values. Cost incorporates the reimbursement costs of chemotherapy, administration, complications and surveillance. Modeled complications include neuropathy for T and bowel perforation for B. Key estimates are based on literature and expert opinion, Medicare reimbursement rates, and the Agency for Healthcare Research and Quality Database. The model assumes equal PFS and OS for Arms 2 and 3, recognizing that responses were defined differently in each study and may account for survival differences. Sensitivity analyses were performed to account for uncertainty in assumptions.

Results: Cost-effectiveness analysis revealed the incremental cost-effectiveness ratio (ICER) for CT + T is $12,888 per quality-adjusted life-year (QALY) gained compared with CT. For CTB + B compared with CT, the ICER is $326,562/QALY. When all three strategies are compared simultaneously, CTB + B is dominated, that is, more costly and less effective than CT + T. Sensitivity analyses demonstrated results were robust to PFS variation. At a willingness to pay threshold of $100,000/QALY, CT + T was the preferred option throughout most of the decision space (see figure). CTB + B would become the preferred option if it were to improve OS by 5.6 years over CT + T.

Conclusions: In this model, consolidation B following upfront treatment of advanced EOC was associated with a modest improvement in effectiveness that is less than that obtained with consolidation T and more costly. Significant improvement in survival may improve the value of B relative to T. In the current health care environment where costs are

highly scrutinized, the C/E of consolidation chemotherapy, as well as the agent of choice, may be questioned.



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Cytoreductive surgery for serous ovarian cancer in patients 75 years and older

K. Long, E. Tanner, M. Guy, M. Leitao, G. Gardner, Y. Sonoda, C. Brown, R. Barakat, D. Chi
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The purpose of this study was to evaluate the clinical course and outcomes of patients 75 years and older who underwent primary cytoreductive surgery for advanced serous ovarian cancer.

Patient demographics, surgical procedures, and perioperative and long-term outcomes were collected for all patients with advanced-stage serous cancer of the ovary, fallopian tube or peritoneum who underwent primary cytoreductive surgery (CRS) at our institution from December 2000 to December 2009. Patients who received neoadjuvant chemotherapy were excluded. Standard statistical analysis and Kaplan–Meier survival analysis were used.

Results: Of the 427 patients identified, 52 (12.2%) were 75 years or older at diagnosis and were selected as appropriate surgical candidates by their primary surgeons. The American Society of Anesthesiologists (ASA) score was significantly higher in the older cohort, with 57.7% having an ASA of 3, compared to 26.7% in the younger group ($P<0.001$). Carcinomatosis was identified on preoperative imaging in 69.2% of the older cohort versus 68.8% of the younger cohort ($P=0.47$). Stage IV disease was diagnosed in 13.5% of the older cohort versus 17.9% of the younger cohort ($P=0.66$). Optimal CRS (<1 cm of residual disease) was achieved in 71.2% of the older cohort versus 76% of the younger cohort ($P=0.45$). In the older cohort, there was an increased rate of postoperative cardiovascular complications ($P=0.048$), but no difference in overall complication rates ($P=0.99$). There was also no difference in the postoperative length of stay ($P=0.42$). In the older cohort, median progression-free survival (PFS) was 25.9 months (95% CI = 10.4–41.4) in those with optimal CRS versus 8.1 months (95% CI = 6.6–9.6) in those with suboptimal CRS ($P=0.001$). In patients younger than 75 with optimal CRS, median PFS was 22.1 months (95% CI = 19.0–25.2) ($P=0.98$). In the older cohort, median overall survival (OS) was 38.5 months (95% CI = 13.8–63.2) in those with optimal CRS versus 20.8 months (95% CI = 15.5–26.1) in those with suboptimal CRS ($P<0.01$). In patients younger than 75 with optimal CRS, median OS was 66.1 months (95% CI = 58–74.2) ($P<0.01$).

Conclusions: Although patients 75 or older have an increased risk of postoperative cardiovascular complications, the overall complication rate is not increased. Optimal CRS results in a significant survival benefit in highly selected patients 75 years or older. In addition, optimal CRS in patients 75 years or older results in a PFS comparable to that of younger patients. Age alone should not be used to determine operative candidacy.

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Discovery of novel monoclonal antibodies (MC1–MC6) to detect ovarian cancer in serum and differentiate it from benign tumors

E. Orr[1], D. Vassilakos[1], A. Gonenne[1], B. Piura[2], A. Rabinowich[2], T. Van Gorp[3], I. Vergote[3]
[1]*MabCure, N.V., Diepenbeek, Belgium,* [2]*Soroka Medical Centre, Beer-Sheva, Israel,* [3]*University Hospital Leuven, Leuven, Belgium*

Objective: Early and correct diagnosis of ovarian cancer (OVCA) in patients with a pelvic mass is paramount because it might improve survival. To date, there are no validated serum markers specific enough to screen for OVCA. The current study was aimed at evaluating the ability of six new monoclonal antibodies (MAbs) to detect OVCA and to distinguish between OVCA and benign ovarian tumors in sera.

Mice were immunized with OVCA cell lines, pretreated to maintain their antigenic properties, yielding >30,000 hybridomas. Extensive screening of MAbs against different cells identified six that highly cross-reacted with all tested OVCA cell lines, but not with controls, such as different colon carcinoma, metastatic melanoma, and nevi cell lines. These six MAbs were selected for further testing. Assays were used to determine the cutoff points for the six selected MAbs. Negative control sera were obtained from healthy young females ($n=24$) and males ($n=8$). Sera from patients with confirmed advanced OVCA ($n=17$) and from patients with benign ovarian tumors ($n=5$) were tested blindly.

Results: All six MAbs, MC1–MC6, cross-reacted with sera obtained from (12 + 4) OVCA patients*. None cross-reacted with serum from healthy control patients (Figs. A and B). Three of the six, MC1–MC3, cross-reacted with 16 of 17 OVCA sera* and did not cross-react with sera from five patients* with benign ovarian tumors. The diagnostic specificity and sensitivity of these three Mabs were 100 and 94%, respectively (Fig. B).

Conclusions: We have assessed the specificity of six new MAbs, obtained from more than 30,000 hybridomas against OVCA antigens. Three of six selected MAbs identified OVCA in patients' sera with advanced disease, displaying high sensitivity (94%), and distinguishing it from benign ovarian tumors (zero false positives). These MAbs are currently being tested in a larger number of patients with pelvic masses.

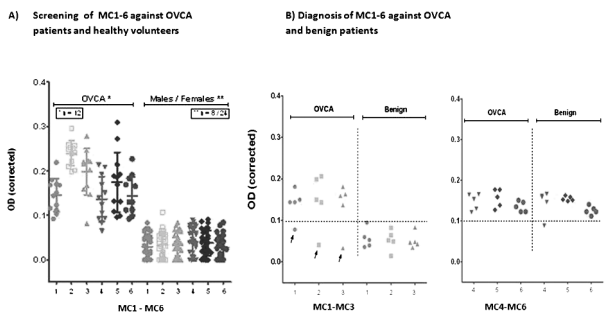

Figure 1: A) Cross-reactivity between each of the Mabs, MC1-MC6 (represented by different colours) with control sera obtained from 24 young and healthy females and 8 males (right panel) and with sera obtained from 12 patients with malignant ovarian cancer (left panel). **B**): Cross-reactivity of MC1-MC6 with sera from 5 patients with malignant ovarian cancer (OVCA), and 5 patients with benign ovarian cancer. Repeated tests produced similar results. Arrows at the bottom left of the left figure refer to a single serum sample which did not cross-react with MC1-MC3.
*The 2 sets of sera in A and B were analysed separately and obtained from different medical centres.

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Elevated serum adiponectin levels correlate with survival in epithelial ovarian cancers

E. Diaz, I. Chen, N. Liburd, B. Karlan, C. Walsh, I. Cass, A. Li
Cedars–Sinai Medical Center, Los Angeles, CA

Objective: The adipocyte-secreted hormone adiponectin influences the regulation of inflammation and angiogenesis, and serum concentrations are determined not only by adiposity but also by genetic factors and nutrition. Translational studies indicate adiponectin may exert antiproliferative effects in cancer biology, but data in pancreatic cancer suggest elevated levels promote carcinogenesis. We sought to examine the correlation between serum adiponectin and clinical outcome in a cohort of women with epithelial ovarian cancers.

After institutional review board approval we queried the institutional tumor registry for consecutive patients with ovarian cancer with available banked fasting prediagnostic serum. All patients underwent cytoreductive surgery with histologically confirmed epithelial ovarian or primary peritoneal cancer, followed by platinum-based chemotherapy. We assayed frozen serum for adiponectin using ELISA (R&D, Inc.) and abstracted clinicopathologic data from medical records. Adiponectin levels were considered elevated if greater than 10.0 μg/mL. Statistical tests included rank correlation, Kaplan–Meier, and Cox regression analyses.

Results: We examined serum and clinical data from 95 patients. Adiponectin concentrations ranged from 2.7 to 28.4 μg/mL (mean = 11.2); body mass index (BMI) ranged from 16.9 to 39.9 kg/m^2 (mean = 24.7). We did not determine a significant correlation between BMI and adiponectin ($r = -0.21$). Women with elevated adiponectin levels demonstrated statistically shorter disease-specific survival (44 months) compared with those with normal levels (67 months) ($P = 0.03$). When examining the cohort in three strata (low, moderate, and high levels of adiponectin), we identified a significant trend of decreasing survival with increasing adiponectin concentration (median survival = 125, 58, and 44 months, respectively) ($P = 0.02$). On multivariate analysis, after controlling for BMI, age, stage, and grade, we determined that adiponectin and cytoreductive status retained significance as independent prognostic factors for overall survival ($P = 0.02$ and 0.004, respectively).

Conclusions: These data suggest adiponectin concentration, independent of adiposity, is negatively associated with clinical outcome in this cohort. Translational studies and prospective trials are indicated to determine the role of adiponectin as a potential therapeutic target in women with ovarian cancer.

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Evaluation of the risk of ovarian malignancy algorithm in women with a pelvic mass presenting to general gynecologists

R. Moore[1], C. Miller[2], P. DiSilvestro[1], L. Landrum[3], W. Gajewski[4], P. Renneisen[5], S. Skates[6]
[1]Women & Infants Hospital/Brown University, Providence, RI, [2]Statistical Consultant, Quakertown, PA, [3]University of Oklahoma, Oklahoma City, OK, [4]New Hanover Regional Medical Center, Wilmington, NC, [5]Fujirebio Diagnostics, Malvern, PA, [6]Massachusetts General Hospital/Harvard University, Boston, MA

Objective: Women with epithelial ovarian cancer (EOC) have improved outcomes when surgically managed by gynecologic oncologists. It is often difficult to distinguish a benign pelvic mass from a malignancy, and tools to help referring physicians are needed. The objective of this trial was to validate the Risk of Ovarian Malignancy Algorithm (ROMA) in a population of women presenting to a gynecologist with a pelvic mass.

This was an institutional review board-approved multicenter blinded prospective trial. All women had a pelvic mass and surgical intervention. Serum levels of HE4 and CA-125 were determined preoperatively. An initial clinical assessment (ICA) was performed by a gynecologist. A ROMA risk was calculated for each patient. Sensitivity, specificity, and negative (NPV) and positive (PPV) predictive values were calculated for ROMA, ICA, and ROMA plus ICA.

Results: Thirteen sites enrolled 512 women with 468 evaluable patients, of whom 255 were premenopausal and 213 were postmenopausal. There were 48 cases of EOC (8 stage I, 4 stage II, 32 stage III, two stage IV, and two unstaged), 18 low-malignant-potential (LMP) tumors, 21 cases of nonepithelial ovarian cancer, and 381 benign cases. In evaluation of premenopausal women with benign tumors ($n = 235$) versus EOC (n = 8), ROMA had a sensitivity of 100% (95% CI = 63.1–100%) and a specificity of 74.5% (95% CI = 68.4–79.9%). In postmenopausal women with benign tumors ($n = 146$) versus EOC ($n = 40$), ROMA had a sensitivity of 92.5% (95% CI = 79.6–98.4%) and a specificity of 76.0% (95% CI = 68.3–82.7%). In all women with benign tumors ($n = 381$) versus EOC ($n = 48$), ROMA had a sensitivity of 93.8% (95% CI = 82.8–98.7%), a specificity of 75.1% (95% CI = 70.4–79.3%), a PPV of 32.1% (95% CI = 24.5–40.6%), and a NPV of 99.0% (95% CI = 97.0–99.8%). In contrast, the ICA had a sensitivity of 83.3% (95% CI = 69.8–92.5%), a specificity of 84.5% (95% CI = 80.5–88.0%), a PPV of 40.4% (95% CI = 30.7–50.7%), and a NPV of 97.6% (95% CI = 95.3–98.9%). In analysis of benign versus EOC and LMP tumors, ROMA had a sensitivity of 87.9% (95% CI = 77.5–94.6%) and a specificity of 75.1% (95% CI = 70.4–79.3%), whereas the ICA had a sensitivity of 75.8% (95% CI = 63.6–85.5%) and a specificity of 84.5% (95% CI = 80.5–88.0%). In analysis with the combination of ICA and ROMA in benign versus EOC and LMP tumors, the two methods together had a sensitivity of 90.9% (95% CI = 81.3–96.6%) and a specificity of 66.9% (95% CI = 62.0–71.6%). Of the 8 cases of EOC the ICA missed, ROMA detected 5 (3 stage I or II and 2 stage III or IV).

Conclusions: ROMA has a high sensitivity for evaluating women with a pelvic mass for EOC. ROMA should be used in conjunction with ICA to aid in the triage of women to gynecologic oncologists.

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Factors associated with hospice use in ovarian cancer

C. Casey, H. Deshmukh, A. Sherman, L. Chen, J. Chan
UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Objective: The purpose of this study was to determine the factors and trends in hospice use in patients with ovarian cancer in the Medicare population.

All women aged 65 and older who were diagnosed and died of ovarian cancer between 1991 and 2002 were identified from the Medicare–SEER database. χ^2 analyses were used to examine hospice use and length of stay in hospice.

Results: Among 8740 patients, the overall rate of hospice use was 30.5% ($n = 2667$). Of these patients, 29.8% were white and 41.3% were black. The proportions of patients aged 65–70, 71–75, 76–80, and >80 years were 30.4, 32.3, 30, and 29.7%, respectively. The median

length of stay was constant (approximately 30 days) across all age groups. Hospice was used by 28% of married women versus 33% of widowed and/or single women. There was an association between higher income (<$30,000, $30,000–$75,000, and >$75,000) and decreased hospice use (35.4, 21.6, and 19%). Over the periods 1991–1994, 1995–1998, and 1999–2002, hospice use varied from 35.17% to 36.7% to 22.7%, while the average length of stay remained constant (32.2 days vs 32.09 days vs 31.9 days).

Conclusions: In this patient cohort, race and income level are factors associated with hospice use. Factors associated with hospice use can help guide the development of palliative care programs to improve the quality of care given to patients with ovarian cancer.

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Genes functionally regulated by methylation in ovarian cancer are involved in cell proliferation, development and morphogenesis

K. Yamaguchi[1], T. Baba[2], I. Konishi[2], N. Matsumura[2], S. Murphy[1], Z. Huang[1], A. Berchuck[1]

[1]Duke University Medical Center, Durham, NC, [2]Kyoto University, Kyoto, Japan

Objective: Gene promoter methylation leads to transcriptional repression, but genomewide relationships between methylation and expression in ovarian cancer (OVCA) have not been reported. We sought to elucidate genes directly regulated by methylation using genomic approaches and determine the biologic functions targeted by this epigenetic modification.

Illumina HumanMethylation27 BeadChip (HM27) data and Affymetrix HT HG-U133A (Affy) expression data (generated following culture ± DNMT inhibitor decitabine) for the same 32 OVCA cell lines were analyzed. HM27 and Affy data for 508 TCGA OVCAs were also analyzed. Pearson correlation analysis identified "Genes Functionally Regulated by Methylation" (GFRM) showing: (1) positive correlation between methylation and expression induction by decitabine, and (2) inverse correlation between methylation and expression in mock-treated cells. Methylation status was confirmed using MS-PCR. Gene functions were analyzed using Web-based GATHER software. GSE6008 (OVCAs) and GSE5846 (NCI60 cell lines) were used for validation.

Results: We identified 225 genes as GFRM. MS-PCR showed that six of 6 GFRM (DAPK1, IER3, IGFBP3, KLK10, KRT7 and VEGFC) exhibit methylation; mRNA expression also differed between methylated and unmethylated groups ($P<0.05$). GFRM included Gene Ontology annotations of "Cell Proliferation" ($P=0.0002$), "Development" ($P=0.00006$), and "Morphogenesis" ($P=0.00016$). Hierarchical clustering of 51 OVCA cell lines by GFRM identified two major clusters with different population doubling times ($P<0.0001$). Hierarchical clustering of GSE6008 and GSE5846 generated histology-based clusters. Two GSE5846 clusters also showed different population doubling times ($P=0.008$).

Conclusions: Using genomic approaches, we have identified 225 GFRM in OVCA that are involved in regulating cell proliferation and morphologic development. Distinct patterns of methylation based on growth characteristics and histologic type may be useful toward development of disease biomarkers.

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Horm-A domain-containing protein 1 (HORMAD1) and outcomes in patients with ovarian cancer

M. Shahzad[1], K. Matsuo[2], Y. Shin[3], R. Stone[4], J. Bottsford-Miller[4], C. Lu[4], H. Han[4], A. Rajkovic[3], A. Sood[4]

[1]University of Wisconsin School of Medicine and Public Health, Madison, WI, [2]University of Southern California, Los Angeles, CA, [3]University of Pittsburgh Medical Center, Pittsburgh, PA, [4]University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: HORMAD proteins are recognized for their role in cell cycle regulation and meiosis. Recent data indicate a potentially oncogenic role for HORMAD1 in breast carcinoma. However, the clinical and biologic significance of HORMAD1 in ovarian carcinoma is not known.

In vitro effects of HORMAD1 silencing on 2774 ovarian cancer cell viability, invasion, and migration were determined. In vivo targeting of HORMAD1 using siRNA incorporated into DOPC nanoliposomes was done in a well-characterized orthotopic mouse model of ovarian carcinoma (2774). Additionally, we evaluated HORMAD1 mRNA levels using quantitative RT-PCR from 92 human epithelial ovarian tumors and looked for potential correlations with clinical outcome.

Results: Compared with normal cells, ovarian cancer cells had high expression of HORMAD1. In vitro HORMAD1 siRNA treatment in 2774 ovarian cancer cells resulted in a >80% reduction ($P<0.05$) in the IC_{50} of docetaxel. Hormad1 siRNA and docetaxel treatment increased apoptosis by 53% compared with docetaxel treatment alone ($P<0.05$). HORMAD1 siRNA reduced 2774 ovarian cancer cell invasion and migration by 65 and 42% (both $P<0.05$), respectively. In therapy experiments (2774 ovarian cancer model), HORMAD1 siRNA-DOPC or cisplatin treatment resulted in 45 and 81% ($P<0.05$, both) reductions in tumor weight. Combination treatment resulted in a 94% reduction in tumor weight compared with control treatment ($P<0.01$) and a further 72% reduction in tumor weight compared with cisplatin monotherapy ($P<0.05$). Similar results were noted with tumor nodules and ascites formation. HORMAD1 siRNA-DOPC or cisplatin treatment alone resulted in 38 and 62% reductions in microvessel density (MVD) ($P<0.05$), respectively compared with control siRNA-DOPC treatment. Combination treatment resulted in a 75% ($P<0.05$) reduction in MVD compared with control siRNA-DOPC and a further 20% reduction in MVD compared with cisplatin alone. Levels of HORMAD1 mRNA were increased in 76.1% of ovarian cancer specimens (fold change >1). Median fold change of HORMAD1 expression was 5.6-fold higher (range: 0.23–1297.5) than that of the normal ovarian epithelium. FIGO stage and preoperative CA-125 values were associated with therapy response ($P<0.01$). Patient age, preoperative CA-125 level and chemotherapy response significantly affected overall survival. High levels of HORMAD1 were significantly associated with the presence of ascites ($P=0.01$).

Conclusions: HORAMD1 expression is frequently increased in ovarian carcinoma. Our data indicate that HOMRAD1 may be an important therapeutic target.

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Human epididymis protein 4 increases specificity for the detection of invasiive epithelial ovarian cancer in premenopausal women presenting with an adnexal mass

K. Holcomb[1], C. Miller[2], Z. Vucetic[2], R. Knapp[3]

[1]Weill Medical College of Cornell University, New York, NY, [2]Fujirebio Diagnostics, Inc., Malverne, PA, [3]Harvard Medical School, Boston, MA

Objective: An estimated five to 10% of women in the United States will undergo surgery for a suspected ovarian neoplasm and 13 to 21% of these will be diagnosed with an ovarian malignancy. Although the incidence of invasive ovarian cancer in premenopausal women is low, the primary goal in these patients is to estimate the risk of malignancy in order to tailor treatment and to manage the patient expectantly when appropriate. Serum CA-125, clinical evaluation and radiographic findings have traditionally been used in the evaluation. CA-125 is often elevated in benign conditions and its ability to detect ovarian cancer is limited in premenopausal women. Human epididymis protein 4 (HE4), a novel tumor marker, has been proposed to improve specificity in the differentiation between benign and malignant ovarian neoplasms.

A prospective, multicenter clinical trial conducted at 14 sites enrolled women 18 years of age or older who presented with an adnexal mass and were scheduled to undergo surgery. Serum CA-125 and HE4 levels were obtained. Established cutoff values for the upper limit of normal for each marker were used. Sensitivities and specificities for the differentiation of benign ovarian neoplasm and invasive epithelial ovarian cancer (EOC) were determined and compared.

Results: Of the 472 evaluable patients, 344 (73%) were diagnosed with benign disease (195 premenopausal and 149 postmenopausal), while 128 (27%) were diagnosed with stage I–IV EOC (18 premenopausal and 110 postmenopausal). For CA-125, a threshold of >35 U/mL was used. For HE4 a threshold of >70 pM was used. The sensitivity of CA-125 for the detection of EOC in premenopausal women was 83.3%, compared with 88.9% for HE4. The specificity of CA-125 was 59.5%, compared with 91.8% for HE4. At a preset specificity of 95%, HE4 showed significantly increased sensitivity compared with CA-125 (77.8% vs 33.3%, $P=0.018$).

Conclusions: When established cutoffs are used, HE4 offers a sensitivity comparable to that of CA-125 for detection of EOC in premenopausal women with an adnexal mass, but at a significantly increased specificity. At a preset specificity of 95%, HE4 is significantly more sensitive than CA-125. Specificity is critical in the management of these patients. HE4, together with clinical evaluation and imaging, is a valuable tool in the assessment of premenopausal women with an adnexal mass.

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Identification of biomarkers to improve specificity in preoperative assessment of ovarian tumor for risk of cancer

Z. Zhang, L. Sokoll, X. Sun, D. Meany, D. Elliott, D. Chan
Johns Hopkins Medical Institutions, Baltmore, MD

Objective: The purpose of this study was to identify biomarkers complementary to CA-125 to improve specificity in preoperative assessment of ovarian tumor for risk of cancer.

ELISAs of five biomarkers were performed on tissues from 15 patients with ovarian cancer and 22 patients with benign pelvic masses. The biomarkers MMP7, tenascin C, NAP2, uPAR, and MMP9 were selected through a literature search because of their ability to detect ovarian tumors with a reasonably high level of specificity. The 22 patients with benign disease were purposely chosen for their relatively high serum CA-125 levels (mean = 155.5 IU, median = 101.6 IU). For statistical analysis, the biomarkers were first evaluated individually by receiver operating characteristic (ROC) curve analysis. The biomarkers, after log transformation, were further assessed by multivariate logistic regression for their significance in complementing CA-125 to differentiate malignant from benign pelvic masses.

Results: The AUC for CA-125 alone was 0.824. The individual AUCs for MMP7, tenascin C, NAP2, uPAR, and MMP9 were 0.870, 0.685, 0.748, 0.718 and 0.670, respectively. The *P* values from logistic regressions testing the significance of each of the five markers in complementing CA-125 to differentiate ovarian cancer from benign pelvic masses were 0.008, 0.052, 0.080, 0.357, and 0.212, respectively. Finally, in a multivariate logistic regression model that included CA-125, MMP7, tenascin C, and NAP2 as its input variables, the *P* values for the four input variables were 0.105, 0.044, 0.034 and 0.050, respectively.

Conclusions: In this preliminary analysis of five biomarkers using a limited clinical specimen set, MMP7, tenascin C and NAP2 demonstrated both relatively high discriminatory power individually and a potential to complement CA-125. With additional large-scale validation, these biomarkers may be used as part of a multivariate panel to differentiate malignant from benign ovarian tumors preoperatively.

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Impact of FDG-PET in suspected recurrent ovarian cancer and optimization of patient selection for cytoreductive surgery

Y. Ebina[1], N. Sakuragi[2]
[1]*Kobe University, Kobe, Japan,* [2]*Hokkaido University, Sapporo, Japan*

Objective: The purpose of this study was to investigate the impact of PET scan findings on making a decision regarding management plans and to identify the optimal setting for selecting surgery candidates from patients with suspected recurrent ovarian cancer.

A retrospective chart review was performed on patients with possible recurrent ovarian cancer who underwent FDG-PET or FDG-PET/CT scans from July 2002 to August 2008. This analysis included 44 patients who underwent a total of 89 PET scans. All patients had histologically confirmed ovarian cancer and underwent primary optimal cytoreduction. The positive PET scans were classified into three categories with those uptake patterns of FDG: (1) localized––one or two localized uptakes, (2) multiple––more than three uptakes, (3) diffuse––extensive low-grade activity outlining the serosal and peritoneal surface. Systemic chemotherapy is given to patients with multiple or diffuse FDG uptake patterns. Otherwise, cytoreductive surgery is proactively considered for the patients whose FDG uptake pattern is localized.

Results: In total, the proportion of patients whose management plans changed after the PET scan was 63.4%. After the PET scan, the total number of patients for whom surgery was planned increased from 12 to 35. The frequency of a localized FDG uptake pattern was significantly higher in the patients with treatment-free intervals (TFIs) >6 months than in those with TFIs <6 months (70.0% vs 42.9%, $P<0.05$). Thirty-five cytoreductive surgeries were performed on 25 patients. In all patients, recurrent tumors predicted by PET scans were recognized during surgery, and no macroscopic tumors undetectable by PET scan were discovered. However, miliary disease, which cannot be detected with PET, was observed in 22.2%. At the end of cytoreduction, macroscopically complete resection was achieved in 91.4%. On the other hand, 8.6% of the patients had residual tumors <0.5 cm. Miliary disease was detected in six of the 12 patients with a TFI <12 months compared with none of those with a TFI ≥ 12 months ($p<0.01$).

Conclusions: We found that management plans changed in 63% of patients because of PET scan findings. PET was especially helpful in

selecting candidates for site-specific treatment (e.g., surgery, irradiation). As for cytoreductive surgery, the rate of complete resection is high at 91%. Even if PET indicates localized disease, to avoid miliary dissemination, patients with TFIs 12 months are the best candidates for complete resection.

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Influence of the novel histone deacetylase inhibitor panobinostat (LBH589) on the growth of ovarian cancer

L. Garrett, L. Zhang, L. Guo, V. Therrien, W. Growdon, R. Foster, B. Rueda
Massachusetts General Hospital/Harvard University, Boston, MA

Objective: Preclinical studies in gynecologic and other malignancies demonstrate that HDAC inhibitors can impede cancer cell line proliferation in vitro and block the growth of tumors derived from those cell lines in vivo. We used both established ovarian cancer lines and a xenograft model of patient-derived primary serous ovarian tumors to evaluate the efficacy of the HDAC inhibitor panobinostat (LBH589) as a single agent in vitro or in combination with cytotoxic chemotherapy in vivo.

Ovarian cancer cell lines were treated in vitro with increasing doses of LBH589. Cell growth inhibition by LBH589 was analyzed using the MTT assay. For the in vivo study, primary human high-grade serous ovarian adenocarcinoma tumors were serially transplanted in NOD/SCID mice. Following the development of tumor xenografts, mice were randomized into one of four treatment groups: (1) paclitaxel 15 mg/kg and carboplatinum 50 mg/kg (T/C) administered by intraperitoneal injection (IP) weekly + LBH589 vehicle IP five times per week; (2) T/C vehicle IP weekly + LBH589 (2.5 mg/kg) IP five times per week; (3) T/C vehicle IP weekly + LBH589 vehicle IP five times per week; or (4) T/C IP weekly + LBH589 IP five times per week. Mice were treated for 21 days, and tumor volumes and mouse weights were assessed every three days. Experiments were performed with primary human tumors derived from three individual patients to validate our findings.

Results: In vitro treatment with LBH589 significantly suppressed the growth of both taxol-sensitive and taxol-resistant ovarian cancer cell lines. In vivo treatment with LBH589 as a single agent appeared tumorstatic with reduced tumor growth when compared with vehicle ($P<0.007$) after 21 days. This single-agent activity was confirmed in two additional experiments with other primary serous tumors ($P<0.03$, $P<0.05$). We observed additional tumor regression compared with vehicle ($P<0.02$) following administration of LBH589 and T/C in only one of the three patient tumors analyzed. The only significant weight loss occurred in those animals receiving combination therapy ($P<0.005$) compared with the other treatment arms.

Conclusions: Inhibition with panobinostat prevents proliferation of human ovarian cancer cell lines in vitro and blocks growth of primary human tumor xenografts. An added benefit of LBH589 to standard T/C therapy was observed in one of three xenografted human serous tumors, suggesting synergistic effects in a subset of serous ovarian cancers.

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Resident/Fellow Plenary Session
Sunday, March, 6, 2011, 9:20AM–10:00AM
Grand Ballroom I

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Inhibition of stress-induced phosphoprotein 1 decreases proliferation of ovarian cancer cell lines

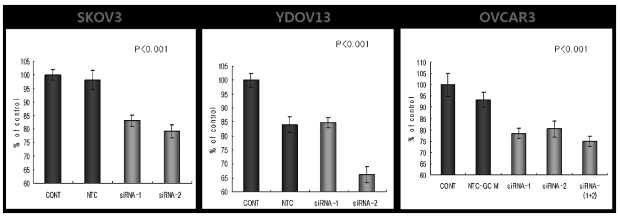
B. Kim[1], J. Kim[1], Y. Kim[1], S. Kim[1], S. Kim[1], E. Nam[1], D. Chay[2]
[1]*Gangnam Severance Hospital, Seoul, Republic of Korea,*
[2]*Yongin Severance Hospital, Yongin, Republic of Korea*

Objective: Stress-induced phosphoprotein 1 (STIP-1) was previously identified by comparing different tumor-associated antigen levels between pretreatment and posttreatment sera from patients with ovarian cancer. STIP-1 acts as an adapter to assemble HSP 90 to HSP 70–client protein complexes, which are associated with antiapoptosis in various cancers. We attempted to determine whether the inhibition of STIP-1 influences proliferation in ovarian cancer cell lines.

STIP-1 expression in the ovarian cancer cell lines SKOV3 and OHK was silenced by small interfering RNA (siRNA). The sequences selected for siRNA transfection were 5′-ACGAGGCAAA-TAACCCTCAACTGAA-3′ and 5′-TCAACATGCCTAATCTGTATCAGAA-3′. Knockdown of STIP-1 was checked by real-time RT-PCR and Western blot. MTS assay and RT-PCR of Ki-67 were used to evaluate proliferation in ovarian cancer cell lines that were inhibited by the siRNA of STIP-1. After xenografting of the SKOV3 cell line to nude mice, intratumoral siRNA injections were given every three days.

Results: Quantitative RT-PCR showed that after siRNA transfection, mRNA of STIP-1 was reduced to 15.5% with siRNA1 and 12.5% with siRNA2 in SKOV cancer cells. After siRNA transfection, the STIP-1 protein level also decreased to 27% and, 72 hours later, to 16%. Three days later, siRNA-transfected cells showed less proliferation than the control ($[I]P<0.001$). Ki-67 mRNA level decreased significantly in siRNA-transfected SKOV3 cells compared with the control and negative control. In the xenograft, tumor mass size decreased in mice injected intratumorally with siRNA.

Conclusions: We determined that downregulation of STIP-1 by siRNA decreased proliferation of ovarian cancer cells.



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Insulin-like growth factor receptor 1 pathway signature correlates with adverse clinical outcome in ovarian cancer

B. Winterhoff[1], P. Haluska[1], K. Kalli[1], W. Cliby[1], B. Gostout[1], A. Oberg[1], M. Maurer[1], L. Hartmann[1], D. Slamon[2], G. Konecny[2]
[1]*Mayo Clinic, Rochester, MN,* [2]*UCLA School of Medicine, Los Angeles, CA*

Objective: Dysregulation of the insulin-like growth factor receptor 1 (IGFR1) pathway has been implicated in malignant transformation, proliferation, metastasis, and resistance to chemotherapy in ovarian cancer. Strategies inhibiting the IGFR1 signaling pathway are currently being investigated in patients with ovarian cancer. Our aim was to determine the expression pattern and prognostic relevance of the IGFR1 pathway components in a large cohort of patients with ovarian cancer of diverse histologic types.

Expression and activity of 19 of the most important components of the IGFR1 pathway were measured using a multiplex ELISA that allows assessment of multiple total and phosphorylated proteins in parallel. A total of 273 fresh-frozen ovarian cancer samples were analyzed, including 189 serous, 46 endometrioid, 25 clear cell and 13 mucinous ovarian cancers. Associations between protein levels and overall survival (OS) were assessed using Cox proportional hazards models and Kaplan–Meier survival analyses.

Results: In multivariate analyses adjusting for histologic type and tumor stage, increased expression of phosphorylated insulin receptor substrate 1 (pIRS, >59 relative light units, which is above the median) was significantly associated with adverse overall survival (OS) (relative risk [RR] = 1.46, $P = 0.004$). Similarly, low expression of IGF-binding protein 3 (IGFBP3, <10 pg/μg protein, which is below the median) was associated with poor OS (RR = 1.40, $P = 0.039$). Both high expression of pIRS and low expression of IGFBP3 combined were seen in 36% of all patients and were associated with significantly worse OS (RR = 1.34, $P = 0.040$), when compared with the remainder of the cohort.

Conclusions: These clinical observations confirm the hypothesis that an activated IGFR1 pathway, as seen here with low IGFBP3 and high pIRS1, correlates with adverse clinical outcome in ovarian cancer. This effect was independent of the histologic subtype. Low IGFBP3 expression with high pIRS1 expression was found in approximately one-third of the entire study cohort. IGFBP3 and pIRS1 levels may be useful biomarkers to select patients for IGFR1-targeted therapy in ovarian cancer.

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Intraperitoneal catheters placed at the time of bowel surgery: A review of complications

J. Carter, E. Dickson, R. Kothari, L. Downs, P. Argenta
University of Minnesota, Minneapolis, MN

Objective: Intraperitoneal (IP) chemotherapy has a proven survival advantage in patients with optimally cytoreduced advanced epithelial ovarian cancer, but uncertainty related to the placement of IP catheters at the time of bowel surgery may limit its use in some patients. Some authors suggest avoiding placement of IP ports in patients at the time of large bowel surgery. The goal of this study was to review the surgical complication rates of patients who had an IP catheter placed at the time of bowel surgery.

Patients undergoing surgical debulking or staging for stage II–IV ovarian, fallopian tube or primary peritoneal carcinoma between January 2006 and July 2010 were included in a retrospective review. Charts were abstracted for patient demographics, surgical procedure, stage, histology, medical comorbidities and complications within 30 days of surgery.

Results: Four hundred debulking or staging procedures were identified. There were 48 grade 3–4 complications (most commonly grade 3 small bowel obstruction) and seven grade 5 complications, which included cardiovascular effects ($n = 3$), sepsis ($n = 2$), and abdominal infection ($n = 2$). Bowel surgery (including appendectomy) was performed in 176 cases with an 18% ($n = 32$) complication rate. Of these, 71 patients had an IP port placed; in 82% ($n = 58$) the port was inserted primarily, and in 18% ($n = 13$) it was placed secondarily. IP port insertion at the time of bowel surgery was not associated with an increased risk of surgical complications (RR = 1.08, 95% CI = 0.53–2.14), compared with those who did not have bowel surgery at the time of IP port placement. Among 14 patients with large and small bowel surgery (excluding appendectomy alone), primary IP port placement was not associated with an increased risk of surgical complications (RR = 0.81, 95% CI = 0.212–2.583). IP port-specific complications in those placed at the time of bowel surgery included inflow obstruction ($n = 1$) and extravasation ($n = 1$). There was no association between surgical complication rate and age, body mass index, type of bowel surgery (large bowel, small bowel, enterotomy, appendectomy), use of Cavitron ultrasonic surgical aspiration, primary or secondary placement of IP port or medical comorbidities.

Conclusions: The placement of an IP port at the time of bowel surgery did not increase the risk of surgical complications compared with cases in which no bowel surgery was performed at the time of IP port placement. IP ports may be safely placed at the time of bowel surgery.

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Laparoscopic versus laparotomic surgical staging for early-stage epithelial ovarian cancer

J. Park, D. Kim, J. Kim, Y. Kim, Y. Kim, J. Nam
Asan Medical Center, Seoul, Republic of Korea

Objective: The purpose of this study was to compare the feasibility, accuracy and safety of laparoscopic versus laparotomic surgical staging in early-stage epithelial ovarian cancer (EOC).

Outcomes of patients with early-stage EOC who underwent complete surgical staging at Asan Medical Center between 2004 and 2010 were retrospectively evaluated.

Results: Eighty-four patients were surgically staged through laparoscopy and 128 through laparotomy. There were no between-group differences in mean age, parity, body mass index, lymph nodes retrieved and omentum specimen size, nor in the percentage of patients who were postmenopausal and the interval to restaging, in those upstaged after surgery and those with intraoperative tumor rupture. The laparoscopy group had a significantly shorter operating time (207 ± 91 minutes vs 262 ± 70 minutes, $P < 0.001$), less blood loss (252 ± 217 mL vs 454 ± 370 mL, $P < 0.001$),fewer transfusions required (13% vs 28%, $P = 0.012$), faster return of bowel movement (1.8 ± 1.5 days vs 3.1 ± 1.5 days, $P < 0.001$), shorter postoperative hospital stay (6.3 ± 3.6 days vs 13.5 ± 7.9 days, $P < 0.001$), and shorter interval to adjuvant chemotherapy (15.8 ± 5.7 days vs 20.7 ± 9.1 days, $P < 0.001$). Intraoperative complications did not differ between groups (7.1% vs 5.5%, $P = 0.619$), but postoperative complications were higher in the laparotomy group (7.1% vs 19.5%, $P = 0.013$). After a median follow-up time of 28 months (range: 1–79 months), five-year disease-free survival rates were 78 and 78% ($P = 0.873$) and five-year overall survival rates were 89 and 86% ($P = 0.731$) for the laparoscopy and laparotomy groups, respectively.

Conclusions: Laparotomy and laparoscopy showed similar surgical staging adequacy and accuracy and oncologic outcomes. But, laparoscopy showed more favorable operative outcomes.

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Oncologic and reproductive outcomes of cystectomy compared with oophorectomy as treatment for borderline ovarian tumor

T. Song, D. Bae, C. Choi, H. Kim, M. Kim, T. Kim, B. Kim, Y. Lee, J. Lee, J. Lee
Samsung Medical Center, Seoul, Republic of Korea

Objective: The purpose of this study was to compare the oncologic and reproductive outcomes of patients with borderline ovarian tumors (BOTs) who were treated with cystectomy or unilateral salpingo-oophorectomy (USO).

The medical records of patients with BOTs who were treated between 1997 and 2009 were reviewed, retrospectively. Recurrence rates were compared between the USO and cystectomy groups. Reproductive outcomes were assessed by telephone interviews.

Results: Patients with BOTs underwent either USO ($n=117$) or cystectomy ($n=38$). Twelve patients experienced a recurrence: One had an invasive recurrence and 11 had a borderline recurrence. The recurrence rate was lower in the USO group (5.9%) than in the cystectomy group (13.2%); however, this difference was not statistically significant ($P=0.110$). All patients experiencing recurrences were successfully treated with surgery and with no clinical evidence of disease. One hundred thirteen (97.4%) of the 116 patients contacted by telephone experienced menstruation following surgery, and 45 (86.5%) of the 52 patients who attempted to conceive had successful pregnancies. USO (89.2%), like cystectomy (85.7%), resulted in excellent pregnancy outcomes for patients with BOTs.

Conclusions: Unilateral salpingo-oophorectomy is an adequate treatment for women with BOTs who wish to preserve fertility. However, when cystectomy is the only viable option, it appears to be a satisfactory fertility-sparing therapy.

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OVA1 has high sensitivity in identifying ovarian malignancy compared with preoperative assessment and CA-125

F. Ueland[1], C. DeSimone[1], L. Seamon[1], R. Miller[1], S. Goodrich[1], I. Podzielinski[1], L. Sokoll[2], A. Smith[3], J. van Nagell[1], Z. Zhang[2]
[1]University of Kentucky Medical Center, Lexington, KY, [2]Johns Hopkins Medical Institutions, Baltimore, MD, [3]Applied Clinical Intelligence, Bala Cynwyd, PA

Objective: OVA1 is a multivariate index assay approved by the Food and Drug Administration to help identify high-risk ovarian tumors for referral to a gynecologic oncologist (GO) before surgery. The performance of OVA1 is compared with physician assessment (PA) and CA-125 in predicting ovarian malignancy.

OVA1 was evaluated in women scheduled for surgery for an ovarian tumor in a prospective, multi-institutional trial involving 27 primary care and specialty sites throughout the United States. Preoperative serum levels and clinical information were collected, and results for OVA1, PA and CA-125 were correlated with surgical pathology. PA was documented by each enrolling physician before surgery. CA-125 cutoff values were chosen in accordance with published ACOG guidelines.

Results: The study enrolled 590 women; 524 were evaluable with CA-125 and 516 with a presurgical assessment. Fifty-two percent were enrolled by physicians who were nongynecologic oncologists (non-GOs). There were 161 malignancies, including: 96 epithelial ovarian cancers, nine nonepithelial ovarian malignancies, 28 borderline tumors, 18 malignancies metastatic to the ovary and 10 pelvic malignancies with no ovarian involvement. The table summarizes the test performance in predicting ovarian malignancy. OVA1 demonstrates higher sensitivity compared with PA and CA-125. Specificity and positive predictive value were both lower for OVA1. PA plus OVA1 correctly identified 70% (14/20 for non-GOs) and 95% (19/20 for GOs) of malignancies missed by PA alone. OVA1 also identified 76% (38/50) of malignancies missed by CA-125, and PA plus OVA1 identified 86% (43/50) of malignancies missed by CA-125, including all advanced-stage cancers. The results remain consistent for early- and late-stage disease and for pre- and postmenopausal women.

Conclusions: OVA1 has high sensitivity in detecting ovarian malignancy compared with PA and CA-125, and is independent of cancer stage or menopausal status. When combined with PA, OVA1 can help determine the risk of malignancy for an ovarian tumor before surgery and facilitate decisions about referral to a gynecologic oncologist.

	CA-125 (67 U/mL) ($n=524$)	CA125 (200 U/mL) ($n=524$)	OVA1 ($n=524$)	PA alone ($n=516$)	PA plus OVA1 ($n=516$)
Sensitivity, %	**77.0** (124/161)	**68.9** (111/161)	**92.5** (149/161)	**75.2** (121/161)	**95.7** (154/161)
95% CI	69.9–82.8	61.4–75.6	87.4–95.7	67.9–81.2	91.3-97.9
Specificity, %	**73.3** (266/363)	**83.7** (304/363)	**43.0** (156/363)	**79.2** (281/355)	**34.6** (123/355)
95% CI	77–87	79.6–87.2	38.0–48.1	74.6–83.1	29.9-39.7
PPV, %	**56.1** (124/221)	**65.3** (111/170)	**41.9** (149/356)	**62.1** (121/195)	**39.9** (154/386)
95% CI	49.5–62.5	57.9-–72.0	36.8–47.0	55.1–68.6	35.1-44.9
NPV, %	**87.8** (266/303)	**85.9** (304/354)	**92.9** (156/168)	**87.5** (281/321)	**94.6** (123/130)
95% CI	83.6–91.0	81.9–89.1	87.9–95.9	83.5–90.7	89.3-97.4

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OVA1 improves the sensitivity of the ACOG referral guidelines for an ovarian mass

R. Miller[1], A. Smith[2], C. DeSimone[1], L. Seamon[1], S. Goodrich[1], I. Podzielinski[1], J. van Nagell[1], Z. Zhang[3], F. Ueland[1]
[1]University of Kentucky, Lexington, KY, [2]Applied Clinical Intelligence, Bala Cynwyd, PA, [3]Johns Hopkins Medical Institutions, Baltimore, MD

Objective: The American Congress of Obstetrics and Gynecology (ACOG) has published referral guidelines for women with a pelvic mass. The guidelines use CA-125 and are reported to be less effective in early-stage disease and premenopausal women. OVA1 is a multivariate index assay approved for the preoperative evaluation of ovarian tumors. Our objective was to evaluate the performance of the ACOG guidelines using OVA1 in place of CA-125.

This prospective, multi-institutional trial included 27 primary care and specialty sites throughout the United States. The ACOG guidelines were evaluated in women scheduled for surgery for a known ovarian mass. Study information was collected prior to surgery, including: Blood for biomarkers, presence of ascites, evidence of abdominal or distant metastases (by exam or imaging), family history of breast or ovarian cancer (first-degree relative), and nodular or fixed pelvic mass. Assays for OVA1 and CA-125 were

performed by the same laboratory. Study results were correlated with surgical pathology. Women were excluded from analysis if surgery was not performed, pathology report was not available or blood specimen was unusable.

Results: Five hundred ninety women with an ovarian mass on pelvic imaging were enrolled and 516 were evaluable. Fifty-two percent were from nonspecialty centers. There were 161 malignancies (45 premenopausal and 116 postmenopausal women), including: 96 epithelial ovarian cancers, nine nonepithelial ovarian malignancies, 28 borderline tumors, 18 malignancies metastatic to the ovary and 10 pelvic malignancies with no ovarian involvement. The table outlines the performance of the ACOG guidelines for OVA1 and CA-125. In premenopausal women, the ACOG criteria with OVA1 improved sensitivity (91.1% vs 57.8%) and negative predictive value (NPV) (95.3% vs 88.6%), but lowered specificity (43.2% vs 77.4%) and positive predictive value (PPV) (27.5% vs 37.7%). Similar trends are noted for postmenopausal women and early-stage disease.

Conclusions: When evaluated in a large multi-institutional trial, replacement of CA-125 with OVA1 improves the sensitivity and NPV of the ACOG referral guidelines, while decreasing specificity and PPV. The high sensitivity is maintained in premenopausal women and early-stage disease. Using OVA1 with the ACOG guidelines will help identify more malignancies before surgery, but further study is needed to determine how this will affect patient referral.

	ACOG/CA-125	ACOG/CA-125	ACOG/CA-125
	All subjects ($n=516$)	Premenopausal ($n=235$)	Premenopausal ($n=281$)
Sensitivity%	**77.0**	**57.8**	**84.5**
95% CI	69.9–82.8	43.3–71.0	76.8–90.0
Specificity%	**67.6**	**77.4**	**56.4**
95% CI	62.6–72.3	70.9 to 82.7	48.7–63.7
PPV%	**51.9**	**37.7**	**57.6**
95% CI	45.6–58.1	27.2 to 49.5	50.1–64.8
NPV%	**86.6**	**88.6**	**83.8**
95% CI	82.1–90.2	82.8 to 92.5	75.8–89.5

	ACOG/OVA1 **All subjects**	ACOG/OVA1 Premenopausal	ACOG/OVA1 Postmenopausal
	($n=516$)	($n=235$)	($n=281$)
Sensitivity%	**93.8**	**91.1**	**94.8**
95% CI	88.9–96.6	79.3–96.5	89.2–97.6
Specificity%	**34.9**	**43.2**	**25.5**
95% CI	30.2–40.0	36.3–50.3	19.4–32.6
PPV%	**39.5**	**27.5**	**47.2**
95% CI	34.8–44.5	21.0–35.2	40.9–53.6
NPV%	**92.5**	**95.3**	**87.5**
95% CI	86.8–95.9	88.6–98.2	75.3–94.1

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Peritoneal staging biopsies in early-stage ovarian cancer: Are they necessary?

R. Kothari, J. Carter, M. Geller
University of Minnesota, Minneapolis, MN

Objective: Surgical staging of clinical early-stage ovarian cancer includes performing peritoneal staging biopsies. We sought to determine the percentage of cases in which these biopsies revealed malignancy and whether biopsy results were correlated with malignancy found in other specimens and subsequent sites of recurrence.

A retrospective review of all patients undergoing surgical staging for presumed early-stage ovarian cancer at the University of Minnesota Medical Center was conducted. Patients were identified using a cancer database between January 1, 2004 and September 15, 2010. Information related to the operative procedure performed, final stage, histology, presence of malignancy in staging biopsies or other specimens collected, and recurrence including site was collected. The percentage of cases that were upstaged based solely on peritoneal biopsies was calculated. Data were examined for correlation between site of positive staging biopsies and subsequent site of recurrence.

Results: Five hundred twenty charts were reviewed. One hundred seventy-six patients thought to have disease confined to the ovaries had staging biopsies performed and were included in this review. Nineteen cases were performed laparoscopically and seven were converted to laparotomy once ovarian malignancy was diagnosed. In 27 (15%) cases, malignancy was found in staging biopsies. Fourteen of these 27 (52%) had staging biopsies as the only evidence of extraovarian spread. Fifteen of 27 (56%) were upstaged based on peritoneal biopsies (seven patients from stages I to II, 8 patients from stages I to III). Three patients (11%) received chemotherapy based on positive staging biopsies when they otherwise would not have based on final pathology. Five of 28 patients with malignancy found on staging biopsies recurred. Three of these patients recurred in the pelvis where staging biopsies had been positive; the other two patients had metastatic disease unrelated to site of positive staging biopsies. One patient had persistent disease following chemotherapy in the right diaphragm where diaphragm cytology had been positive.

Conclusions: Although peritoneal staging biopsies show evidence of malignancy in a small percentage of patients with clinically early-stage ovarian cancer, results of these specimens may alter the patient's treatment course and provide valuable prognostic information. Performing peritoneal biopsies is a crucial step in the surgical staging of early-stage ovarian cancer.

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Predictors of severe and febrile neutropenia during primary chemotherapy for ovarian cancer

R. Laskey[1], M. Poniewierski[1], M. Lopez[1], R. Hanna[2], A. Alvarez-Secord[1], P. Gehrig[2], G. Lyman[1], L. Havrilesky[1]
[1]*Duke University Medical Center, Durham, NC,* [2]*University of North Carolina School of Medicine, Chapel Hill, NC*

Objective: The purpose of this study was to identify factors that increase the risk of neutropenic events in women with advanced-stage ovarian carcinoma who are receiving their initial course of chemotherapy following surgery.

This multicenter retrospective study comprised women with surgical FIGO stage III–IV epithelial ovarian cancer treated postoperatively with multi-agent intravenous chemotherapy between the years 1995 and 2008. Data were obtained from each institution's tumor registry and medical records. Outcomes were severe neutropenia (absolute neutrophil count [ANC] $<500/mm^3$) and febrile neutropenia (ANC $<1000/mm^3$ and temperature >38.1 °C). Cumulative risk of neutropenic events was estimated by the product limit method of Kaplan and Meier. Multivariate analysis was based on the proportional hazard regression method of Cox.

Results: Three hundred thirty-one patients met inclusion criteria. There were 142 severe neutropenic events and 22 febrile neutropenic

events. In univariate analysis, significant predictors of severe neutropenia were a body surface area <2.0 m² ($P=0.033$), a body mass index <30 kg/m² ($P=0.004$), and white race ($P=0.003$). Women who received chemotherapy on research protocols had significantly higher rates of severe neutropenia ($P=0.004$) than those not on protocols. Patients for whom at least 85% of standard chemotherapy relative dose intensity (RDI) was planned experienced significantly more severe neutropenia than patients for whom <85% RDI was planned ($P=0.035$). Older women were more likely than younger women to develop febrile neutropenia ($P = 0.05$). In multivariate analysis, significant predictors of severe neutropenia were treatment on research protocols (HR = 1.86, $P=0.001$), body mass index <30 kg/m² (HR = 1.68, $P=0.041$), white race (HR = 2.05, $P=0.015$) and delivery of full-dose-intensity chemotherapy (HR = 1.66, $P=0.056$). Predictors of febrile neutropenia were age >60 (HR = 3.15, $P=0.031$) and use of non-carboplatin-containing chemotherapy regimens (HR = 4.85, $P=0.002$) (see table).

Conclusions: Age, race, body mass index, chemotherapy regimen and planned dose intensity should be considered when making decisions about chemotherapy dosing and the use of bone marrow support factors intended to optimize each patient's cancer-related outcome.

Risk factors associated with severe neutropenia and febrile neutropenia in univariate analysis.

	Severe neutropenia	Febrile neutropenia
BMI <30 kg/m²		
Yes	112 (49.12%)	18 (7.89%)
No	19 (29.23%)	1 (1.54%)
P value	0.0044	0.0664
Caucasian race		
Yes	128 (47.41%)	20 (7.41%)
No	14 (25.45%)	2 (3.64%)
P value	0.0028	0.3103
Age >60 years		
Yes	74 (45.40%)	15 (9.20%)
No	67 (42.14%)	6 (3.77%)
P value	0.5555	0.0485
Planned RDI[a] $\geq 85\%$		
Yes	113 (46.69%)	19 (7.85%)
No	22 (32.35%)	2 (2.94%)
P value	0.0351	0.1833
Chemotherapy study protocol		
Yes	59 (55.14%)	7 (6.54%)
No	83 (38.25%)	15 (6.91%)
P value	0.0040	0.9008
Non-carboplatin-containing chemotherapy regimen		
Yes	26 (66.67%)	5 (12.82%)
No	116 (40.56%)	17 (5.94%)
P value	0.0020	0.1621

[a]Relative dose intensity.

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Prognostic impact of prechemotherapy HE4 and CA-125 levels in patients with ovarian cancer

K. Dahl Steffensen[1,2], M. Waldstrøm[1], I. Brandslund[1,2], A. Jakobsen[1,2]
[1]*Department of Clinical Oncology and Radiotherapy, Vejle Hospital, Vejle, Denmark,* [2]*Institute of Regional Health Services Research, Vejle, Denmark*

Objective: Human epididymis protein 4 (HE4) has attracted a lot of interest as a relatively novel biomarker for ovarian carcinoma and has been shown to be elevated in serum from the majority of patients with epithelial ovarian cancer and patients who do not express CA-125. Research has been focused on HE4 as a diagnostic tool with potential for better triage of women with adnexal masses. Preoperative HE4 serum levels have so far signaled increased sensitivity for ovarian malignancy, but the prognostic aspect of HE4 in patients with ovarian cancer remains to be elucidated. The aim of the present study was to investigate the prognostic value of prechemotherapy serum HE4 levels in patients with ovarian cancer receiving standard combination chemotherapy.

Serum from 170 patients with newly diagnosed ovarian cancer was analyzed for HE4 and CA-125 using ELISAs (Fujirebio Diagnostics AB, Gothenburg, Sweden). Samples were collected just prior to first-line chemotherapy and all patients were treated with carboplatin/paclitaxel combination chemotherapy. Median follow-up time for living patients was 30 months (range: 5–59).

Results: When patients were grouped into quartiles on the basis of prechemotherapy serum HE4 levels, Kaplan–Meier survival curves showed significant differences between the groups, with increasing levels of serum HE4 significantly associated with worse progression-free survival (PFS) ($P<10^{-5}$) and overall survival (OS) ($P<10^{-5}$) (see figure). After adjustment in the Cox proportional hazards model, HE4 serum levels remained an independent prognostic parameter for PFS with a HR of 1.82 (95% CI = 1.09–3.04, $P=0.023$) for patients with HE4 levels above the median compared with patients with HE4 levels below the median. The shorter PFS for patients with high levels of HE4 also translated into a significant difference in OS (HR = 3.64, 95% CI = 1.72–7.71, $P=0.0007$). Serum CA-125 values did not prove to be an independent predictor of PFS or OS (see table).

Conclusions: High levels of serum HE4 constitute a strong and independent indicator of worse prognosis in patients with epithelial ovarian cancer.

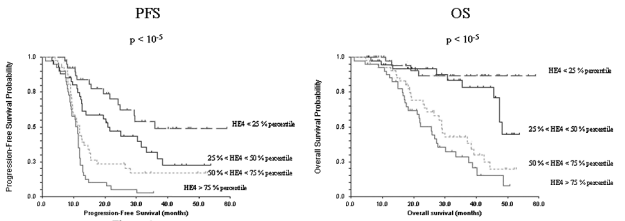

Figure 1. Pre-chemotherapy serum HE4 protein levels separated into quartiles and relation to PFS and OS

Multivariate Cox regression analysis for CA-125 AND HE4 divided by the median into below- and above-the-baseline median serum levels.

Clinicopathologic characteristics	Progression-free survival			Overall survival		
	HR	95% CI	*P*	HR	95% CI	*P*
FIGO stage						
I/II	1.0			1.0		
III/IV	5.67	2.29–14.0	0.0002	4.9	1.09–22.0	0.038
Tumor grade						
1	1.0			1.0		
2	2.22	0.59–8.41	0.241	0.56	0.10–3.03	0.497
3	2.79	0.71–10.9	0.141	0.6	0.11–3.33	0.563
Not graded	2.52	0.62–11.0	0.189	0.7	0.11–4.39	0.708
Histology						
Serous	1.0			1.0		
Nonserous	1.66	0.78–3.56	0.191	2.28	0.94–5.57	0.069
Residual tumor						
≤ 1 cm	1.0			1.0		
>1 cm	1.38	0.85–2.24	0.196	1.4	0.76–2.57	0.279
CA-125 level						
Below median	1.0			1.0		
Above median	1.31	0.83–2.06	0.244	1.45	0.80–2.62	0.219
HE4 level						
Below median	1.0			1.0		
Above median	1.82	1.09–3.04	0.023	3.64	1.72–7.71	0.0007

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Revisiting the issue of race-related outcomes in patients with stage IIIC papillary serous ovarian cancer who receive similar treatment

O. Ibeanu[1], S. Ueda[2], M. Gerardi[3], R. Bristow[4]
[1]*Johns Hopkins Medical Institutions, Baltimore, MD,* [2]*UCSF Comprehensive Cancer Center, San Francisco, CA,* [3]*Johns Hopkins Hospital, Baltimore, MD,* [4]*UC Irvine Medical Center, Orange, CA*

Objective: The purpose of this study was to determine differences in outcome between Caucasian and African-American patients similarly treated for stage IIIC papillary serous ovarian cancer.

This retrospective study comprised 433 patients with stage IIIC ovarian cancer. Of these, 366 Caucasians and 39 African-Americans were identified for study and analysis. The two groups of patients were compared on tumor histology, grade, surgery and chemotherapy, as well as progression-free survival. Descriptive statistics were used to present data and the χ^2 test was used to compare categorical data. Multivariate analysis was used for outcome variables.

Results: Three hundred fourteen Caucasians (86%) and 31 African-Americans (80%) had serous tumors. Two hundred ninety-four Caucasians (80%) and 33 African-Americans (85%) had poorly differentiated tumors. Optimal cytoreduction was achieved in 267 Caucasians (73%) and 27 African-Americans (69%), and 323 Caucasians (88%) and 34 African-Americans (87%) received platinum/taxane adjuvant chemotherapy. Neoadjuvant chemotherapy was used in 35 Caucasians (9.6%) and six African-Americans (15.4%). The surgeries performed were lymphadenectomy in 166 Caucasians (45%) and 14 African-Americans (36%), rectosigmoid resection in 99 Caucasians (27%) and 7 African-Americans (18%), small bowel resection in 17 Caucasians (4.6%) and two African-Americans (5.1%), diaphragmatic resection in 60 Caucasians (16.4%) and five African-Americans (12.8%), and splenectomy in 28 Caucasians (7.6%) and one African-American (2.6%). The χ^2 test *P* values were all >0.05. Multivariate analysis of outcomes when controlling for residual disease status and chemotherapy revealed no statistically significantly increased risk of death among African-Americans compared with Caucasians. There was no difference in progression-free survival between groups (21.2 months for Caucasians and 19.5 months for African-Americans, $P<0.57$).

Conclusions: In our study, outcomes of Caucasians and African-Americans who received similar treatments for stage IIIC papillary serous ovarian cancer did not significantly differ. It is possible that previously reported differences in ovarian cancer mortality may be explained by health system factors that determine access to appropriately qualified surgeons. Further research is needed on a larger patient sample.

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Sequencing of therapy and outcomes associated with use of neoadjuvant chemotherapy in advanced epithelial ovarian cancer in the Medicare population

M. Thrall, H. Gray, R. Symons, D. Flum, N. Weiss, B. Goff
University of Washington Medical Center, Seattle, WA

Objective: The role of chemotherapy prior to surgery (neoadjuvant) for advanced ovarian cancer is controversial and there are few population-based data describing its use in the United States. We aimed to examine the use of neoadjuvant chemotherapy in the U.S. Medicare population and the short- and long-term outcomes associated with the use of neoadjuvant chemotherapy in women with advanced ovarian cancer.

Using the Surveillance, Epidemiology and End-Results (SEER) data with Medicare data, we identified a cohort of 6844 women with stage III/IV epithelial ovarian cancer diagnosed between 1995 and 2005 who had Medicare claims for surgery and/or chemotherapy in the year following diagnosis. Surgical complexity and 30-day complication rates were determined. Patients receiving primary chemotherapy were stratified into neoadjuvant and palliative groups based on whether or not surgery was recommended as reported to SEER at the time of diagnosis. Multivariate Cox hazard models and Kaplan–Meier survival analysis were used to examine differences in overall mortality.

Results: Four thousand eight hundred twenty-seven (70.5%) women were treated with primary surgery and 2017 (29.5%) women had primary chemotherapy. Women treated with chemotherapy prior to surgery had lower rates of ostomies compared with those treated with primary surgery (8.47% vs 19.2%, $P<0.001$). Chemotherapy prior to surgery resulted in shorter hospital stays (median: six days vs nine days, $P<0.001$) and lower overall rates of many 30-day complications (see table). Thirty-day mortality was 8.95% in women treated with primary surgery versus 2.77% in women who had chemotherapy prior to surgery ($P<00.1$). Of the 2017 treated with primary chemotherapy, 958 (47.5%) were classified as receiving neoadjuvant chemotherapy. Women treated with primary surgery had a median survival of 24.6 months compared with 21.4 months for women treated with neoadjuvant chemotherapy (59.8% of whom had surgery). Women with stage IV disease treated with neoadjuvant chemotherapy had no increased risk of death compared with women who had initial surgery (HR = 0.98, 95% CI = 0.88–1.11).

Conclusions: Chemotherapy is frequently used in the community prior to surgery in women with advanced ovarian cancer. The use of chemotherapy prior to surgery appears to be associated with lower rates of 30-day complications and short-term mortality. Women with stage IV disease do not have appear to have a higher risk of death when treated with neoadjuvant chemotherapy, despite the fact that only about half go on to have cancer-directed surgery.

	Primary debulking surgery ($n=4797$)	Primary chemotherapy followed by surgery ($n=637$)	*P*
Length of stay			
Median	9	6	**<0.001**
Mean (SD)	11.53 (10.27)	8.10 (7.09)	**<0.001**
ICU stay	2049 (42.71%)	185 (29.04%)	**<0.001**
Transfusion	329 (6.86%)	39 (6.12%)	0.487
Discharge sestination			**<0.001**
Home	3517 (73.32%)	547 (85.87%)	
SNF/other facility	955 (19.91%)	81 (12.72%)	
Died	290 (6.05%)	8 (1.26%)	
Hospice	35 (0.73%)	1 (0.16%)	
30-Day mortality	432 (8.95%)	18 (2.77%)	**<0.001**
30-Day complications			
Anastamotic failure	52 (1.08%)	4 (0.62%)	0.273
Cardiac	556 (11.52%)	64 (9.86%)	0.210
Deep-vein thrombosis/ pulmonary embolism	229 (4.75%)	30 (4.62%)	0.890
General Infections	854 (17.70%)	74 (11.40%)	**<0.001**
Gastrointestinal	1701 (35.25%)	188 (28.97%)	**0.002**
Neurologic	47 (0.97%)	6 (0.92%)	0.904
Renal	161 (3.34%)	7 (1.08%)	**0.002**
Reoperation	479 (9.93%)	54 (8.32%)	0.195
Respiratory	542 (11.23%)	27 (10.39%)	**<0.001**
Shock	134 (2.78%)	9 (1.29%)	**0.037**
Surgical injury	316 (6.55%)	34 (5.24%)	0.201
Wound infection/ complication	997 (20.66%)	98 (15.10%)	**0.001**

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Serum HE4 level is an independent risk factor of surgical outcome and prognosis of epithelial ovarian cancer

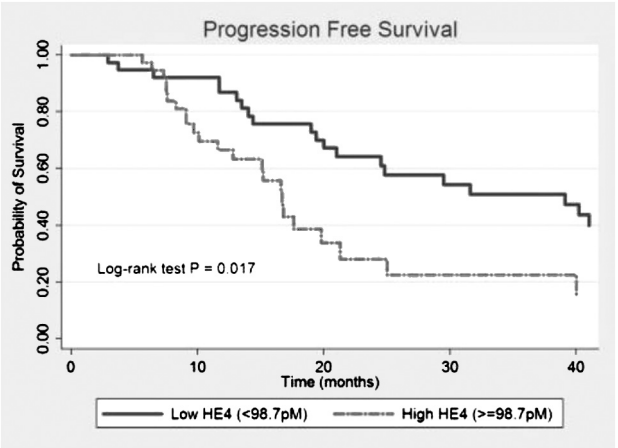
S. Kang[1], S. Kong[1], S. Park[1], S. Seo[1], J. Kim[2]
[1]*National Cancer Center, Goyang, Republic of Korea,* [2]*Gangnam Severance Hospital, Goyang, Republic of Korea*

Objective: Though optimal cytoreduction is the most important prognostic factor, it is not easy to predict the feasibility of optimal cytoreduction. It has been suggested that biomarkers, such as CA-125, be used to predict surgical outcome. However, other markers are needed owing to the low classification performance of CA-125.

By using enzyme immunoassay, we explored the predictive performance of human epididymal secretory protein 4 (HE4) for the feasibility of complete cytoreduction and progression-free survival (PFS) in 80 patients with primary epithelial ovarian cancer.

Results: In patients who achieved complete cytoreduction, the median serum level of HE4 was 92.7 pM (interquartile range: 77.2–139.7), whereas it was 118.9 pM (interquartile range: 82.0–364.6) in patients with incomplete cytoreduction. High serum HE4 levels were found to be strongly correlated with failure of successful cytoreduction in univariate analysis (OR = 2.5, 95% CI = 1.15–5.81, $P = 0.007$) and with FIGO stage in multivariate analysis ($P = 0.023$). Moreover, serum HE4 level was observed to be significantly correlated with PFS (HR = 1.6, 95% CI = 1.2–2.2, $P = 0.004$), though CA-125 level was not correlated with PFS.

Conclusions: This study showed that an increased serum HE4 level is associated with increased risk of cytoreduction failure and poor progression-free survival in ovarian cancer.



Multivariate analysis between serum HE levels and surgical outcome (adjusted for age, stage, histology, and initial serum CA-125 level)

	Using stage only		Using all variables	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Complete cytoreduction	2.2 (1.1–4.4)	0.023	2.3 (1.1–4.8)	0.021
Multiple upper abdominal surgery	3.0 (1.5–6.0)	0.002	4.5 (1.9–10.9)	0.001
Estimated blood loss (mL)	178 (-4-360)[a]	0.055	190 (5-376)[a]	0.045
Operation time (min)	46 (45-88)[a]	0.030	40 (-3-83)[a]	0.067

[a]Regression coefficient (95% CI).

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Should we treat patients with ovarian cancer with positive retroperitoneal lymph nodes with intraperitoneal chemotherapy? Impact of lymph node status in women undergoing intraperitoneal chemotherapy

H. Gray, M. Thrall, H. Tamimi, R. Swensen, R. Garcia, B. Goff
University of Washington Medical Center, Seattle, WA

Objective: The purpose of this study was to evaluate the role of lymph node status in recurrence patterns and progression-free and overall survival in women undergoing intraperitoneal (IP) chemotherapy following optimal surgical debulking.

Women with advanced ovarian cancer who received surgical cytoreduction followed by IP chemotherapy were identified from a single institution. Data were abstracted from medical records and operative reports, and pathology was reviewed by a gynecologic pathologist. Variables of interest were recurrence sites, progression-free survival and overall survival. Statistical analysis was performed using STATA.

Results: Sixty women with advanced-stage (III/IV) ovarian cancer who were treated with optimal surgical debulking followed by IP chemotherapy were identified. Median number of IP chemotherapy cycles was five (range: 1–7), and median number of total (IV + IP) chemotherapy cycles was eight (range: 5–12). Type of IP chemotherapy given was evenly distributed, with 53% (32/60) receiving cisplatin and 47% (28/60) carboplatin. The majority underwent pelvic and paraaortic lymph node dissection (47/60, 78%) as part of their surgical debulking. Nearly half (45%) of patients had positive lymph nodes: 48% both pelvic and paraaortic positive, 38% pelvic only, and 14% paraaortic only. Average number of LNs removed was 15.5 (range: 1–48). At a median follow-up of 32 months, 36 of 60 women had experienced recurrences (60%). There was no difference in recurrence rate between patients with negative and those with positive lymph nodes (56% vs 59%, $P = 0.8$). Site of first recurrence following IP therapy was categorized as extraperitoneal only (lung, mediastinal, lymph node), intraperitoneal (abdominal or pelvic), or both. Women with positive lymph nodes were more likely to experience extraperitoneal-only recurrence compared with those with negative lymph nodes (83% vs 30%, $P = 0.009$). Median progression-free survival of women with positive lymph nodes was 21 months versus 29 months for women with negative lymph nodes. There was no difference in median progression-free survival between patients treated with IP carboplatin versus cisplatin (29 months vs 30 months, $P = 0.8$). Median overall survival has not been reached.

Conclusions: Patients with ovarian cancer with positive lymph nodes treated with IP chemotherapy do not appear to have increased recurrence rates, but more commonly recur in extraperitoneal sites compared with patients with negative lymph nodes. Our data suggest that women with positive lymph nodes may benefit from IP therapy in conjunction with IV therapy for potential improvement in outcome.

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Significance of perioperative infectious disease in patients with ovarian cancer

K. Matsuo[1], C. Prather[2], E. Ahn[3], M. Eno[4], D. Im[5], N. Rosenshein[5], A. Yessaian[1], Y. Lin[1]

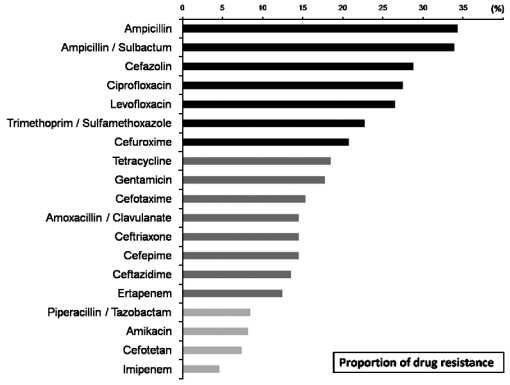
[1]University of Southern California, Los Angeles, CA, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]Beth Israel Deaconess Medical Center, Boston, MA, [4]Cedars-Sinai Medical Center, Los Angeles, CA, [5]Mercy Medical Center, Baltimore, MD

Objective: Perioperative infectious diseases constitute some of the most common causes of mortality in ovarian cancer patients. This study aims to evaluate the significance of perioperative infections in patients with epithelial ovarian, fallopian and peritoneal cancers.

Patients who underwent primary and recurrent cytoreductive surgery were included in the analysis ($n=276$ and 80, respectively). The enumeration and speciation of pathogens, antimicrobial agents used, and sensitivity assay results were culled from medical records and correlated to clinicopathologic demographics and clinical outcome.

Results: The incidence of perioperative infection within a 6-week postoperative period was 15.7% (common sites: urinary tract 48.6% and surgical wound 28.4%). The most common pathogens were *Enterococcus* species (17.6%), *Escherichia coli* (12.8%), and *Klebsiella pneumoniae* (10.8%). Pathogens tested with sensitivity assays were shown to be most commonly resistant to ampicillin (34.3%), ampicillin/sulbactum (33.9%), cefazolin (28.8%), ciprofloxacin (27.5%), levofloxacin (26.5%) and trimethoprim/sulfamethoxazole (22.7%). On the other hand, relatively few were resistant to piperacillin/tazobactum (8.2%), cefotetan (7.4%) and imipenem (4.6%) (Table 1). In primary surgery cases, perioperative infection was associated with older age ($P=0.039$), hypertension ($P<0.001$), diabetes ($P=0.012$), hyperlipidemia ($P=0.03$), bowel resection ($P=0.033$), suboptimal surgery ($P<0.001$), serous histology ($P=0.028$), nodal metastasis ($P=0.01$), lymphovascular space invasion ($P=0.005$), and advanced stage ($P=0.043$). In multivariate analysis, suboptimal surgery, lymphovascular space invasion and hypertension remained significant factors associated with increased risk of perioperative infectious disease after primary cytoreductive surgery. Common prophylactic antibiotics given at the time of primary surgery were cefazolin (46.7%) followed by cefotetan (31.5%). The risk of perioperative infections was not associated with type of prophylactic antibiotics ($P=0.28$). Perioperative infections were associated with decreased chemotherapy response (66.7% vs 86.0%, $P=0.008$), shorter progression-free survival (median time: 8.4 months vs 17.6 months, $P<0.001$), and decreased overall survival (29.0 months vs 51.8 months, $P=0.011$). Multivariate analysis showed that perioperative infections remained a significant risk factor for decreased progression-free survival ($P=0.016$).

Conclusions: Perioperative infections constitute an independent risk factor for survival of patients with ovarian cancer.



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Single-nucleotide polymorphism in DNA repair and drug resistance genes alone or in combination in epithelail ovarian cancer

J. Connor, J. Kolesar

University of Wisconsin, Madison, WI

Objective: Single-nucleotide polymorphisms (SNPs) in both DNA repair genes (associated with platinum resistance) and multi-drug-resistant pathway genes (associated with taxane resistance) are known to influence outcomes in cancer patients treated with chemotherapy. Results in epithelial ovarian cancer are controversial for any one gene. We therefore sequenced seven SNPs in three genes (ERCC1 8092 and 118, XPD 312 and 751, and ABCB1 2677, 3435, and 1236) in women with stage III–IV ovarian cancer from a single institution to evaluate individual SNPs and combinations of SNPs for both progression-free survival (PFS) after primary therapy and overall survival (OS).

Subjects were recruited at treatment or follow-up visits. Peripheral blood DNA was extracted and sequenced for each SNP. Clinical data were extracted from the medical record and included dates of last chemotherapy, first recurrence and last contact with cancer status. Standard Kaplan–Meier survival analysis was performed.

Results: One hundred eighteen cases were evaluable from 79 platinum-sensitive cases and 39 resistant, with a median follow-up of 36 months. At the time of analysis eight women had never recurred after primary therapy at a median of 52 months, and a total of 16 were without evidence of disease (NED). No single SNP was clearly associated with either PFS or OS; however, trends suggestive of improved OS were seen for ERCC1 8092 C/C > C/A and A/A, and this was enhanced when the ABCB1 2677 genotype was included. Although OS was not significant for ERCC1 8092, all 16 (100%) women who were NED at the time of analysis ($P=0.0004$ by Fisher's exact test C/C vs C/A and A/A), including all eight women who never recurred ($P=0.02$), carried the C/C genotype, and this genotype accounted for only 53% of the overall population. Assuming that the ERCC1 8092 C/C genotype represented a good prognostic group, we then sub-analyzed these cases based on wild type versus SNPs of ABCB1 2677 with similar results. Although survival analysis was not significant, 75% of the never recurred subjects and 81% of the NED subjects had beneficial SNPs at this locus. Despite these findings, 40% of the subjects were still censored at the time of this analysis.

Conclusions: In this unselected population wild-type expression of ERCC1 8092 appears to provide a survival advantage. In this wild-type subgroup the presence of polymorphisms in ABCB1 appears to define the population with best outcomes. Expansion of this sub-population and continued follow-up are needed to draw definitive conclusions.

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Sonographic predictors of ovarian malignancy

L. Barroilhet, B. Benacerraf, T. Shipp, A. Vitonis, M. Muto

Brigham & Women's Hospital, Boston, MA

Objective: The purpose of this study was to identify a combination of sonographic features that best predict ovarian malignancy and distinguish borderline from invasive cancer.

Subjects for this study included 249 women who had a transvaginal ultrasound for a pelvic mass at the ultrasound unit at Brigham and Women's Hospital between January 2005 and Septem-

ber 2009. A standardized examination technique and standardized terms and definitions were used. Subjects included in our data analysis underwent surgery for removal of the mass at the same institution. Final pathologic diagnosis of the pelvic mass was available for all patients included in our study. Images were retrospectively reviewed by one sonologist blinded to the pathologic diagnosis and clinical information. Twelve sonographic features were scored for each mass. The data set was randomly divided into training ($n=149$) and testing ($n=100$) sets. Within the training set we used stepwise logistic regression to weigh each variable and combination of features. We created a three-level risk score that we then applied to the subjects in the testing set to assess its ability to distinguish benign conditions from malignancies.

Results: The highest risk category in our scoring system included masses with internal blood flow. The intermediate category included masses without blood flow but with thick walls, thick septations, or solid areas. Subjects without these features were classified as low risk. We observed similar results when applying the score to the training and testing sets and, therefore, present the results of the combined data here. Among 249 masses, 196 were benign, 29 were invasive cancer and 14 were borderline tumors. Twenty-nine of 51 (57%) masses with internal blood flow were malignant. Of the 29 invasive cancers, 24 (75.9%) had internal blood flow compared with 5 of 14 (36%) for borderline cancer (see table). In patients without internal flow, features including thick walls, thick septations and solid areas identified nine more borderline tumors and three more invasive cancers. Masses with low-risk features had a 4/106 (3.8%) incidence of malignancy with a negative predictive value of 95.9%.

Conclusions: Internal blood flow predicted most of the invasive tumors (75.6%). Masses without internal flow but with other suspicious features predicted nine of 14 (64.3%) borderline tumors and three additional invasive cancers. Our proposed scoring system has a negative predictive value similar to that of the OVA1 blood test (95.9% vs 92.7%) and may be more cost effective for the triage of patients with pelvic masses.

Ultrasound characteristics and pathology diagnosis

	No cancer ($n=206$)	Borderline ($n=14$)	Invasive cancer ($n=29$)
Internal blood flow	24 (11.7%)	5 (35.7%)	22 (75.8%)
Thick septations or thick walls or solid areas without internal blood flow	76 (38.9%)	9 (64.3%)	3 (10.3%)
Benign features (simple cyst, thin septations, calcifications, etc.)	106 (51.5%)	0 (0.0%)	4 (13.8%)

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STAC: A phase II study of carboplatin/paclitaxel/bevacizumab followed by randomization to either bevacizumab alone or erlotinib and bevacizumab in the upfront management of patients with ovarian, fallopian tube or peritoneal cancer

S. Campos[1], T. Atkinson[1], S. Berlin[1], M. Roche[2], C. Whalen[1], U. Matulonis[1], N. Horowitz[3], M. Birrer[2], R. Penson[2]
[1]Dana–Farber Cancer Institute, Boston, MA, [2]Massachusetts General Hospital/Harvard University, Boston, MA, [3]Brigham & Women's Hospital, Boston, MA

Objective: The purpose of this study was to determine the response rate and progression-free survival of carboplatin/paclitaxel/bevacizumab (induction therapy) followed by either bevacizumab alone or bevacizumab + erlotinib (consolidation therapy) in patients with ovarian, fallopian tube or peritoneal cancer.

A phase II trial of carboplatin/paclitaxel /bevacizumab (CPB) as induction therapy, followed by randomization to erlotinib and bevacizumab (E + B) or bevacizumab alone (B) as consolidation therapy, was conducted. Eligible patients included those with stage II– IV disease, a performance status of 0–1, and adequate hematologic and nonhemaologic parameters.

Results: Sixty patients have been enrolled. Patients eligible for enrollment received CTB followed by randomization to E + B or B alone. Eligible patients were those with ovarian, fallopian tube,or peritoneal cancer. Patients with UPS were also eligible. Of the 60 patients enrolled, 44 were optimally debulked and 16 were suboptimally debulked; 23 were randomized to B and 25 were randomized to E + B; 12 patients were taken off study prior to randomization. Best response achieved was a complete response in six, a partial response in 26, and stable disease in 20. Thirteen patients were removed for toxicity. The most prevalent toxic effects were hypertension (grade 3, 16 events) and sensory neuropathy (grade 1, 101 events). Vaginal dehiscence was noted in two patients. There were two thrombotic events. No gastrointestinal perforations were observed. Progression-free survival analysis comparing both arms is not mature.

Conclusions: Bevacizumab is an active regimen with manageable toxicity. Although overall survival benefit is often the desired endpoint, progression-free survival is an endpoint with merit. Small incremental benefits (i.e., intraperitoneal therapy + B) may in time result in an overall survival benefit. GOG 252 aims to address this question.

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Symptom-triggered screening for ovarian cancer: A pilot study of feasibility and acceptability

B. Goff[1], K. Lowe[2], J. Kane[1], M. Robertson[1], M. Gaul[2], M. Andersen[2]
[1]University of Washington School of Medicine, Seattle, WA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA

Objective: Our goal was to determine if symptom-based ovarian cancer screening was feasible in a primary care clinic and acceptable to women and practitioners. In addition, we wanted to describe the outcomes for women screened in the pilot study.

A total of 2262 women over age 40 with at least one ovary participated in symptom-based screening using a symptom index (SI). The first 1001 were in a non-intervention arm and the next 1261 were screened for symptoms and referred on to testing with CA-125 and transvaginal ultrasound (TVS) if the SI was positive. Patients and practitioners were surveyed about acceptability. All patients were linked to the Western Washington SEER Cancer Registry to determine if ovarian cancer was diagnosed in any women.

Results: Of the eligible women visiting the clinic, 72.5% were interested in participating. Of the 1261 who participated in the screening arm, 51 (4%) were SI positive, with women 40–49 having a 6% and women 50+ having a 3% positive rate. Of the SI-positive women, 47 were tested with CA-125 (45/47 normal) and TVS (32/47 normal). Of note, 17 of 47 TVSs and four of 47 CA-125 levels were ordered as part of routine care. Repeat TVS and CA-125 were performed secondary to study involvement in four and one woman, respectively. Two endometrial biopsies and one hysteroscopy D&C were performed secondary to study enrollment (pathology benign). Survey of patients and providers on a scale of 1–5 (worst–best) revealed mean scores of 4.8 for acceptability of SI screening and 4.7 for TVS and CA-125. Providers also had high levels of acceptability

with a mean score of 4.8. Two participants were diagnosed with ovarian cancer.

Conclusions: Although our pilot study is not large enough to assess the sensitivity or specificity of a symptom-based screening approach, we did find that this type of screening was feasible and acceptable at the time of a primary care visit. Approximately 4% of women were referred for additional diagnostic testing. In addition, symptom-based screening resulted in minimal additional procedures.

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The feasibility of mediastinal lymphadenectomy in the management of advanced and recurrent ovarian carcinoma

J. Diaz[1], B. Park[2], J. Stine[2], R. Flores[2], Y. Sonoda[2], N. Abu-Rustum[2], R. Barakat[2], D. Chi[2]
[1]University of Miami Miller School of Medicine, Miami, FL, [2]Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The purpose of this study was to assess the role of mediastinal lymphadenectomy at the time of cytoreductive surgery in the management of advanced and recurrent ovarian carcinoma.

Using a prospectively maintained database, we identified all patients with advanced or recurrent ovarian carcinoma who underwent a mediastinal lymphadenectomy at the time of cytoreductive surgery at our institution from January 2006 to January 2010. The medical records were reviewed for patient demographics and clinical characteristics, operative findings, procedures performed and adverse outcomes.

Results: Twenty-three patients, with a median age of 55 years (range: 26–73), underwent a mediastinal lymphadenectomy at the time of cytoreductive surgery. Seventeen patients underwent cytoreduction at the time of initial diagnosis and six at the time of recurrence. The carcinoma was of serous histology in 21 patients (91%). All patients had evidence of mediastinal lymphadenopathy on their preoperative CT scans. Eight patients had their mediastinal lymphadenectomy via a minimally invasive approach: robotics, three (13%); video-assisted thoracic surgery, five (22%). Fifteen patients (65%) underwent a subxiphoid mediastinal approach via a laparotomy incision. All procedures were performed with the goal of optimal cytoreduction. All patients had an optimal ($\leq$1 cm residual) cytoreductive procedure; 10 patients (43%) were left with no gross residual disease in the thorax and peritoneum at the conclusion of their cytoreductive procedures. All patients had metastatic disease in the mediastinal nodes confirmed on final pathologic analysis. All patients received postoperative chemotherapy. With a median follow-up time of 23 months (range: 7–169), there were 11 recurrences. No patient experienced a mediastinal or intrathoracic recurrence. Five patients (22%) experienced grade 3 complications within 30 days of surgery. Only one of the five complications was related to the intrathoracic cytoreductive procedure: a chylothorax requiring drainage. There were no 30-day mortalities.

Conclusions: Mediastinal lymphadenopathy at the time of initial presentation or at the time of recurrence in select patients with advanced ovarian carcinoma should not preclude an attempt at cytoreductive surgery. This procedure has acceptable morbidity and mortality. Larger studies are needed to confirm our findings and evaluate the potential survival benefit.

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The impact of diabetes on survival in women with ovarian cancer

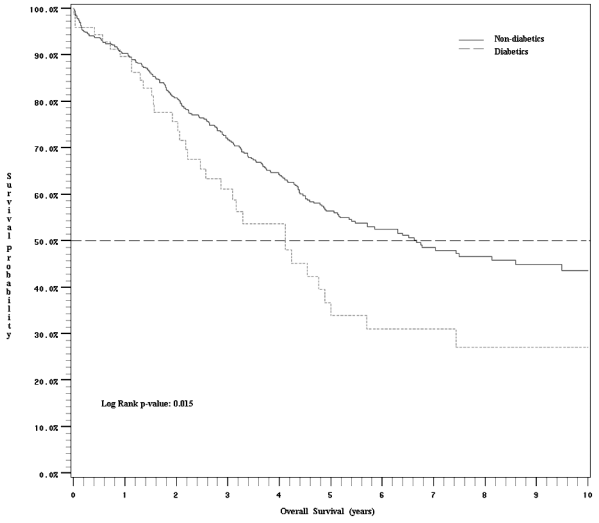
A. Bakhru, J. Griggs, R. Buckanovich
University of Michigan, Ann Arbor, MI

Objective: Given that diabetes is increasingly common among patients with cancer and that plausible biologic mechanisms exist by which diabetes may influence cancer prognosis, we aimed to investigate the impact of diabetes on ovarian cancer outcomes.

We assessed the outcomes of 570 nondiabetic and 72 diabetic patients with epithelial ovarian, fallopian tube, and primary peritoneal cancer over a 10-year period. All inpatient and outpatient records were reviewed. The primary endpoints were overall survival and disease-free survival.

Results: Of the 642 cases, 11.2% had type II diabetes. Diabetics were more likely to be older, have a higher body mass index (33.4 vs 27.8), and have more comorbid conditions. Diabetics were less likely to have been surgically staged as compared with nondiabetics ($P = 0.04$), although the groups were similar with respect to stage, grade, and likelihood of optimal cytoreduction. Over a 10-year period, with an average 44 months of follow-up, median time to recurrence was 1022 days among nondiabetics and 578 days among diabetics (log rank test, $P = 0.13$). The median overall survival for diabetics was 1503 days. The median overall survival for nondiabetics was 2435 days (log rank test, $P = 0.01$) (see figure).

Conclusions: Diabetics with ovarian cancer demonstrate strikingly poorer survival. The underlying reason for this is yet unknown and deserves further attention. Differences in care, competing risks of death and changes within the tumor biology are plausible mechanisms for the observed difference in survival.



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Women without ovarian cancer reporting disease-specific symptoms

E. Pavlik, C. DeSimone, R. Miller, I. Podzielinski, J. Ubellacker, S. Goodrich, F. Ueland, L. Seamon, R. Kryscio, J. van Nagell
University of Kentucky Chandler Medical Center/Markey Cancer Center, Lexington, KY

Objective: Women without ovarian cancer who report disease-specific symptoms were examined to determine how demographics and coincident nonspecific symptoms would characterize this group.

Thirteen thousand five hundred sixty-nine women were recruited and completed evaluation for 22 symptoms between April 2008 and May 2009. These women were followed by transvaginal ultrasonography and remained free of an ovarian cancer diagnosis for at least 12 months of follow-up to May 2010. Symptom results were cross-correlated with demographics. Cross-sectional analyses used stepwise logistic regression to find the set of disease-nonspecific symptoms that would be the most effective in predicting the probability of reporting disease-specific symptoms. Variables were added to the logistic regression equation using the statistical criterion of improving prediction. After each variable was entered, each of the included variables was tested to see if the model would be better if the variable was excluded. Significance for entry into the stepwise logistic model was set at 0.05.

Results: Of the women considered to be free of malignancy, 380 reported disease-specific symptoms. Disease-specific symptoms were reported by women who did not have ovarian cancer at a rate that was 60–1500 times higher than the estimated age-related prevalence of ovarian cancer. Disease-specific symptoms decreased with age >60 years, and increased with weight and BMI. Premenopausal women reported pelvic pain twice as often as postmenopausal women. The 88.9% reporting a disease-specific symptom also reported other symptoms so that coincident disease-specific and disease-nonspecific reporting was frequent. After adjustment for age, menopausal status, weight, BMI and any prior pelvic surgery, the adjusted odds ratio for reporting disease-specific symptoms increased from 1.6 to 2.1 when there were also reports of indigestion, nausea or vomiting, weight loss, feeling an abdominal mass, urinary urgency, fatigue, or leg swelling, thereby identifying conditions where the likelihood of reporting disease-specific symptoms was increased in women who did not have ovarian cancer.

Conclusions: Disease-specific symptoms are reported by women who do not have ovarian cancer at a rate that is much higher than the estimated prevalence of ovarian cancer. The extent to which personal demographics and coincident nonspecific symptoms are associated with disease-specific symptom reporting in women who do not have ovarian cancer should be helpful for reassuring patients and in deciding subsequent care.

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Quality of Life

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A cost analysis of postoperative pain management in patients with endometrial cancer: Robotics versus laparoscopy

M. Martino[1], S. Kimmel[1], R. Miller[1], J. Schindler[1], J. Shubella[1], S. Williams[2], M. Thomas[1], R. Boulay[1]
[1]Lehigh Valley Health Network, Allentown, PA, [2]University of South Florida College of Medicine, Tampa, FL

Objective: The purpose of this study was to compare postoperative pain management and associated costs in patients with endometrial cancer who had a robot-assisted or laparoscopy-assisted hysterectomy. Primary outcomes included patient-recorded pain scores and nursing pain management interventions. Secondary outcomes included the cost of postoperative pain medication.

This is a retrospective cohort study of all patients diagnosed with endometrial cancer who had a completed robot-assisted or laparoscopy-assisted hysterectomy from September 2005 to June 2010. All surgeries were performed by gynecologic oncologic surgeons using the Da Vinci S surgical system. Demographic data, patient-recorded pain scores, nursing pain management interventions and postoperative pain medication costs were compared. Pain scores and nursing interventions were analyzed for five intervals over a 24-hour postoperative period, beginning once the patient entered the floor. Nursing interventions were categorized as either a drug or nondrug intervention. Drug interventions were subcategorized as narcotic or nonnarcotic. Data were analyzed using Student's t test and Pearson's χ^2 test in SPSS. This study was institutional review board approved.

Results: Two hundred fifteen (101 robotic and 114 laparoscopic) patients met the inclusion criteria. There were no significant differences between the two groups in age, body mass index, clinical stage, comorbidities, lymph nodes retrieved and number of narcotic versus nonnarcotic drug interventions administered. Robotic patients had a smaller number of initial drug interventions (21 vs 52, $P<0.01$) and total drug interventions (162 vs 219, $P<0.01$) than laparoscopic patients. The robotic cohort also had a lower initial patient-recorded pain score (2.1 vs 3.0, $P=0.012$). There was a 50% reduction in the postoperative pain medication cost on the day of surgery for robotic patients ($12.24 vs $24.45, $P<0.01$), and a 56% cost reduction for the rest of their length of stay ($3.63 vs $8.17, $P<0.01$).

Conclusions: Patients with endometrial cancer who have robotic surgery experience less initial postoperative pain and have fewer drug interventions to manage their pain. The cost associated with delivering that care represents a savings of greater than 50% when compared with a laparoscopic cohort. These factors demonstrate the value of robotic surgery by delivering higher-quality care at a lower cost. Additional prospective studies are needed to confirm these findings.

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A longitudinal evaluation of sexual functioning and quality of life in cervical cancer survivors

D. Bodurka, C. Sun, A. Jhingran, D. Urbauer, C. Levenback, P. Eifel, L. Ramondetta, P. Ramirez, M. Frumovitz, L. Schover
University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: Sexual functioning is a critical issue for women undergoing treatment for cervical cancer. This study sought to longitudinally: (1) assess sexual functioning and quality of life (QOL) in patients with newly diagnosed cervical cancer; and (2) objectively measure changes in vaginal length.

Women with newly diagnosed stage IB1+ cervical cancer were asked to participate. QOL was assessed using the FACT-CX; functional status using the SF-36; and sexual functioning using the Female Sexual Functioning Index (FSFI). Vaginal length was measured using a calibrated plastic vaginal cylinder (similar to a dilator) attached to a digital pressure gauge. Women undergoing radical hysterectomy (RH) and chemoradiation (CRT) completed surveys and vaginal measurements at multiple time points (baseline, ALTO #1, and one, four, and seven months post-radiation therapy [Rx]). Correlations between QOL, functional status, and sexual functioning were evaluated with clinical–demographic variables and vaginal measurements. Multivariate linear regression analysis was conducted to evaluate potential factors associated with QOL outcomes.

Results: Of 88 patients, 74 (84%) completed the baseline surveys (66.7% = CRT, 33.3% = RH). Median age was 39 years (range: 25–69). Most were white, married, employed full-time, and had an annual income level <$50K. The majority reported having vaginal discharge, had not used a dilator, and did not use a lubricant with sexual activity. Ten to 15 percent gave a history of sexual abuse, rape, or physical abuse. General QOL (measured by FACT) for RH and CRT patients was lowest 1 month post-Rx. QOL was similar at four and seven months post-Rx. RH patients reported better functional status (by SF-36) in all domains except for mental health. Cancer-related QOL (by FACT-

CX) was positively correlated with overall sexual function (by FSFI) at baseline ($P=0.07$) and seven months post-Rx ($P=0.007$). Several factors appear to jointly explain sexual functioning and QOL. Longer vaginal length was positively associated with improved QOL (FACT-G, $P=0.04$). Increased age was associated with diminished arousal ($P=0.02$). Longer vaginal length was associated with less pain (by FSFI, $P=0.05$). The RT group showed an overall decrease in vaginal length seven months post-Rx.

Conclusions: Cancer-related QOL is positively correlated with overall sexual functioning at baseline and seven months post-Rx. Educational and intervention programs must be developed to determine optimal care to preserve sexual function of cervical cancer survivors.

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Age-related preferences regarding end-of-life care discussions among gynecologic oncology patients

A. Brown[1], M. Johnson[2], R. Giuntoli[1], T. Diaz-Montes[1]
[1]*Johns Hopkins Hospital, Baltimore, MD,* [2]*Baylor College of Medicine, Houston, TX*

Objective: The purpose of this study was to assess age-related preferences regarding end-of-life care (EOLC) discussions among women with gynecologic cancer.

A questionnaire related to EOLC issues was distributed anonymously to patients presenting to the gynecologic oncology clinic. Only patients with a gynecologic cancer diagnosis were invited to participate. The group was arbitrarily divided between those <60 years and those ≥60 years of age. Responses were compared among groups, and answers were analyzed via SPSS using descriptive statistics and χ analysis to calculate *P* values.

Results: A total of 72 patients completed the questionnaire. The median age was 56 years. Women <60 constituted 55.5% of the group; 44.4% were ≥60. Among women <60 years, 47.5% preferred to initiate the EOLC discussion with their physician compared with 34.4% of women ≥60 ($P=0.36$). However, the majority of older women (56.3%) preferred their physician to initiate the discussion. Both groups were familiar with advanced directives (<60 = 72.5% vs ≥60 = 68.8%, $P=0.79$). The largest subgroup in each age group thought that the best time to discuss advanced directives is when treatment is no longer an option (35% vs 28.1%, $P=0.57$). Both groups were also familiar with do not resuscitate/do not intubate (DNR/DNI) (87.5% vs 90.6%, $P=0.96$). The largest subgroup in the younger group (40%) found it more pertinent to discuss DNR/DNI when disease progresses. Conversely, the largest subgroup in the older group (28.1%) found it best to discuss DNR/DNI when there are no remaining treatment options. Most of the older group (84.4%) had designated someone to make decisions on their behalf, compared to only 45% of those in the younger group ($P=0.04$). The majority of the older group (71.9%) had expressed their decision regarding DNR/DNI, compared with only 47.5% of the younger group ($P=0.20$). The largest subgroup in each age group found it ideal to discuss EOLC expectations when there are no remaining treatment options (37.5% vs 53.1%, $P=0.36$). Both age groups were familiar with hospice (97.5% vs 96.9%, $P=0.90$) and agreed that hospice should be discussed when there are no remaining treatment options (57.5% vs 59.4%, $P=0.98$).

Conclusions: Older and younger women have similar preferences with respect to EOLC. A statistically significant majority of older women had previously expressed their EOLC preferences to someone as compared with younger women.

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Menopausal symptoms and use of hormone replacement therapy: The gynecologic cancer survivors' perspective

M. Huang, S. Westin, C. Sun, L. Meyer, C. Tung, D. Urbauer, D. Bodurka
University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: As overall survival for gynecologic cancers has increased, many gynecologic cancer survivors now face undesirable side effects that accompany treatment-related menopause. The objective of this study was to describe hormone-related issues faced by gynecologic cancer survivors.

As part of a larger study, a stratified sample of women with gynecologic cancers at our institution from 1997 to 2007 were surveyed for health issues occurring during or after treatment. Women who had menstrual cycles at the time of the survey or were ≥55 years of age were excluded from analysis. The χ^2 test and Fisher's exact test were used for statistical analysis.

Results: There were 544 survivors evaluable for this study. Median age at diagnosis was 42 years with a median of six years since diagnosis. Among respondents, 42.1% had cervical cancer; 19.4% endometrial cancer; 24.4% ovarian, primary peritoneal, or fallopian tube cancer; 9.8% vulvar cancer; and 4.3% vaginal cancer. Approximately 43.3% of all patients received radiation as part of their treatment; 37.2% had surgery alone. Women were predominantly white (77.6%) or Hispanic (14.0%). Eighty percent reported at least one menopausal symptom regardless of cancer diagnosis. Menopausal symptoms included hot flashes in 54%, vaginal dryness in 48%, vaginal atrophy in 19%, pain with vaginal intercourse in 33%, and mood swings in 37%. Compared with women who did not report menopausal symptoms, those with menopausal symptoms were more likely to report fatigue ($P=0.04$), memory difficulty ($P=0.02$), sleep disturbances ($P=0.04$), depression ($P=0.04$), anxiety ($P=0.04$), urinary incontinence ($P=0.006$) and sexual problems ($P<0.001$). Although 128 of 544 (24%) survivors were prescribed some type of hormonal therapy, 79% still reported menopausal symptoms (hot flashes in 54%, vaginal dryness in 54%, vaginal atrophy in 23%, pain with intercourse in 36%, and mood swings in 38%). Patients with cervical cancer reported significantly more vaginal dryness when compared with patients with endometrial cancer ($P=0.002$) and ovarian cancer ($P<0.0001$). Patients with cervical cancer also experienced more vaginal atrophy compared with patients with ovarian cancer ($P=0.004$) and vaginal cancer ($P<0.0001$). Patients with vaginal cancer reported more vaginal atrophy than both patients with endometrial cancer ($P=0.002$) and those with ovarian cancer ($P=0.01$).

Conclusions: This is the first study reporting the high prevalence of menopausal symptoms among gynecologic cancer survivors. Menopausal symptoms were associated with other health-related issues known to negatively impact quality of life. These results highlight the need to better acknowledge and define the utility of hormonal therapy in this population.

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Palliative care education in gynecologic oncology: A survey of the fellows

J. Lesnock[1], R. Arnold[2], L. Meyn[1], M. Buss[3], M. Quimper[4], T. Krivak[1], R. Edwards[1], J. Chang[1]
[1]*Magee–Womens Hospital of UPMC, Pittsburgh, PA,* [2]*University of Pittsburgh Medical Center, Pittsburgh, PA,* [3]*Harvard Medical School, Center for Palliative Care, Boston, MA,* [4]*University of Pittsburgh School of Medicine, Pittsburgh, PA*

Objective: Gynecologic oncologists regularly care for patients at the end of life (EOL), yet little is known about their training or preparedness with respect to the issues of palliative care (PC). We sought to examine what training is provided to current gynecologic oncology fellows (GOFs) and their attitudes and needs regarding PC.

A validated, self-administered survey was distributed to all GOFs enrolled in fellowship during the 2009 academic year. It was adapted for use among GOFs and designed to assess training, experience, preparedness, and attitudes. All candidates received surveys by mail and a link to an online electronic version via email. Items were designed to allow comparison between outcomes. Descriptive analyses and comparisons were conducted using SPSS, Release 17.0.

Results: The survey completion rate was 61% (103/168). Demographics are summarized in the table. Although 81% reported active involvement in EOL care and decision making, only 67% rated themselves highly prepared ($\geq$6 of 10, median = 7) to provide EOL care. Also, most (83%) feel that PC is integral to their training, but few (15%) have had formal PC training. Using a 0–10 Likert scale, with 10 being "a lot of teaching," GOFs rated teaching on two common informal training opportunities, specifically managing postoperative complications (7.8) and endometrial cancer patients (8.7), as significantly higher than teaching on managing patients at the EOL (5.5, $P<0.001$). They were also more likely to have been observed by an attending physician while performing a colposcopy than discussing PC issues with patients ($P=0.01$). GOFs assessed the quality of EOL teaching as significantly lower than their overall teaching ($P=0.001$). There was no significant difference in these outcomes by age, gender, religion, marital status or year of fellowship. However, more U.S. medical school graduates (88%) than non-U.S. graduates (11%) felt prepared to provide EOL care ($P=0.045$).

Conclusions: Among current GOFs, most feel that PC is important, but few have formal training. The quantity and quality of education and training in PC were less compared with other common procedural and oncologic issues and even overall training. The reasons for this lack of training and its impact on patient care need to be better elucidated. Our results suggest a need for improved PC training for GOFs.

Characteristic	Value	Characteristic	Value
Sex		Medical school	
Male	29 (28.2%)	U.S. Grad	82 (79.6%)
Female	70 (68%)	Non-U.S. Grad	17 (16.5%)
Missing	4 (3.9%)	Missing	4 (3.9%)
Ethnicity		Year of fellowship	
White	72 (69.9%)	First	28 (27.2%)
Asian	13 (12.7%)	Second	33 (32%)
Black	8 (7.8%)	Third	29 (28.2%)
Hispanic	3 (2.9%)	Fourth	9 (8.7%)
Other	3 (2.9%)	Missing	4 (3.9%)
Missing	4 (3.9%)		
Religion		Marital status	
Catholic	31 (30.1%)	Married	64 (62.1%)
Protestant	24 (23.3%)	Never married	31 (30.1%)
None	24 (23.3%)	Separated/	
Other	7 (6.8%)	divorced	4 (3.9%)
Muslim	6 (5.8%)		
Jewish	3 (2.9%)	Missing	4 (3.9%)
Hindu	3 (2.9%)	Median age (range)	34 (30–52)
Missing	5 (5.9%)		

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Clinical Trials – Ovary/Fallopian Tube/PPC/Breast Phase I/II

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Pegylated liposomal doxorubicin with bevacizumab in the treatment of platinum-resistant ovarian cancer: Toxicity profile results

S. Czok[1], A. Jewell[1], S. Shawki[1], L. Boyd[1], H. Smith[2], S. Blank[1], C. Muller[3], C. Verschraegen[3], F. Muggia[1]
[1]New York University School of Medicine, New York, NY, [2]Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [3]University of New Mexico, Albuquerque, NM

Objective: Given the modest activity of pegylated liposomal doxorubicin (PLD) and the proven activity of bevacizumab (B) as single agents in platinum-resistant ovarian cancer (OC), a phase II study of PLD + B was initiated in the treatment of platinum-resistant OC at our institutions to determine the nature and degree of toxicity associated with this combined regimen, as both PLD and B alone can be associated with serious side effects.

This phase II study of PLD + B was started in 2007 to accrue 48 patients. PLD was dosed at 30 mg/m^2 followed by B 15 mg/kg on cycles 2–7 (with an option to continue) every 21 days. Patients recurring within 6 months of platinum-based treatment for OC after fewer than three prior regimens (but no PLD or B) were eligible. Exclusions included bowel obstruction, prior perforation, uncontrolled hypertension and vascular disease. MUGA scans were obtained every third cycle, and disease status was determined by CA-125 and/or RECIST every third cycle.

Results: Accrual completed in July 2010: 48 patients with 41 presently evaluable for toxicity. The average age was 64, with most patients having undergone two prior regimens. The average number of cycles was eight (range: 3–18). Excluding baseline and conditions unrelated to study drug, adverse events (AEs) included 134 grade 2, 43 grade 3, and five grade 4 (severe ileus, decreased left ventricular ejection fraction [LVEF], severe headache, speech disorder,and microangiopathic glomerulopathy, the last event after completing accrual). The most common AEs were dermatologic ($n=101$), gastrointestinal ($n=48$), and cardiovascular ($n=42$). Most grade 3 AEs were dermatologic (hand–foot syndrome and mucositis) and cardiovascular (hypertension). LVEF declined 5% overall with four patients (9.7%) to less than 50% from a 62% baseline.

Conclusions: The combination of PLD + B met anticipated tolerance expectations (defying hypothetical predictions of antagonistic interactions). Some safety considerations have emerged: Declines in LVEF occurred in 10%, and dermatologic side effects and hypertension increased with number of cycles given. We await follow-up to confirm the effectiveness of this combination.

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Phase II Trial of docetaxel and bevacizumab in recurrent ovarian cancer within 12 months of prior platinum-based chemotherapy

R. Wenham[1], J. LaPolla[2], L. Hui-Yi[1], S. Apte[1], W. Roberts[1], J. Lancaster[1], J. Gonzalez Bosquet[1], S. Theodore[1], L. Havrilesky[3], A. Alvarez-Secord[3]
[1]H. Lee Moffitt Cancer Center, Tampa, FL, [2]Women's Cancer Associates, St. Petersburg, FL, [3]Duke University Medical Center, Durham, NC

Objective: Bevacizumab has activity in ovarian cancer (OC). Docetaxel is an active chemotherapeutic in recurrent OC and the combination with bevacizumab appears to be tolerable and efficacious in other cancers. We therefore studied the efficacy and tolerability of combination docetaxel and bevacizumab in patients with recurrence of OC within one year of platinum-based therapy.

Eligible patients included those with progression or recurrence of OC within 12 months of platinum therapy and who had received a maximum of three prior chemotherapy regimens. Patients had measurable disease or elevated CA-125 (twice normal). The treatment regimen was docetaxel (40 mg/m^2) days one and eight and bevacizumab (15 mg/kg) day one in a 21-day cycle. Treatment continued for at least eight cycles or until progression or severe toxicity. Primary and secondary endpoints included progression-free survival, response and clinical benefit rates and toxicity.

Results: Enrollment is near completion with 39 (of 40 planned) patients and five receiving ongoing treatment. Thirty-seven (94.8%) patients are now evaluable (≥2 cycles) for response. Best responses for the 37 evaluable patients are: 3% complete response ($n=1$), 54% partial response ($n=20$), 27% stable disease ($n=10$), 11% progressive disease ($n=4$), and 5% not yet determined ($n=2$). Of 39 enrolled patients, 34 have met criteria for progressive disease (based on RECIST criteria [$n=8$], CA-125 criteria [$n=15$], both CA-125 and RECIST [$n=2$], physical exam [$n=1$], global deterioration [$n=1$], and elective withdrawal, toxicity, or change of therapy [$n=7$]). Two patients were taken off treatment for unrelated surgical procedures, two patients electively withdrew without progression or toxicity, and one patient discontinued due to inability to achieve timely anticoagulation for a deep vein thrombosis. One patient had a bowel perforation and one patient developed a vesicovaginal fistula during cycles 1 and 2, respectively. Median duration on study for the 37 evaluable patients was 32 weeks (interquartile range = 22.6–45.1 weeks). The 37 evaluable patients received a total of 253 treatment cycles with (median = 6, range: 2–13). Fifteen patients (40.5%) have had progression-free survival >6 months; median progression-free survival is 25 weeks (95% CI = 21.9 V–31.6). Updated data based on final enrollment will be available.

Conclusions: Combination bevacizumab and docetaxel administered to patients with recurrent ovarian cancer is an active regimen without new unanticipated toxicity.

Toxic effect (grade 3/4, of 37 evaluable patients)	Treatment cycles ($n=253$) with toxicity, n (%)	Pts with toxicity: n (%)*
Leukopenia or neutropenia	16 (6)	8 (22)
Thrombocytopenia	1 (<1)	1 (<1)
Fatigue/Anorexia	5 (2)	5 (14)
Infection	3 (1)	3 (8)
Metabolic	6 (2)	4 (11)
Fistula (vesicovaginal)	1 (<1)	1 (<1)
Neuropathy	2 (1)	2 (5)
Gastrointestinal	4 (2)	3 (8)
Other (rash, hot flash, respiratory, pain)	6 (2)	6 (16)
All grade 3/4	45 (18)	24 (65)*

Note. Some patients may be listed in more than one toxicity category.

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Clinical Trials/Phase I

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A phase I/II trial of IDD-6, an autologous dendritic cell vaccine for women with advanced ovarian cancer in remission

C. Chu[1], J. Boyer[2], P. Gimotty[2], S. Rubin[2], G. Coukos[2], M. Morgan[3], J. Bender[4], C. June[2]
[1]*University of Pennsylvania Medical Center, Philadelphia, PA,* [2]*University of Pennsylvania, Philadelphia, PA,* [3]*Fox Chase Cancer Center, Philadelphia, PA,* [4]*ImmunoCellular Therapeutics, Woodland Hills, CA*

Objective: This phase I/II trial was aimed at determining the safety and efficacy of IDD-6, an autologous dendritic cell vaccine, administered with or without low-dose cyclophosphamide for consolidation in patients with advanced ovarian and primary peritoneal cancer after achieving a complete clinical response to primary therapy.

Patients underwent apheresis for collection of peripheral blood monocytes, which were cultured and pulsed ex vivo with Her2/neu, hTERT, and PADRE peptides. All subjects received both IDD-6 and Prevnar as a control. Patients were randomized to receive a single dose of cyclophosphamide (300 mg/m^2) two days prior to first vaccination. Four intradermal vaccinations were administered at three-week intervals. Blood was collected for immunoassessment by ELISPOT and Treg quantification. Primary endpoints included safety and immune reponse; secondary endpoints included effect of cyclophosphamide on Tregs and survival.

Results: Fourteen subjects were enrolled, with seven randomized to each arm. Patients ranged in age from 18 to 70 (mean = 51). Three did not ultimately meet criteria for vaccination after apheresis (one developed a lung infection, one developed dermatomyositis, and one recurred). Of 11 treated patients, two recurred during the course of vaccination, and nine received all four doses. Of those, three patients recurred at six, 17, and 26 months, respectively. The remaining six patients have no evidence of disease at a median of 36 months of follow-up. Overall estimated three-year progression-free and overall survival for all evaluable patients was 60 and 90%, respectively. Though there is a trend toward improved survival in patients receiving cyclophosphamide, this did not reach statistical significance. All subjects tolerated the vaccine well, with the most common toxic effects being erythema, induration, and pruritis at the injection site, fatigue and fever. No grade 3 or 4 vaccine-related toxicity was noted. ELISPOT to detect peptide-specific interferon γ-releasing T cells demonstrated modest responses to Her2/neu and hTERT. Flow cytometry for FoxP3-positive cells revealed transient Treg depletion in patients receiving cyclophosphamide. Patients demonstrated low reactivity to the diphtheria conjugate protein CRM197.

Conclusions: Vaccination of patients with ovarian cancer presents many challenges. Even traditional bacterial vaccines such as Prevnar demonstrate poor immunogenicity. Vaccination with IDD-6 is safe, and though immune responses are modest, survival after vaccination is very promising.

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Poster Area 3
Endometrial Cancer, Chemotherapy, Clinical Practice Issues and Endometrial Clinical Trials: Abstracts 194–240
Sunday, March 6 – Tuesday, March 8, 2011
Exhibit Hall – Bonnet Creek Ballroom

Endometrial Cancer

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Abnormal cervical cytology in the preoperative diagnosis of uterine papillary serous carcinoma: Earlier detection of a poor prognostic uterine cancer?

M. Skaznik-Wikiel[1], S. Ueda[2], A. Fleury[2], H Frasure[3], F. Grumbine[2], P. Rose[1], A. Nickles Fader[2]
[1]*The Cleveland Clinic, Cleveland, OH,* [2]*Johns Hopkins Medical Institutions, Baltimore, MD,* [3]*University Hospitals of Cleveland, Cleveland, OH*

Objective: Uterine papillary serous (UPSC), clear cell (CCC), and grade 3 endometrioid (G3EC) carcinomas are biologically aggressive, high-grade malignancies. Early detection of these poor prognostic variants of endometrial carcinoma (EC) is of particular clinical relevance. Few studies have assessed the role of the Pap test in the diagnosis of high-grade EC. The study objective was to assess the utility of liquid-based cervical cytology in the detection of high-grade EC.

A retrospective, two-institution analysis of patients diagnosed with UPSC, CCC, or G3EC between 1999 and 2010 was conducted. Patients who had undergone a preoperative Pap with liquid-based technology within six months of diagnosis and had clinical follow-up data available were included. Patient demographic and clinical variables were examined in uni- and multivariate analyses by use of χ^2 tests and logistic regression.

Results: One hundred one patients were evaluated. The median age was 67.7 years, median BMI was 31.7, and all patients underwent surgical staging. Fifty-two patients (51.5%) had UPSC, 28 (27.7%) had CCC, and 21 (20.8%) had G3EC. The majority of patients (69.3%) had stage I/II disease, and histology subgroups were well matched by stage. Forty-six of 101 (45.5%) had an abnormal preoperative Pap result; carcinoma cells were identified in 41.3%, abnormal glandular cells in 41.3%, abnormal endometrial cells in 6.5%, ASCUS in 6.5%, and LSIL in 4.3%. Significantly more patients with UPSC had an abnormal Pap (34/52; 65.7%) than those with CCC (25%) or G3EC (23.8%) ($P<0.001$). Interestingly, abnormal Pap was the only presenting clinical finding in a significant number of asymptomatic patients with UPSC (26.9%) compared with four and 4.8% of patients with CCC and G3EC, respectively ($P=0.005$). Moreover, on multivariate analysis, UPSC histology was the only variable significantly associated with abnormal Pap.

Conclusions: Our preliminary data indicate a high incidence of abnormal Pap tests in women with high-grade EC, particularly in patients with UPSC, suggesting that serous tumor cells exhibit a propensity for shedding irrespective of disease stage. Furthermore, a proportion of patients with UPSC had an abnormal Pap in the absence of other findings, signifying that liquid-based cytology may help detect high-grade EC before clinical symptoms are evident. The addition of Pap data to other clinical tests may enhance the ability to preoperatively identify poor prognostic variants of EC, which may influence the surgical management and selection of adjuvant therapies.

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Adiposity and endometrial cancer: The stress of excess

K. Matsuo, S. Srivastava, P. Tripathi, L. Sonoda, E. Yoo, K. Pfaffenbac, L. Dubeau, A. Lee, Y. Lin
University of Southern California, Los Angeles, CA

Objective: Glucose-regulated protein (GRP) 78 is a critical component of the unfolded protein response that is activated in conditions of endoplasmic reticulum (ER) stress, such as obesity. Given the association of endometrial carcinoma with obesity, we hypothesize that higher levels of visceral adipocyte GRP78 in patients with endometrial carcinoma are associated with increased risk of recurrence.

Using a 1:2 case–control design, 90 patients with endometrial carcinoma, including 29 with recurrences (cases), were evaluated for GRP78 expression within the tumor and visceral (omental and perinodal) adipose tissue obtained at the time of primary surgical staging. Semiquantitative GRP78 expression was determined by immunohistochemical analysis of intensity and distribution of expression. Clinicopathologic information and clinical outcomes were analyzed by uni- and multivariate analyses.

Results: GRP78 was expressed in 98.9% of tumors and 93.3% of adipose specimens. Tumor GRP78 expression was inversely correlated with grade (Spearman's $r=-0.34$, $P=0.001$) and not associated with stage or recurrence. On the other hand, adipocyte GRP78 expression was positively correlated with grade ($r=0.23$, $P=0.028$) and stage ($r=0.31$, $P=0.003$). Logistic regression showed that high GRP78 expression in adipocytes was associated with endometrial cancer recurrence and mortality (both $P<0.005$). Tumor cell GRP78 expression was not correlated with adipocyte GRP78 expression. Among recurrent endometrial cancer cases, tumor GRP78 was inversely correlated with progression-free survival ($r=-0.41$, $P=0.027$). Compared with patients with lower GRP78 expression in adipocytes, patients with higher adipocyte GRP78 expression had significantly decreased progression-free survival (15.4 months vs 36.8 months, $P=0.001$). Multivariate analysis showed that increased GRP78 expression in adipocytes ($P=0.03$), stage ($P=0.007$), histology ($P=0.008$), lymphovascular space invasion ($P=0.002$) and optimal tumor reductive surgery ($P=0.001$) remained significant risk factors for disease recurrence.

Conclusions: GRP78 expression in visceral adipocytes is associated with indicators of poor prognosis in patients with endometrial cancer including tumor grade, tumor stage, time to recurrence and early death. The results suggest a novel link between obesity and endometrial cancer via ER stress.

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Analysis of risk factors for isolated paraaortic lymph node metastasis in endometrial cancer: A clinicopathologic study of 210 consecutive patients

S. Chang, W. Kim, T. Kong, S. Yoo, J. Yoon, K. Chang, H. Ryu
Ajou University School of Medicine, Suwon, Republic of Korea

Objective: Paraaortic lymph node (LN) metastasis in endometrial cancer occurs mainly by way of pelvic LN metastasis. However, direct spread to paraaortic LNs via ovarian vessels is a possible route of lymphatic spread and patients have isolated paraaortic LN metastasis without pelvic LN metastasis. A relationship between various pathological risk factors and isolated paraaortic LN metastasis has not been reported so far. The purpose of this study was to investigate pathologic risk factors associated with isolated paraaortic LN metastases in surgically staged patients with endometrial cancer.

We performed a retrospective analysis of 210 consecutive patients with endometrial cancer who were surgically staged from 2000 to 2010. The association of the various pathologic variables with paraaortic LN metastases was determined with univariate and multivariate analyses. All patients had complete surgical staging procedures including pelvic and paraaortic lymphadenectomy up to the renal vessels. All relevant clinicopathologic data were statistically analyzed.

Results: Of 210 patients, 30 (14.3%) had LN metastases. Ten (4.8%) patients had only pelvic LN metastases, 17 (7.1%) had both pelvic and paraaortic LN metastases, and five (2.4%) had isolated paraaortic LN metastases. On univariate analysis, histologic type ($P=0.001$), tumor grade ($P<0.001$), tumor size ($P=0.003$), depth of myometrial invasion ($P<0.001$), cervical invasion ($P<0.001$), parametrial invasion ($P=0.002$), lymphovascular space invasion (LVSI) ($P<0.001$), serosal invasion ($P<0.001$), adnexal invasion ($P<0.001$), positive cytology ($P=0.002$), and pelvic LN metastasis ($P<0.001$) were significant risk factors for paraaortic LN metastases. On multivariate analysis, cervical invasion ($P=0.042$), LVSI ($P=0.016$) and positive pelvic LNs ($P=0.001$) were independent risk factors for paraaortic LN metastases. To determine risk factors associated with isolated paraaortic LN metastases, we excluded patients with positive pelvic LNs and those with both pelvic and paraaortic LN involvement from 210 patients. A total of 185 patients were identified and we conducted a statistical analysis of this subgroup. With respect to isolated

paraaortic LN metastasis, tumor grade ($P=0.016$) and LVSI ($P=0.002$) were significant factors for LN involvement. On multivariate analysis, LVSI ($P=0.004$) was the only independent factor.
Conclusions: Lymphovascular space invasion is an independent risk factor for isolated paraaortic lymph node metastasis in patients with endometrial cancer.

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Complete gross resection is associated with improved survival in advanced-stage uterine carcinosarcoma

E. Tanner, G. Gardner, Y. Sonoda, K. Garg, D. Chi, M. Leitao, E. Jewell
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The objective of this study was to evaluate the role of cytoreductive surgery for the treatment of primary uterine carcinosarcoma (CS).

Demographics, tumor histology, surgical procedures and survival data were collected for all patients with stage IIIC or IV uterine CS diagnosed between 1990 and 2009 at our institution. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier method. Eighteen factors (e.g., age, adjuvant therapy, histologic features, and residual disease following cytoreductive surgery) were evaluated for their prognostic association with survival. Factors significant on univariate analysis were evaluated by multivariate analysis.
Results: Of 44 evaluable patients with gross disease outside of the pelvis, 14 (32%) were stage IIIC (retroperitoneal lymph node metastases) and 30 (68%) were stage IVB (gross intraabdominal metastases). Of the 14 patients with stage IIIC disease, 13 (93%) underwent complete gross resection. Of the 30 patients with stage IV disease, the cytoreductive outcomes were: no gross residual in 12 (40%), 1- to 10-mm residual in nine (30%), and >10-mm residual in 9 (30%). Twenty-seven patients (61%) received adjuvant platinum-based chemotherapy, four (9%) received adjuvant pelvic radiation and platinum-based chemotherapy, two received non-platinum-based chemotherapy, seven (16%) progressed prior to starting adjuvant therapy, and four (9%) declined/did not receive adjuvant therapy. Thirty-eight patients (86%) recurred during a median follow-up of 17.8 months (range: 0.2–98). Patients with stage IIIC versus stage IV disease had a PFS of 8.1 months versus 8.3 months ($P=0.023$) and OS of 52.3 months versus 17.5 months ($P=0.005$). Patients who did or did not receive adjuvant therapy had a PFS of 12.8 months versus 1.0 month ($P<0.0001$) and OS of 30.1 months versus 4.7 months ($P<0.0001$). Patients with and without residual disease following primary cytoreductive surgery had a PFS of 1.8 months versus 10.8 months ($P=0.001$) and OS of 8.6 months versus 52.3 months ($P<0.0001$). On multivariate analysis, only the presence or absence of residual disease and administration of adjuvant chemotherapy were independently associated with PFS/OS.
Conclusions: Complete gross resection of extrauterine disease may influence PFS/OS in advanced uterine CS. Patients with intraabdominal metastases have a survival similar to that of patients with lymph node-only disease if completely resected. Surgical cytoreduction with the goal of achieving a complete gross resection may be warranted for advanced uterine CS.

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Distribution of extrauterine disease in uterine papillary serous carcinoma: Is minimally invasive surgery a suitable approach?

T. Ayeni, M. Al Hilli, A. Mariani, M. McGree, A. Weaver, W. Cliby, K. Podratz, S. Dowdy
Mayo Clinic, Rochester, MN

Objective: Uterine papillary serous carcinoma (UPSC) has a propensity for peritoneal spread, yet surgical staging for UPSC has historically been less comprehensive than that for serous ovarian carcinoma. As a result, higher-stage disease may go undetected, particularly as staging for endometrial carcinoma increasingly incorporates minimally invasive techniques. Our aim was to define the pattern of disease spread in UPSC to guide optimal staging.

We analyzed records of patients with UPSC who underwent surgical resection between 1999 and 2008. Abstracted data included stage, depth of myometrial invasion and disease location.
Results: Two hundred fifteen patients with UPSC were identified. Stage distribution was: 43, 1, 23, and 33% for stages I, II, III, and IV, respectively. Comprehensive staging with hysterectomy, adnexectomy, pelvic and paraaortic lymphadenectomy, omentectomy, and cytology was performed in 125 patients. In the staged cohort, 44% had extrauterine, nonnodal, disease (EUD), 18% of whom had only microscopic EUD. Sites of EUD included: omentum (22%), mesentery (14%), diaphragm (12%), cul-de-sac (11%), general carcinomatosis (11%), and splenic/liver parenchyma (4%). Forty-eight percent of patients with EUD had involvement of two or more sites. Average size of gross disease, when present, was 28 mm. When EUD was present, the omentum was never the only site of disease. EUD was present in 36% of patients without myometrial invasion, 17% of whom had diaphragm involvement. Patients with deep invasion had a higher likelihood than patients without invasion of developing pelvic (48% vs 20%) and paraaortic (44% vs 10%) nodal metastases. Peritoneal washings were negative in all 70 cases of uterine-only disease and positive in 100% of patients with microscopic EUD.
Conclusions: This large single-institution cohort demonstrates that extrauterine spread in patients with UPSC is often small volume and present in locations that may be difficult to identify laparoscopically, particularly the mesentery and diaphragm. However, it is unlikely that the improvement in morbidity associated with laparoscopic staging is outweighed by reductions in staging accuracy for the 8% of patients with microscopic-only EUD. Rates of lymphatic involvement approach 50% in both the pelvic and paraaortic areas in the presence of deep myometrial invasion, highlighting the known importance of lymphadenectomy. Finally, we find no evidence that omentectomy influences ultimate stage or treatment when it lacks gross disease on visual inspection, and resection may be omitted in these cases.

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Early-stage high-risk endometrial cancer: Adjuvant treatment with chemotherapy and vaginal brachytherapy

S. Schuman, J. Stine, W. Zhao, P. Yali, A. Wolfson, J. Lucci
University of Miami Sylvester Cancer Center, Miami, FL

Objective: The standard treatment for early-stage high-risk endometrial cancer is whole-pelvis radiation. Although whole-pelvis radiation reduces recurrences by reducing pelvic failures, it does not improve survival. In this study, we report our experience of treating early-stage

high-risk endometrial cancer with vaginal brachytherapy (VB) and chemotherapy and compare the results with those of GOG-99.

Between April 2006 and July 2010, 31 patients with early-stage high-risk endometrial cancer underwent surgical staging followed by adjuvant VB and three to six cycles of carboplatin and paclitaxel. Patients' demographics, pathological and treatment characteristics, toxicity rates, and outcomes were compared with those for the high-intermediate-risk whole-pelvis radiation group of GOG-99.

Results: Thirty-one patients met eligibility criteria. Median age was 62 (range: 36–81).Seventy-one percent ($n=22$) and 29% ($n=9$) had FIGO stage I and II disease, respectively. Myometrial invasion involved the outer third in 48% ($n=15$). Histology was endometrioid in 64% ($n=20$), clear cell in 10% ($n=3$), and papillary serous in 26% ($n=8$). Tumor grade was 1 in 19% ($n=6$) and 2 or 3 in 81% ($n=25$). Lymphovascular space invasion was present in 65% ($n=20$). Thirty patients received three to six cycles of carboplatin (AUC 5–6) and paclitaxel (175 mg/m^2) every 21 days. Six cycles were given to 56% ($n=17$), five cycles to 10% ($n=3$), four cycles to 7% ($n=2$), and three cycles to 27% ($n=8$). Twenty-nine patients received VB (low-dose radiation in 55% and high-dose radiation in 45%). Two patients received adjuvant chemotherapy but no VB, and one patient received VB but declined chemotherapy. Although patient ages in our study and GOG-99 were similar ($P=0.855$), we had significantly more stage II disease (29% vs 10%, $P<0.0001$) and grade 3 tumors (55% vs 15%, $P<0.0001$). None of our patients had locoregional, vaginal, or pelvic recurrences; one patient had a distant recurrence. The cumulative recurrence rate was 11.1% (95% CI = 1.6%, 56.7%) at 2.5 years with a median follow-up time of 1.8 years (range: 0.3–4.1). As no death occurred during the follow-up period in this cohort, median survival time was not reached. Gastrointestinal toxicity was significantly lower in our study than in GOG-99 (12.9% vs 34.2%, $P=0.02$).

Conclusions: Adjuvant treatment of high-risk early-stage endometrial cancer with vaginal brachytherapy and chemotherapy is feasible and well tolerated with a favorable toxicity profile. Longer follow-up is needed to compare recurrence and overall survival outcomes with those for whole-pelvis radiation.

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Evaluation of intrauterine progesterone for the treatment of complex atypical hyperplasia and low-grade endometrial cancer

M. Billow[1], L. Nieves-Arriba[2], R. DeBernardo[1]
[1]University McDonald Women's Hospital, Cleveland, OH, [2]The Cleveland Clinic, Cleveland, OH

Objective: The purpose of this study was to evaluate the outcomes of patients with complex atypical hyperplasia (CAH) and low-grade endometrial cancer (EC) who have been treated with a levonorgestrel-releasing intrauterine device (IUD) and to describe the efficacy, side effects and feasibility of this management strategy in a patient population deemed high risk or unwilling to consent for definitive surgical management.

In this retrospective chart review, after institutional review board approval was obtained, the medical records of all patients treated using an IUD from January 2005 to September 2010 were reviewed. Patients were identified based on CPT code for IUD insertion. Inclusion criteria included: a diagnosis of CAH or grade 1–2 endometrial adenocarcinoma. All patients underwent endometrial biopsy at placement of the IUD. Patients were serially sampled to assess progestin effect and resolution of disease. Women underwent hysterectomy or alternative treatment at the discretion of the treating oncologist. Descriptive statistics were used to summarize outcomes in both cohorts.

Results: Thirty patients were identified, 16 with CAH and 14 with endometrial cancer. Median age of the population was 60.5, and median body mass index was 47. Median follow-up time was 17.1 months (range: 1.3–85.8). The table outlines comparisons between the groups. One patient in the CAH group (6%) had progression of disease. Only two patients in the EC group (14%) required surgery for progression of disease. No differences in race and ASA stratification were identified between the two groups. A total of 19 patients had ASA III (63%) class and seven patients had ASA IV (23%).

Conclusions: A progestin-containing IUD is a feasible alternative in high-risk women or those declining surgical management of CAH or EC. It is well tolerated and associated with low complication rates in this population. Although the sample size is small, the overall response rates were high and, to our knowledge, have not been previously reported.

	CAH ($n=16$)	EC ($n=14$)
Age, median (range)	58 (26–72)	62 (25–82)
Body mass index, median (range)	52 (38–82)	37 (20–68)
Prior treatment		
Megace	3	3
Depo-Provera	3	0
Type of sampling		
EMB	7	4
D&C	2	6
D&C/hysteroscopy	7	4
Reason for insertion of IUD		
Poor surgical candidate	11	10
Desires fertility	4	2
Declines surgery	1	2
Complications of IUD		
Expulsion	1	1
Vaginal bleeding	2	1

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Fertility-sparing management with progestin for young women with stage I endometrioid endometrial cancer: Long-term outcomes

J. Park, D. Kim, J. Kim, Y. Kim, Y. Kim, J. Nam
Asan Medical Center, Seoul, Republic of Korea

Objective: The purpose of this study was to investigate the long-term oncologic and reproductive outcomes of fertility-sparing management with progestin for young women with stage I endometrioid endometrial cancer who wish to preserve fertility.

This retrospective analysis included 83 young patients (<40 years old) with stage I endometrioid endometrial cancer who were treated conservatively with medroxyprogesterone acetate (MPA) or megestrol acetate (MA). Pathologic slides were reviewed. Oncologic and reproductive outcomes were analyzed.

Results: The mean age of patients was 31 years (range: 21–40). Fifty patients were given MPA orally daily (500 mg/day) and 33 patients were given MA orally daily (160–240 mg/day). Pathologic complete response was observed in 73 of 83 patients (88%); the remaining 10 patients (12%) underwent hysterectomy. After a median follow-up time of 47 months (range: 6–170), 23 of 73 patients who had had a

complete response (33%) had recurrent disease. Mean interval to recurrence was 25 months (range: 4–114), and all recurrences were confined to the uterus. At recurrence, four underwent hysterectomy. However, 19 again tried conservative management with progestin, and 17 of them showed a complete response and two underwent hysterectomy. No one experienced progression of disease. At the time of analysis, 32 patients attempted to conceive, 24 patients succeeded in pregnancy, and 16 healthy babies were born.

Conclusions: Fertility-sparing management with MPA or MA for young women with stage I endometrioid endometrial cancer was safe and highly efficacious. The pregnancy outcomes were promising. However, because a significant proportion of patients had recurrent disease during the follow-up period, close surveillance and definitive surgical management after completion of family planning is required.

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Hysterectomy for uterine adenocarcinoma in the oldest old: Tumor characteristics and long-term outcome

O. Gayar, J. Robbins, K. Parikh, M. Lu, T. Buekers, A. Munkarah, M. Elshaikh
Henry Ford Health System, Detroit, MI

Objective: The goal of this study was to evaluate the outcomes of elderly patients ≥75 years of age with early-stage endometrioid endometrial carcinoma.

We identified 675 surgically staged patients with 1988 FIGO stage I/II endometrioid endometrial carcinoma who were treated from 1985 to 2009. Their medical records were retrospectively reviewed in this institutional review board-approved study. Patients were classified as ≥75 vs <75 years of age and compared with respect to outcome. Following a univariate analysis, multivariable modeling was done using Cox regression analysis.

Results: Of 675 patients reviewed, 121 (18%) were ≥75 years old at the time of hysterectomy. For this group of elderly patients, median age was 79 years. Median follow-up was 5.4 years. All patients were surgically staged and some received adjuvant vaginal cuff brachytherapy alone (21%), pelvic radiotherapy alone (11%), or a combination (9%). Older patients were found to have higher FIGO stage ($P<0.001$), higher-grade tumors ($P<0.001$), deeper myometrial involvement ($P<0.001$), and greater lower uterine segment involvement ($P<0.001$). There was no significant difference found between older and younger patients with respect to lymphovascular space involvement (LVSI) ($P=0.415$), number of lymph nodes examined ($P=0.440$), and adjuvant radiotherapy received ($P=0.089$). Older patients had more tumor recurrences (15% vs 7%) ($P=0.005$). The five- and 10-year disease-specific survival rates were 91 and 89% for elderly patients compared with 96 and 93% for younger patients ($P\leq0.0265$). Five- and 10-year overall survival rates were 68 and 32% for elderly patients versus 87 and 72% in younger patients ($P=<0.0001$). For these elderly patients, LVSI ($P=0.0413$), grade 3 tumors ($P=0.0021$), and deep myometrial invasion ($P=0.0429$) were significant independent predictors of tumor recurrence. Significant independent predictors of disease-specific survival were LVSI ($P=0.0371$), grade 3 tumors ($P=0.032$), and deep myometrial invasion ($P=0.046$). Significant independent predictors of overall survival include LVSI, grade 3 tumors, deep myometrial involvement and age as a continuous variable ($P<0.001$).

Conclusions: Despite similar surgical staging and adjuvant radiation treatment, patients ≥75 years old diagnosed with FIGO stage I/II endometrioid endometrial adenocarcinoma were found to have more adverse pathologic features and worse outcomes than younger patients. Additional studies are warranted to elucidate the possible different biologic factors underlying these worse tumor characteristics and clinical outcomes.

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Incidence and salvage rates of isolated vaginal recurrence in uterine papillary serous carcinoma

K. Zanotti[1], P. Rose[2], P. Gehrig[3], K. Moore[4], H. Frasure[1], L. Havrilesky[5], A. Alvarez-Secord[5], W. Huh[6], D. OMalley[7], A. Nickles Fader[8]
[1]University McDonald Women's Hospital, Cleveland, OH, [2]The Cleveland Clinic, Cleveland, OH, [3]University of North Carolina School of Medicine, Chapel Hill, NC, [4]University of Oklahoma, Oklahoma City, OK, [5]Duke University Medical Center, Durham, NC, [6]University of Alabama, Birmingham, AL, [7]Ohio State University, Cleveland, OH, [8]Johns Hopkins Medical Institutions, Baltimore, MD

Objective: The generally high reported incidence and favorable subsequent salvage rates of islolated vaginal recurrence (IVR) in endometrial carcinoma (EC) are based largely on data generated from low-risk/low-grade EC populations. Although vaginal brachytherapy is a common adjuvant treatment recommendation in high-risk/high-grade EC, the incidence and salvage rates of IVR in this population have not been reported and cannot be assumed to be similar to those for low-risk EC. The purpose of this study was to document the incidence of IVR and subsequent salvage rates in patients with uterine papillary serous carcinoma (UPSC).

A retrospective, multi-institution study of patients with stage I–II UPSC diagnosed from 1993 to 2006 was performed. All patients underwent comprehensive surgical staging. Postoperative treatment included either observation, radiation therapy (RT: brachytherapy, whole-pelvis, or both) or carboplatin/paclitaxel (CT) alone or in combination with RT (CT + RT).

Results: We identified 197 patients with stage I–II UPSC; 23% of (45/197) experienced a primary recurrence during a median follow-up of 32 months. Median time to recurrence after diagnosis was 16 months. Extrapelvic and multisite recurrences occurred in 61% (27/44) and 30% (13/44), respectively. Isolated vaginal recurrences occurred in only 6% of patients (12/197). Rates of IVR were lower in those who received some form of adjuvant RT as compared with those who did not (2% vs 9%, $P=0.07$). The majority of UPSC recurrences (86%) were not salvaged by second-line therapy, with a median time from recurrence to death of 8.9 months. However, five of the 12 women with IVR (42%) were salvaged, with a median follow-up in this group of 22.5 months. All of the women who were salvaged were naïve to radiation; one had received prior CT. For their salvage, all patients received RT and three also received CT.

Conclusions: In the absence of randomized trials, the relative merit of adjuvant postoperative therapies such as vaginal brachytherapy is based on both recurrence incidence and salvage data. Isolated vaginal recurrences in UPSC are rare. A lower percentage are salvaged for cure than reported in low-risk EC; however, salvage rates are more favorable in patients naïve to radiation. These data suggest that although adjuvant vaginal brachytherapy may reduce risk for isolated vaginal recurrence, the net benefit in early-stage UPSC may not be as high as previously assumed.

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Indole-3-carbinol supplements in obese women: Chemoprevention or carcinogenic?

J. Connor, S. Fleming, N. Onujiogu
University of Wisconsin, Madison, WI

Objective: Abnormal or exaggerated production of estrogens, including estrone, is theorized to be responsible for the association of obesity with endometrial cancer. Indole-3-carbinol (I3C) is a hydrolysis product of cruciferous vegetables that has been shown to exert chemoprotective effects in estrogen-sensitive cancers by increasing urinary 2/16α-hydroxyestrone (2/16OHE1) ratios. However, there is limited information on this effect in obese women. Therefore, our objective was to determine the effects of I3C on estrone metabolism in women over a spectrum of body mass index.

This pilot study was an open-label trial of oral I3C at 200 mg twice daily for eight weeks. Women were recruited by fliers and self-referral. Women were placed in four categories based on BMI: healthy (H, BMI <25), overweight (OW, BMI 25–29), obese (O, BMI 30–39) and morbidly obese (MO, BMI >40). First morning urine was collected at enrollment and after eight weeks of I3C. Urinary 2OH and 16OH estrone levels were determined with the Estramet system, and results reported as numeric concentrations in ng/mL and ratios that were analyzed by ANOVA. In addition, cases were categorized as positive (increased level or ratio) or negative (decreased level or ratio) and analyzed with the χ^2 test as two groups: H + OW (low) and O + MO (high).

Results: Thirty-three women (10 H, 10 OW, 10 O, and 3 MO) completed the study. There was an increase in urinary 2/16OHE1 ratios in each group except MO cases (H, +1.1; OW, +0.52; O, +0.32; and MO, –0.26), indicating decreased responsiveness to I3C with increasing BMI. In this pilot population these changes were not significant by ANOVA ($P = 0.66$). Similarly there were more positive changes in the 2/16OHE1 ratio in women with low BMI (71%) than in those with high BMI (42%) ($P = 0.09$). There were no changes in the levels of 2OHE1 after I3C; however, 16OHE1 levels demonstrated an unexpected significant increase after I3C in obese women. Forty-four percent of women with low BMI had increased 16OHE1 compared with 80% of women with high BMI ($P = 0.04$). The mean change in 16OHE1 concentrations also significantly differed between these groups: –2.6 ng/mL vs 5.7 ng/mL ($P = 0.04$).

Conclusions: I3C results in a favorable change in 2/16OHE1 ratio in women with healthy and overweight BMIs, with a trend toward toward an unfavorable ratio in obese women based on a significant increase in 16OHE1 in obese women after I3C treatment. Further study is needed to determine if this is a matter of underdosing in obese women or if there is a difference in metabolism in response to I3C in obese women.

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Laparoscopic surgery for endometrial cancer: Why don't all patients go home the day after surgery?

R. Spencer, J. Schorge, M. Del Carmen, A. Goodman, W. Growdon, D. Boruta
Massachusetts General Hospital/Harvard University, Boston, MA

Objective: Laparoscopic surgery (LS) for endometrial cancer results in more rapid recovery and reduced morbidity when compared with laparotomy. Length of hospital stay (LOS) in published studies is low, with discharge on the first postoperative day (POD) common. Both patients and hospital systems benefit from short LOS. Our aim was to identify factors related to a LOS greater than the first POD in patients undergoing LS for endometrial cancer.

Between August 2006 and September 2010, 174 women underwent LS for endometrial cancer at our academic institution. Patient demographics, surgical approach, operative times, staging extent, operative complications and use of postoperative intravenous pain medication were examined as potential variables contributing to LOS greater than the first POD using standard statistical tests.

Results: Fifty-four percent ($n = 94$) of women undergoing LS for endometrial cancer were discharged on POD 1. The proportion of women discharged on POD 1 versus >POD 1 did not differ between surgical approaches (straight-stick, $n = 133$; robot-assisted, $n = 36$; single-incision LS, $n = 5$) or extent of staging (no lymph node dissection [LND]), $n = 33$; pelvic LND, $n = 83$; pelvic and paraaortic LND, $n = 58$). Postoperative administration of intravenous narcotic pain medication resulted in a 2.7-fold higher risk of being discharged after POD 1 (95% CI = 1.058–6.849). Patients whose procedures began after 3 PM or ended after 5 PM, respectively, experienced 2.6-fold (95% CI = 1.2–5.9) and 2.1-fold (95% CI 1.1–4.1) increases in the risk of staying in the hospital past POD 1. Complications included bowel injury (0.7%), vascular injury (0.7%), pelvic hematoma (0.7%), vaginal cuff dehiscence (1.3%), and infection (1.3%). Univariate analysis demonstrated that perioperative complications were associated with an 11-fold increase (95% CI = 1.3–88) in the risk of staying past POD 1. Multivariable logistic regression controlling for complications demonstrated that postoperative intravenous narcotic administration and procedure start time after 3 PM were independent factors associated with increased LOS.

Conclusions: Laparoscopic surgery for endometrial cancer should be preferentially scheduled early in the day and postoperative administration of intravenous narcotic pain medication minimized to facilitate discharge on POD 1. Neither the type of laparoscopic surgical approach used (e.g., straight-stick vs robot-assisted) nor the extent of staging lymphadenectomy performed influenced hospital length of stay.

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Laparoscopic surgery versus laparotomy in the management of early endometrial cancer: Long-term follow-up outcomes

S. Park, J. Park, D. Kim, J. Kim, Y. Kim, Y. Kim, J. Nam
Asan Medical Center, Seoul, Republic of Korea

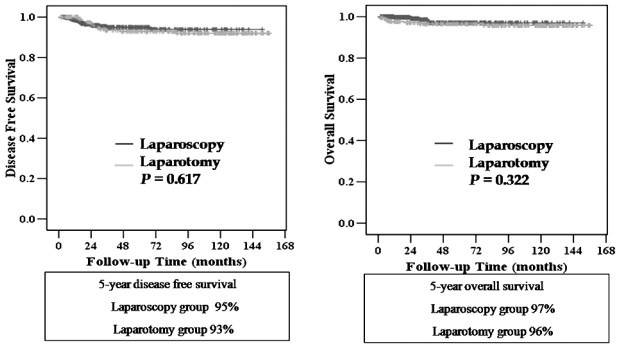
Objective: The purpose of this study was to compare the operative and survival outcomes of laparoscopic surgery and laparotomy in early endometrial cancer.

In this retrospective study, we reviewed medical records for patients admitted at Asan Medical Center, Seoul, Republic of Korea, from January 1997 to December 2009. During the study period, 698 patients with clinical stage I and II endometrial cancer were enrolled. Four hundred sixty-five patients had laparoscopic surgery, and 233 patients had laparotomy. In the laparoscopy group, 11 patients who converted to laparotomy were excluded. Four hundred fifty-four patients in the laparoscopy group and 233 patients in the laparotomy group were included.

Results: Both groups underwent comprehensive surgical staging. Pelvic lymphadenectomy was performed in 407 patients (89.6%) in the laparoscopy group and 208 patients (89.3%) in the laparotomy group

($P=0.879$). Paraaortic lymphadenectomy was performed in 124 patients (27.3%) in the laparoscopy group and 96 patients (41.2%) in the laparotomy group ($P<0.001$). In both groups, a total of 47 patients were upstaged postoperatively. Median age, parity, FIGO surgical stage, histologic type and tumor grade did not differ between the groups. Median body mass index was higher in the laparotomy group (25.2 vs 26.0, $P=0.035$). The median number of lymph nodes obtained (29 vs 28, $P=0.395$) did not differ between the laparoscopy and laparotomy groups. Estimated blood loss (255 ± 224 mL vs 313 ± 268 mL, $P=0.004$), number of transfusions (42 vs 42, $P=0.001$), operative time (162 minutes vs 180 minutes, $P=0.001$), hospital stay (six days vs 13 days, $P<0.001$) and complication rate (5.2% vs 15.5%, $P<0.001$) were better in the laparoscopy group (see table). Median follow-up time was 52 months. Five-year overall ($P=0.322$) and recurrence-free survival ($P=0.617$) were similar in the two groups (see figure).

Conclusions: Laparoscopy is a safe and valid alternative to conventional laparotomy in patients with early endometrial carcinoma. Laparoscopy produced more favorable surgical outcomes than laparotomy without affecting prognosis.



Operative outcomes.

	Laparoscopy	Laparotomy	*P* value
Number (%) with pelvic lymphadenectomy	407 (89.6)	208 (89.3)	0.879
Number (%) with paraaortic lymphadenectomy	124 (27.3)	96 (41.2)	<0.001
Median number (range) of nodes	29 (1–84)	28 (1–99)	0.395
Median number (range) of pelvic nodes	27 (1–70)	26 (1–71)	0.095
Median number (range) of paraaortic nodes (range)	5 (1–39)	6 (1–38)	0.617
Estimated blood loss (mL)	255 ± 224	313 ± 268	0.004
Number of intraoperative blood transfusion	42 (9.3%)	42 (18.0)	0.001
Operative time, min (range)	162 (50–478)	180 (75–360)	0.001
Hospital stay, days (range)	6 (2–38)	13 (5–85)	<0.001

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Location versus extent of nodal metastasis in node-positive uterine cancer: Which is more prognostic?

R. Urban[1], M. DeChant[1], T. Kiet[1], R. Brooks[1], S. Ueda[1], L. Chen[1], D. Kapp[2], J. Chan[1]
[1]*UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA,* [2]*Stanford University Medical Center, Stanford, CA*

Objective: The purpose of this study was to determine the prognostic significance of location of positive nodes versus extent of nodal involvement in stage IIIC endometrioid uterine cancer.

Data were obtained on patients with nodal metastases from 2004 to 2007. Kaplan–Meier estimates and Cox proportional hazard models were used for statistical analyses.

Results: Of 1075 patients with stage IIIC endometrioid uterine cancer (median age: 62 years, range: 28–95), 917 (85.3%), 68 (6.3%), and 79 (7.3%) were white, black and Asian, respectively. Tumors were grades 1, 2, and 3 in 15.7, 39.9, and 36.9%. Seven hundred twenty-five (67%) patients had pelvic and 350 (33%) had paraaortic nodal metastases. Three-year disease-specific survival (DSS) of those with pelvic-only versus paraaortic with or without pelvic nodal disease was 80.5% versus 67.0% ($P=0.001$). The survival rates of those with one, two–five, and >5 (absolute number) positive nodes were 79.5, 75.4, and 62.9%, respectively ($P=0.016$). The ratio of positive nodes (≤10%, 10–50%, >50%) was associated with survival rates of 82.9, 73.9, and 64.5% ($P<0.001$). On multivariate analysis, location ($P=0.025$), ratio of positive nodes ($P<0.001$), and adjuvant radiation ($P=0.001$) were independent prognostic factors associated with DSS. In a subset analysis of 487 patients with single-node-positive disease, the median number of nodes examined was 12. The three-year DSS of these patients was 79.5%. In this subset, the ratio of positive nodes and adjuvant radiation remained as independent prognostic factors. However, the location of positive nodes was not important.

Conclusions: The location and ratio of positive nodes are important prognostic factors for disease-specific survival of node-positive stage IIIC uterine cancer. These factors may have significant implications toward individualizing treatment in patients with advanced uterine cancer.

Kaplan–Meier survival estimates for patients with node-positive stage IIIC uterine cancer ($n=1075$).

	3-Year DSS	*P* value
FIGO stage		0.001
IIIC1	$80.5\pm2.2\%$	
IIIC2	$67.0\pm4.0\%$	
Absolute number of positive nodes		0.016
1	$79.5\pm2.6\%$	
2–5	$75.4\pm3.2\%$	
>5	$62.9\pm7.3\%$	
Ratio of positive nodes		<0.001
≤10%	$82.9\pm2.9\%$	
10–50%	$73.9\pm2.9\%$	
>50%	$64.5\pm5.9\%$	
Adjuvant radiation		<0.001
Yes	$81.5\pm2.3\%$	
No	$67.0\pm3.7\%$	

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Novel brachytherapy device design for treatment of cervical and uterine carcinoma

D. Scanderbeg, C. Saenz, S. Plaxe, M. McHale, E. Alvarez, C. Yashar
UCSD Moores Cancer Center, La Jolla, CA

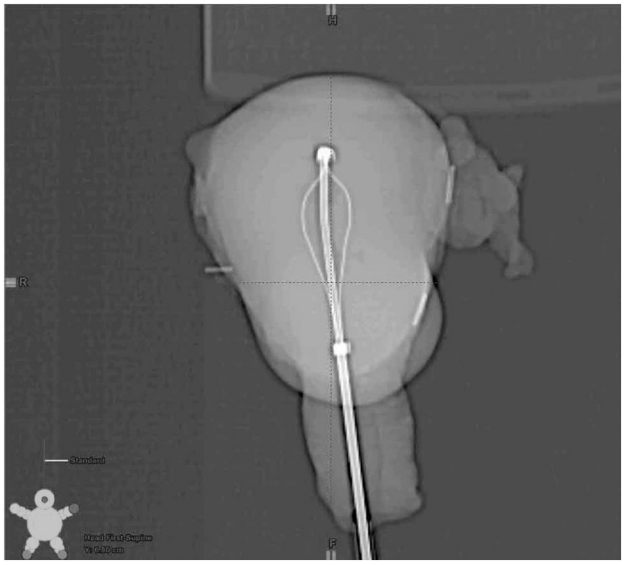
Objective: The purpose of this study was to evaluate the efficacy of a novel, multichannel brachytherapy device for treatment of cervical and uterine carcinoma.

Traditional radiation (brachytherapy) treatment of cervical or uterine carcinoma uses a tandem and ovoid system or a single tandem. However, because the uterus widens cephalad to the cervix, it is difficult to provide maximum dose to the target while minimizing dose to normal tissue with the use of only a single-channel tandem. This study evaluated the dosimetry of a new brachytherapy treatment device, a multichannel tandem. This novel intracavitary device is a one-piece design that is 3 mm in diameter and curved, with insertion similar to that of a traditional tandem. However, on insertion, the two peripheral channels can be released, which allows their expansion away from the central tandem to

approximate the location of the uterine horns. Our hypothesis was that multiple channels and expansion allow improved dose modulation for uterine and cervical conformity, with simultaneous normal tissue sparing. The novel device was inserted into several freshly harvested uteri and then scanned in a GE CT scanner. Traditional tandems were also placed into the uteri and scanned to allow for a dosimetric comparison between the devices. Dosimetry was evaluated with the BrachyVision (Varian Medical Systems) treatment planning system by examining the uterine volume covered by 100% of the prescription dose as well as prescription dose falling outside of the target (dose to surrounding normal tissue, i.e., bladder, sigmoid and rectum).

Results: The device was successfully implanted and expanded properly in all cases. The prescription coverage for the fully loaded device (all three channels) was approximately equal to that of the centrally loaded (single-channel tandem) device at ~96% of the target volume. However, the multichannel loading showed a significant decrease in the tissue receiving prescription dose outside of the target volume with a median decrease of ~50%.

Conclusions: This new multichannel gynecologic device demonstrates dose conformity with more planning freedom secondary to improved geometry. Dosimetric studies reveal maximally targeted endometrial and cervical tissue with less dose to normal tissue than a traditional tandem.



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Outcome assessment following treatment of isolated lymphatic recurrences in patients with endometrial cancer

S. Kumar, K. Podratz, W. Cliby, S. Dowdy, A. Mariani
Mayo Clinic, Rochester, MN

Objective: The purpose of this study was to assess the clinical outcomes of patients with endometrial cancer after experiencing an isolated lymphatic recurrence.

Patients with endometrial cancer with an isolated lymphatic recurrence were retrospectively reviewed. Primary tumor characteristics, sites of recurrence and corresponding treatments and survival were annotated. Anatomic lymphatic sites were stratified according to pelvic (PN), paraaortic (AN), combined pelvic and paraaortic (PAN) and distant (DN) nodes.

Results: Between 1984 and 1996, 1109 patients had hysterectomy for primary endometrial cancer. Of these, 58 (5.23%) had lymphatic recurrences and 28 (2.52%) had an isolated lymphatic recurrence at a median follow-up of 42 months (range: 5–259 months). Tumor characteristics at initial presentation in this cohort (mean age: 61 years) were: stage III/IV (93%), grade II/III (79%), endometrioid histology (75%) and lymph node involvement (71%). Primary treatment incorporated surgery (100%) including lymph node dissection (93%), radiation (63%), systemic chemotherapy (15%) and/or hormonal therapy (15%). The sites of isolated lymphatic recurrence included 4 PN, 5 AN, 8 PAN and 11 DN. Salvage treatment included radiation in 43%, hormonal therapy in 39%, systemic chemotherapy in 32% and/or surgical resection in 21% of cases. The median disease-specific survival (DSS) for the study cohort was 19 months (95% CI = 8–32). The median DSS with respect to anatomic lymphatic sites PN, AN, PAN and DN was 20, 29, seven and 32 months, respectively (Kaplan–Meier Wilcoxon $P = 0.04$). Aggressive surgical resection and/or radiation in appropriately selected patients was associated with a median recurrence-free survival of 14 months versus three months (Kaplan–Meier Wilcoxon $P = 0.02$) and a median DSS of 31 months versus seven months (Kaplan–Meier Wilcoxon $P = 0.03$), respectively, when compared with hormonal therapy and/or chemotherapy. High-grade tumor ($P = 0.01$) and lymph node involvement at primary surgery ($P = 0.04$) predicted a less favorable DSS after treatment for isolated lymphatic recurrences. At the time of censoring, 21% of the cohort remained without evidence of disease (median follow-up: 162 months, range: 92–259 months).

Conclusions: Following isolated lymphatic recurrences, 21% of patients in this endometrial cancer cohort were salvaged. Aggressive surgical resection and/or radiation in appropriately selected patients appears to provide a more favorable outcome as compared with chemotherapy and/or hormonal therapy.

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Platinum sensitivity as a predictor of outcome in recurrent endometrial carcinoma

B. Erickson, K. Bevis, H. Smith, R. Alvarez
University of Alabama, Birmingham, AL

Objective: Sensitivity to platinum-based chemotherapy is an important prognostic factor in recurrent epithelial ovarian cancer. It also directs management of patients with recurrent disease. Platinum sensitivity as a predictor of long-term outcome or as a means of directing therapy has not been described in recurrent endometrial carcinoma (EMCA). The purpose of this study was to determine if the platinum-free interval following primary therapy in EMCA predicts response to second-line chemotherapy and overall survival.

Following institutional review board approval, we retrospectively identified all patients between 2000 and 2009 with EMCA who underwent primary surgical treatment followed by adjuvant platinum-based chemotherapy. Platinum sensitivity was defined as a disease-free interval >6 months following completion of primary therapy. Clinicopathologic and outcome data were collected and compared between patients deemed to be platinum sensitive (PS) and those deemed platinum resistant (PR).

Results: A cohort of 192 patients with EMCA treated with surgery and adjuvant platinum-based chemotherapy were identified. Forty-seven of these, 24 deemed PS (51%) and 23 deemed PR (49%), received systemic chemotherapy as second-line treatment. Analysis of clinicopathologic features demonstrated no difference in age, race, BMI, histologic findings, rate of cytoreduction or use of adjuvant radiation between groups. The overall response rate in patients with PS disease

was significantly higher than the rate of response in PR patients (62.5% vs 17.4%, $P=0.002$). Ten of 17 PS patients re-treated with a platinum-based regimen responded to therapy compared with only three of 11 PR patients (59% vs 27%, $P=0.11$). Patients with PS disease had a longer progression-free survival (12.0 months vs 3.9 months, $P<0.001$) and overall survival (33.2 months vs 17.8 months, $P<0.001$) compared with those with PR disease.

Conclusions: Platinum sensitivity, defined as a disease-free interval >6 months, appears to be an applicable concept in recurrent EMCA as a means to predict prognosis and to potentially direct therapy. Further investigation of this concept in a larger cohort of patients with EMCA is warranted.

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Reliability of frozen-section examination in endometrial carcinoma at a tertiary care center: Is it appropriate for intraoperative guidance of treatment decisions?

A. Mariani, F. Medeiros, S. Dowdy, K. Podratz, J. Bakkum-Gamez, W. Cliby, A. Weaver, M. McGree, G. Keeney *Mayo Clinic, Rochester, MN*

Objective: The purpose of this study was to determine the accuracy of frozen-section diagnosis of endometrial cancer and how discordances affect the operative treatment algorithm.

During the period January 2004 to December 2008, 809 consecutive patients with endometrial cancer underwent hysterectomy at our institution. The need for surgical staging was decided intraoperatively using a combination of four characteristics determined at frozen section: tumor size, histologic grade and subtype, and depth of myometrial invasion. The intraoperative frozen-section results were compared with the final reports to assess discordances in the four parameters.

Results: In 32 cases (4%), the pathology report was amended after surgery in at least one of the four parameters. Tumor size was never amended. Reasons for amendment included 24 changes in subtype or histologic grade (including changes from hyperplasia to cancer). Myometrial invasion was altered in eight cases. A definitive diagnosis of the four aforementioned parameters was not provided via frozen section, but was deferred to permanent sections in 56 cases (7%). Of these, 27 were deferred to better classify a poorly differentiated carcinoma, 20 to differentiate hyperplasia from adenocarcinoma, five to establish histologic grade, one to define myometrial invasion, and three to identify residual tumor in a negative specimen. All these amendments and deferrals altered our surgical algorithm in only 14 patients (1.7, 95% CI = 0.8–2.6%).

Conclusions: Clinically significant inaccuracies at intraoperative frozen section in endometrial cancer occurred in only 1.7% of our population. Despite what has been frequently reported in the literature, we show that frozen-section examination in endometrial cancer can provide highly reliable data to guide appropriate intraoperative treatment decisions.

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Reverse-phase protein lysate array identified potential therapeutic targets in uterine carcinosarcoma

E. Euscher, C. Wei, L. Ramondetta, R. Broaddus
University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: Uterine carcinosarcoma (CS) is a highly aggressive tumor characterized by admixtures of carcinoma (CA) and sarcoma (SA). Standard chemotherapy regimens for endometrial carcinoma are ineffective.The rarity of CS has precluded the ability to discover novel therapeutic targets. We adapted a novel technology, reverse-phase protein lysate array (RPPA), to the use of formalin-fixed, paraffin-embedded sections of uterine CS to determine if potential new targets for therapy can be discovered. RPPA is a high-throughput analysis in which dilutions of protein lysate are spotted onto nitrocellulose slides and then probed with specific antibody. Advantages of RPPA are that its results are easily quantifiable and it requires very little protein. RPPA is traditionally used for protein from cell lines or frozen tissues; it is not yet routinely used for formalin-fixed, paraffin-embedded tissues.

Fifty-two cases of uterine CS were evaluated for the histologic subtype of CA, presence/histologic subtype of heterologous elements (HEs), ratio of CA to SA, depth of myoinvasion (MI), component(s) present in areas of MI, lymphovascular invasion, presence/histology of lymph node metastases and presence/histology of recurrences. Fifty micrograms of tumor protein was extracted from each block, and these proteins were subjected to RPPA analysis using a panel of 120 antibodies previously validated.

Results: All uterine CSs successfully yielded 50 μg of protein. Western analysis verified protein integrity for each case. CSs with HEs showed the most prominent differences in protein expression. In CSs with rhabdomyosarcoma (RS), 14 proteins were upregulated compared with CSs without RS. These results are summarized in the table.

Conclusions: Some studies suggest that the presence of HE is an adverse prognostic sign. The differential expression of proteins in CSs with HEs compared with CSs without HEs supports the idea that uterine CS has distinct subsets. Using a novel technology, we have identified a number of different proteins that may be responsible for more aggressive clinical behavior of CSs with HEs. Pertinent to therapy, some of the identified upregulated proteins (EGFR, ER, Her2, VEGFR, AKT, and SRC) are cell signaling pathway components that are potential therapeutic targets. These findings underscore the need for pathologists to recognize the presence of HEs in CSs. Further study is required to determine if upregulation of protein correlates with clinical response to current targeted therapies.

Protein	*P* value (compared with CSs without RS)
A_RAF	0.01
Caveolin	0.01
CHK1	0.02
ATM	0.01
Cyclin D1	<0.01
EGFR.V	0.01
ER	<0.01
JUNB	0.03
p53	0.03
PAX2	<0.01
SRC	0.02
STAT3	0.01
HER2	0.03
VEGFR	<0.01

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Risk factors for future development of endometrial cancer in patients with benign endometrial biopsy: Epidemiologic study from the Olmsted County population

M. Torres, A. Weaver, W. Cliby, S. Dowdy, F. Abimbola, S. Uccela, B. Gostout, A. Mariani
Mayo Clinic, Rochester, MN

Objective: Optimal prevention strategies for endometrial cancer (EC) are predicated on our ability to accurately identify individuals at significantly increased risk for this disease. A large number of patients undergo D&C or office endometrial biopsy (EBDC) every year in the United States, mostly to rule out endometrial abnormalities. Unfortunately, information on risk factors for developing EC in patients who had a benign EBDC is lacking. The aim of this study was to identify these risk factors.

From the Rochester Epidemiology Project (REP––Olmsted County population), we identified 370 patients with a diagnosis of EC between 1970 and 2008. One hundred twenty (32.5%) of these women had a previous benign EBDC during their lifetime. The timing between the EBCD and EC ranged from 0 to 45 years, with a median of 7.3 years. These 120 patients were matched (2:1) with EC-free controls based on diagnosis on benign EBDC (i.e., hyperplasia vs other benign), age, date of the EBDC and available time of follow-up. Atypical hyperplastic cases and matched controls were excluded.

Results: Patient weight or body mass index, nulliparous status, personal history of HNPCC-related cancer (HNPCC+), unopposed estrogen therapy, and oral contraceptive use (OC), before or at the time of the benign endometrial biopsy, were all associated with EC at univariate analysis ($P<0.05$). In a multivariate conditional logistic regression model, OC (OR = 0.17, 95% CI = 0.09–0.35, $P<0.001$) and HNPCC+ (OR = 4.58, 95% CI = 1.37–15.34, $P=0.014$) were independently associated with EC. After excluding variables related to medication (like OC), weight (OR = 1.18, 95% CI = 1.03–1.37, $P=0.021$) and nulliparous status (OR = 2.53, 95% CI = 1.23–5.15, $P=0.011$) were independently associated with EC.

Conclusions: As many as one-third of patients with EC had a previous benign EBDC. HNPCC+ is the strongest risk factor for developing endometrial cancer after a benign EBDC, while prior or current use of OC is the strongest protective factor. Patient weight and parity status predicted future development of EC as well. A risk prediction model was generated.

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Risk factors for thromboembolism within the first 30 days of endometrial cancer surgery

S. Kumar, K. Podratz, S. Dowdy, J. Bakkum-Gamez, A. Weaver, M. McGree, J. Martin, W. Cliby, A. Mariani
Mayo Clinic, Rochester, MN

Objective: The aim of this work was to study the risk factors associated with venous thromboembolism (VTE) within 30 days of surgery for endometrial cancer (EC).

Data were collected on all patients who underwent endometrial cancer surgery at our institution during the period 1999 to 2008. Confirmed VTE included deep venous thrombosis (DVT) and/or pulmonary embolism (PE) that occurred within 30 days of surgery. A multivariable logistic model was developed using stepwise and backward variable selection methods. Associations were summarized using odds ratios (ORs). P values <0.05 were considered statistically significant.

Results: Of the 1358 (96%) patients with sufficient follow-up, 27 (2.0%) had a diagnosis of VTE in the first 30 days after surgery. Of these, 10 (37%) had DVT, 15 (56%) had PE, and two (7%) had both DVT and PE. Seventy-eight percent with PE had no concomitant DVT on doppler of lower extremities. Sixteen (59%) VTEs occurred between seven and 30 days after surgery. Among the 1358 patients, the prevalence of preoperative, intraoperative, and postoperative VTE prophylaxis in the form of sequential compression device and/or anticoagulation was 7, 64, and 66.4%, respectively. As compared with the non-VTE cohort, the VTE cohort was older (mean age: 69 years vs 64 years, $P=0.02$), had longer operative time (mean: 195 minutes vs 165 minutes, $P=0.03$), and had a longer hospital stay (mean: 15 days vs five days, $P=0.001$). In addition, the VTE cohort had a significantly higher prevalence ($P<0.05$ univariately) of the following variables when compared with the non-VTE cohort: advanced stage of disease (FIGO IV: 30% vs 8%), grade 3 tumors (52% vs 29%), lymph node involvement (33% vs 13%), blood loss >500 mL (52% vs 29%), postoperative fever (22% vs 7%), higher operative complexity (26% vs 6%), and diabetes (48% vs 28%). Receiving any preoperative or intraoperative prophylaxis was not significantly associated with development of VTE ($P>0.05$). Prior history of DVT did not significantly differ between the groups (15% vs 7%, $P=0.12$). In a stepwise multivariable model considering preoperative and intraoperative factors, estimated blood loss (OR = 1.9 per a doubling), age (OR = 1.5 per 10-year increase), and diabetes (OR = 2.5) were identified as significant independent predictors of VTE.

Conclusions: Pulmonary embolism was more frequent than DVT within a 30-day period after EC surgery. Clinical variables predicting VTE may help in identification of patients requiring extended VTE prophylaxis as the majority of these events occur after seven 7 days of surgery.

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Secondary cytoreductive surgery for recurrent endometrial cancer

C. McCann, L. Bradford, D. Boruta, M. Del Carmen, A. Goodman, W. Growdon, J. Schorge
Massachusetts General Hospital/Harvard University, Boston, MA

Objective: The purpose of this study was to determine the survival impact of secondary cytoreductive surgery among patients with recurrent endometrial cancer as few studies have addressed this topic.

After institutional review board approval, all patients diagnosed with endometrial cancer recurrence between 1992 and 2009 who underwent cytoreductive surgery were retrospectively identified from the tumor registry database. Demographic, pathologic and clinical data were abstracted from medical records. Survival estimates were calculated using the Kaplan–Meier method.

Results: Fifty-one patients with recurrent endometrial cancer underwent secondary cytoreductive surgery. Mean age at initial diagnosis was 62.6 years (range: 41– 81). Primary treatment consisted of abdominal hysterectomy with bilateral salpingo-oopherectomy (94%), pelvic lymphadenectomy (78%) and paraaortic lymphadenectomy (27%). Twenty-three patients (45%) had disease confined to the uterus, and 24 patients (47%) had disease outside the uterus. Endometrioid histology predominated (57%), followed by serous (24%) and clear cell (14%). Adjuvant treatment consisted of chemotherapy alone (33%), radiation alone (31%), or a combination (14%). Median time to recurrence was 21 months. Common sites

included the vagina (22%), pelvis (16%), paraaortic lymph nodes (25%), and other distant sites (37%). Of the 13 isolated paraaortic recurrences, only four patients (30%) had undergone paraaortic dissection at the time of primary surgery. Secondary cytoreductive surgery achieved an optimal result with <1 cm residual disease in 92% of patients. Overall, 75% of patients had a complete resection with no residual disease. Patients having a complete resection at secondary cytoreduction had a median survival after relapse of 37 months, compared with seven months in those patients left with any residual disease ($P=0.005$).

Conclusions: Secondary cytoreductive surgery has an important role in the management of selected patients with recurrent endometrial cancer. We observed that the goal of complete resection is frequently possible and appears to offer the most dramatic survival benefit. Our study also demonstrates the importance of paraaortic lymphadenectomy at primary surgery as this was a common site of isolated relapse.

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Sentinel lymph node mapping for grade 1/2 endometrial cancer with superficial myoinvasion: Less is more

F. Khoury Collado[1], M. Murray[2], M. Hensley[2], Y. Sonoda[2], J. Gomez[2], D. Levine[2], M. Leitao[2], D. Chi[2], R. Barakat[2], N. Abu-Rustum[2]
[1]Memorial Sloan–Kettering Cancer Center, Staten Island, NY, [2]Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The purpose of this study was to describe the incidence of metastatic cancer cells in sentinel lymph nodes (SLNs) in patients with low-grade (grade 1/2) endometrial cancer with ≤50% myometrial invasion and to determine the contribution of pathologic ultrastaging and detection of micrometastasis (MM) to the nodal metastasis rate.

All patients who underwent SLN mapping for endometrial cancer with grade 1/2 tumors on preoperative sampling and ≤50% invasion on final pathologic examination of the uterus were reviewed. The mapping technique included a cervical injection of blue dye in all cases. SLNs were examined by routine hematoxylin and eosin (H&E) and, if negative, by a standardized institutional pathology protocol that included additional sections and immunohistochemistry (IHC) to detect MM.

Results: Between March 2006 and March 2010, 172 patients met the above criteria. On preoperative sampling, the grade distribution was: grade 1, 132 (77%), and grade 2, 40 (23%). On final pathologic examination, the histologic types were: endometrioid, 171 (99.4%), and mixed, one (0.6%). One hundred (58%) patients had no myometrial invasion, and 72 (42%) had ≤50% invasion. A SLN was detected in 148 cases (SLN detection rate, 86%). Fifteen (8.7%) of 172 patients were diagnosed with a positive SLN. Of those, seven (4.1%) were detected only on pathologic ultrastaging of SLNs. Among the patients with no myometrial invasion, two (2%) of 100 patients, both with grade 1 tumors on preoperative sampling, had a positive SLN detected by ultrastaging. In one of those two patients, an additional finding was the absence of residual tumor on final pathologic examination of the uterus.

Conclusions: The incorporation of an SLN mapping protocol with pathologic ultrastaging allows the detection of 8% positive regional nodes in a presumably low-risk group of patients who in some practices may not undergo any nodal evaluation. These data emphasize the value of adding SLN mapping to the surgical staging procedure in apparent early endometrial cancer. The addition of pathologic ultrastaging allows the detection of nodal metastasis in a subset of patients in whom lymph node evaluation is not uncommonly altogether omitted.

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Sequential chemotherapy and radiation therapy for the adjuvant treatment of uterine papillary serous carcinoma

V. Kolev[1], R. Zhang[1], W. Bradley[2], R. N'gouamba[1], P. Dottino[1], J. Rahaman[1], M. Hayes[1]
[1]Mt. Sinai School of Medicine, New York, NY, [2]Medical College of Wisconsin, Milwaukee, WI

Objective: Uterine papillary serous carcinoma (UPSC) is a highly aggressive type of endometrial carcinoma with poor prognosis despite extended surgical staging. Optimal adjuvant therapy remains controversial. We sought to evaluate whether the addition of radiation therapy to chemotherapy in the adjuvant setting confers a survival benefit.

A single-institution review was conducted of all adjuvant therapy regimens for patients with UPSC operated on by the Gynecologic Oncology Division with complete surgical staging over a period of 16 years (January 1994 to December 2009). Overall survival (OS) was calculated with the Kaplan–Meier method, and comparisons of survival between treatments were analyzed using the log-rank test.

Results: One hundred twenty-five patients with UPSC were treated at a single institution with a surgical staging procedure. Seventy-five patients had early-stage disease (ES = stages I and II) and 50 patients had advanced stage disease (AS = stages III and IV) at the time of initial surgery. Overall, 68 patients received platinum- based chemotherapy (CT) and 45 patients received sequential platinum-based chemotherapy and radiation therapy (CT + RT). Median OS was 29 months for ES (range: 1–170) and 22 months for AS (range: 0–125). For patients with ES, there was no significant difference in OS between CT and CT + RT ($P=0.52$). However, for patients with AS there was a significant improvement in OS for those who received CT + RT over CT alone. Patients with AS who received CT alone had a median OS of 18 months versus 38 months for those who received CT + RT ($P=0.03$).

Conclusions: In patients with advanced-stage UPSC, the addition of radiation therapy sequentially to platinum-based chemotherapy in the adjuvant setting may offer a survival benefit over chemotherapy alone.

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Surgical staging for endometrial cancer in the elderly: Is there a role for lymphadenectomy?

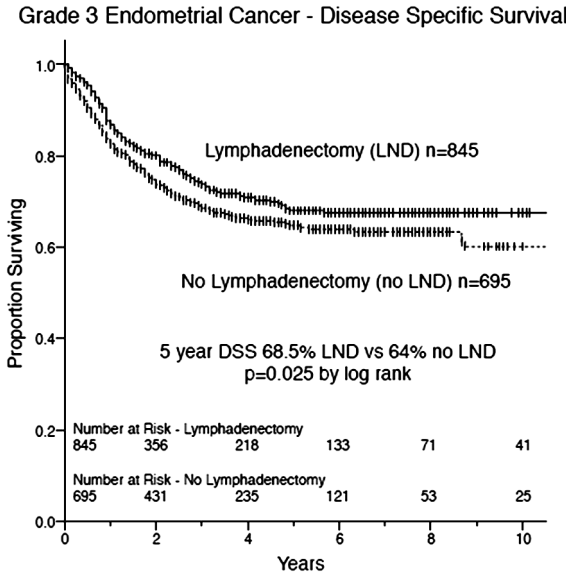
W. Lowery[1], P. Gehrig[2], E. Ko[2], A. Alvarez-Secord[1], J. Chino[1], L. Havrilesky[1]
[1]Duke University Medical Center, Durham, NC, [2]University of North Carolina, Chapel Hill, NC

Objective: Data suggesting a survival advantage for surgical staging in the elderly may be subject to selection bias based on a woman's overall health. We sought to evaluate the effect on endometrial cancer-specific survival of the inclusion or omission of a lymphadenectomy during hysterectomy in an elderly population.

Demographic and clinicopathologic data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program for the period 1988–2006. The data set was queried for patients ≥80 years who underwent primary hysterectomy for nonserous, non-clear cell endometrial carcinoma. Cancer specific survival was analyzed via the Kaplan–Meier method and stratified by postoperative grade. To account for adverse events related to surgery, deaths of any cause within the first 30 days following surgery were included as events. Cohorts were compared using the log-rank test. To estimate the disease-specific survival (DSS) of women who present with preoperative grade 1 endometrial carcinoma, a weighted average survival was calculated using the assumption that approximately 20% of preoperative grade 1 tumors are upgraded to grade 2 and 1% to grade 3.

Results: Six thousand fifty elderly patients with endometrial cancer were identified, of whom 2001 had a final grade of 1, 2218 grade 2, and 1540 grade 3. Lymphadenectomy (LND) was performed in 2572 (42.5%) elderly women: 31% with grade 1 disease, 44% with grade 2 disease, and 55% with grade 3 disease. DSS at five years for the LND and no LND groups was 95 and 96% ($P=0.40$) for grade 1, 86 and 88% ($P=0.27$) for grade 2, and 68.5 and 64% ($P=0.02$) for grade 3, respectively (Fig. 1). Forty percent of women who underwent LND received adjuvant radiotherapy compared with 23% who received no LND. In the simulated preoperative grade 1 group, five-year DSS was 93% in the LND group and 94% in the no LND group, respectively.

Conclusions: In women older than 80, lymphadenectomy is associated with improved DSS for high-grade, but similar DSS for low-grade endometrial cancer. Those with high-grade disease may derive benefit from lymphadenectomy. As there is no clear survival benefit to lymphadenectomy in elderly women presenting with low-grade disease, the surgeon needs to carefully weigh the risks and benefits in this patient population, which may be at higher risk for surgical morbidity.



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Survival outcomes for women with uterine malignancy undergoing robot-assisted laparoscopic staging procedures

L. Brudie[1], F. Backes[2], S. Ahmad[1], N. Finkler[1], G. Bigsby[1], D. Cohn[2], D. O'Malley[2], M. Farrell[2], J. Fowler[2], R. Holloway[1]

[1]Florida Hospital Cancer Institute, Orlando, FL, [2]Ohio State University, Columbus, OH

Objective: The purpose of this study was to evaluate progression-free and overall survival for patients who underwent robot-assisted laparoscopic staging (RALS) for uterine malignancy, with analysis of adjuvant therapies.

Medical records of all patients with uterine malignancy who underwent RALS at Florida Hospital and Ohio State University from March 2006 to March 2009 were retrospectively reviewed for demographics, clinicopathology, adjuvant therapies and survival outcomes. Twenty-six (7.0%) conversions to laparotomy are included in these data as an intent-to-treat analysis. Follow-up for survival analyses ranged from 18 to 54 months as of September 2010.

Results: The mean age of the 372 patients was 61.8 ± 9.8 years with a body mass index of 32.2 ± 8.4 kg/m^2 (range: 19–70 kg/m^2). Fifteen (4.0%) cases underwent RAL hysterectomy (RALH), 98 (26.3%) underwent RALH and pelvic lymphadenectomy, 259 (69.6%) underwent RALH pelvic-and-aortic lymphadenectomy. Histologic distribution was: endometrioid 317 (85.2%), mixed epithelial 21 (5.7%), papillary serous 13 (3.5%), mucinous four (1.1%), clear cell three (0.8%), squamous two (0.5%), sarcoma nine (2.4%), other three (0.8%). Tumor was grade 1 in 244 (65.6%), grade 2 in 69 (18.5%), and grade 3 in 58 (15.6%) cases. FIGO 1988 stages were I in 303 (81.5%), II in 18 (4.8%), III in 45 (12.1%), and IV in five (1.3%). Total mean node count was 23.0 ± 11.6 (pelvic: 16.8 ± 8.7; aortic: 8.3 ± 4.5). Twenty-four of 372 (6.5%) cases had positive nodes (50% cases had both positive pelvic-and-aortic nodes, 37.5% had positive pelvic only, and 12.5% positive aortic only). Adjuvant treatment was prescribed for 28.5% of patients: 8.9% radiation, 7.8% chemotherapy, 11.8% chemotherapy/radiation. The median follow-up time for analysis of overall survival (OS) was 30 ± 9.3 months, and for progression-free survival (PFS), 23.0 ± 11.6 months. The recurrence rate for all stages was 7.3%, and 20 (5.4%) patients died. Disease-specific mortality was 3.5%. Sixteen (5.3%) stage I patients recurred, half of whom had high-risk histologies. Eight (2.6%) low- and intermediate-risk (grade 1/2) stage I cases relapsed (four vaginal, two nodal and two peritoneal). Kaplan–Meier survival analysis for stage I revealed OS and PFS at three-years to be 95.8 and 89.9%, respectively. A Weibull distribution model predicted a five-year OS of 92.4% and PFS of 79.6% for all stage I patients.

Conclusions: RALS appears equivalent to other surgical methods for staging uterine malignancies with respect to stage distribution, PFS, and OS in this early analysis. The recurrence rate of low risk grade 1/2 cases was 2.6%.

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The impact of postoperative therapy on the survival of patients with uterine serous carcinoma

R. Jalloul[1], Z. Al-Wahab[2], R. Ali-Fehmi[2], M. Elshaikh[1], M. Cote[2], T. Buekers[1], R. Morris[2], A. Munkarah[1,2]

[1]Henry Ford Health System, Detroit, MI, [2]Wayne State University, Detroit, MI

Objective: Following surgical staging, the treatment of patients with uterine serous carcinoma (USC) has included chemotherapy, radiation therapy, or a combination of both. The benefit of these approaches, as well as the optimal treatment for each stage, remains unclear. The aim of this study was to compare survival in patients with USC based on postoperative therapy.

From a retrospective review of medical records, we retrieved clinical and histopathologic data on women who underwent surgical

treatment for UPSC in two large academic centers. Staging was assigned based on the 2009 FIGO staging system. The impact of known prognostic factors including age, myometrial invasion, angiolymphatic invasion, surgical stage and type of adjuvant post-operative therapy was analyzed using univariate and multivariate analyses. Overall survival of the various groups was computed using Kaplan–Meier analysis, and comparisons were made using the log-rank test.

Results: One hundred forty-two patients with UPSC were included in the study. In a Cox regression analysis, FIGO stage, myometrial invasion, angiolymphatic involvement, and type of adjuvant therapy were all significant prognostic factors for the whole population. For patients with stage I disease, only myometrial invasion and angiolymphatic invasion were associated with overall survival (HR = 3.3, 95% CI = 1.2–9.1; HR = 3.4, 95% CI = 1.2–10.0). For patients with stage II–IV disease, the only analyzed factor that had an impact on survival in the Cox model was type of adjuvant therapy. Patients who underwent postoperative chemotherapy and radiation had a HR of 0.3 (95% CI = 0.1–0.9). Median survival for patients with stage II–IV disease by adjuvant therapy type was 11 months for no adjuvant treatment, 16.5 months for radiation therapy alone, 33 months for chemotherapy alone, and 75 months for a combination of chemotherapy and radiation.

Conclusions: The combination of chemotherapy and radiation therapy can significantly improve the survival of some patients with advanced-stage UPSC compared with chemotherapy or radiation therapy alone. These results need to be confirmed in a large prospective trial.

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The incidence of endometrial pathology and the effects of weight loss in asymptomatic women undergoing bariatric surgery: A prospective, natural history study

P. Argenta[1], M. Kassing[1], D. Brooker[1], A. Truskinovsky[1], C. Svendsen[2]
[1]*University of Minnesota, Minneapolis, MN,* [2]*Methodist Hospital, St. Louis Park, MN*

Objective: The objectives of this study were to determine the incidence of occult uterine pathology in asymptomatic, morbidly obese patients seeking bariatric surgery and to identify the effect, if any, of bariatric surgery on the prevalence of abnormalities.

We obtained an endometrial biopsy on asymptomatic women at the time of roux en y gastric bypass bariatric surgery and one year later. Both patient and physician were blinded to the results of the biopsy until the conclusion of the study. Pathology specimens were read by independent pathologists with expertise in gynecologic pathology who were blinded to both patient information and the other's assessment. We also collected demographic data and assessed weight loss outcomes.

Results: To date, 59 women have been enrolled and undergone an initial biopsy; 56 women have completed one year of surveillance and 38 consented to a follow-up biopsy. The median (range) age at initial surgery was 42 years (range: 22–62). The median presurgery weight was 281.2 pounds (range: 190.5–389.4). Simple hyperplasia was identified in three women and complex hyperplasia in one preoperatively; the overall prevalence of pathology was 7.1%. The median time to follow-up biopsy was 13 months; the median weight at follow-up was 191.4 pounds (range: 130.0–301.8), and the average excess weight loss was 64.8%. Endometrial pathology was identified in three women at follow-up (all simple hyperplasia), including one whose preoperative biopsy was normal. Spontaneous resolution of hyperplasia was observed in two of the four women following weight loss alone, including the one patient with complex hyperplasia. The overall prevalence of pathology was 7.9% among follow-up patients. No occult carcinomas were detected. Diagnostic agreement between pathologists was excellent ($\kappa = 0.88$ and 0.85, respectively, for the preoperative and postoperative sets).

Conclusions: Obese women who present for bariatric surgery are at relatively high risk of harboring a premalignant condition even in the absence of symptoms. Weight loss associated with bariatric surgery appears to be therapeutic for some patients, but does not eliminate the risk for endometrial pathology. Increased surveillance of this population may be appropriate even after weight loss.

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The prognostic significance of lymphovascular space invasion in laparoscopic versus abdominal hysterectomies for endometrioid endometrial cancer

S. Dewdney[1], Z. Jiao[1], A. Roma[2], F. Gao[1], B. Rimel[1], P. Thaker[1], M. Powell[1], L. Massad[1], D. Mutch[1], I. Zighelboim[1]
[1]*Washington University School of Medicine, St. Louis, MO,* [2]*The Cleveland Clinic, Cleveland, OH*

Objective: Recent reports have suggested that uterine manipulators and/or balloons induce lymphovascular space involvement by endometrial cancer in laparoscopic hysterectomy (LSC) specimens, referred to as "pseudo" lymphovascular space invasion (LVSI). We sought to assess the existence and clinical relevance of this entity by comparing the prognostic significance of LVSI in endometrial cancer cases approached by laparotomy versus laparoscopy.

This study was a retrospective, single-institution chart review of all patients who underwent initial surgery for grade 1 and grade 2 endometrioid endometrial cancers with LVSI between January 2000 and March 2010. Laparoscopic cases converted to laparotomy and those with stage IV disease were excluded. Clinicopathologic characteristics, procedure details and outcome data were obtained from medical records. Cases were stratified by surgical approach (laparoscopy vs laparotomy). Univariate and multivariate analysis was performed. Disease-free survival (DFS) after initial surgical management was analyzed using the Kaplan–Meier product limit method. Given the small number of events, a variable-by-variable approach was employed in the multivariate analysis.

Results: A total of 113 patients with LVSI (20 LSC, 84 laparotomy) were identified. Nine were excluded for stage IV disease ($n = 8$) and conversion ($n = 1$). Mean age was 65 years for laparoscopic cases and 64 years for laparotomies. Mean BMI was 30 kg/m^2 for the laparoscopy group versus 35 kg/m^2 for the laparotomy group. The mean numbers of lymph nodes in laparotomy and laparoscopy cases were similar (18 and 21, respectively). Mean follow-up was 24 months (range: 0.1–102). Univariate analysis demonstrated that LVSI in the laparoscopic setting was associated with worse DFS ($P = 0.02$). After adjustment for stage and grade, the risk of recurrence remained higher for laparoscopic cases (HR = 4.69, 95% CI = 1.14–19.21, $P = 0.03$, and HR = 4.10, 95% CI = 1.00–16.84, $P = 0.05$, respectively).

Conclusions: In this series of endometrioid endometrial cancer cases with LVSI the adjusted risk of recurrence was significantly higher in cases approached laparoscopically. Our findings argue against the concept of "pseudo" lymphovascular space invasion associated with the use of uterine manipulators/balloons. LVSI should be regarded as serious risk factor even when identified in laparoscopically treated early-stage endometrial cancer.

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The transforming growth factor β signaling pathway in endometrial cancer: Expression and clinical significance

J. Kesterson, D. Wang, S. Akers, N. duPont, K. Clark, S. Lele, S. Liu, P. Mhawech-Fauceglia
Roswell Park Cancer Institute, Buffalo, NY

Objective: Transforming growth factor β (TGF-β) is a multifunctional polypeptide that controls many aspects of cell function, including proliferation, differentiation, migration, apoptosis, and angiogenesis. The goal of this study was to evaluate the components of the TGF-β signaling pathway and its regulators in human endometrial adenocarcinoma and to correlate their expression with histologic–clinical data and patient outcomes.

Seventy endometrial cancer specimens from women with newly diagnosed endometrial cancer were evaluated for mRNA levels of components of the TGF-β pathway (i.e., T βRI, T βRII, Smad3, Smad4, Skil, DAB2) using RT-PCR-TLDA format. Univariate and multivariate logistic regression models were used to determine the association of each clinical parameter with the gene expression (RT-PCR) value. The protein expression of two major regulators, Skil and DAB2, was determined by immunohistochemistry in 362 endometrial cancer specimens and correlated with mRNA levels and patient outcomes.

Results: mRNA levels of all components of the TGF-β pathway tested were decreased in the majority of the 70 cases. Skil mRNA level was correlated with tumor stage ($P = 0.03$). Smad3 and Smad4 were associated with tumor grade ($P = 0.03$, 0.02, and 0.00, respectively). Smad4 mRNA levels was also associated with tumor size ($P = 0.05$), tumlor subtype ($P = 0.04$), and disease-free survival (DFS) ($P = 0.05$). TGF-β1 mRNA level was associated with DFS ($P = 0.04$). For DAB2, the mRNA level was correlated with protein expression level ($P = 0.04$). Finally, tumors with positive Skil protein expression had shorter recurrence times, whereas those with positive DAB2 protein expression had longer recurrence times.

Conclusions: The TGF-β signaling pathway was downregulated in a large percentage of cases of human EC, with specific components of this pathway appearing to be independent prognostic predictors. Exploration of future therapies targeting the TGF-β–Smad pathway is warranted in patients with endometrial cancer.

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Usefulness of serial CA-125 levels in surveillance of endometrial cancer

K. Pennington, R. Reynolds
University of Michigan, Ann Arbor, MI

Objective: The use of serial CA-125 levels for posttreatment surveillance of endometrial cancer is controversial. Some authors report CA-125 levels are useful only if pretreatment levels are elevated or in the setting of advanced-stage disease, whereas others disagree. We hypothesized that CA-125 is a useful surveillance tool and that levels do not need to be elevated preoperatively to be a marker of recurrence. This is the largest reported study to date of CA-125 as a marker of endometrial cancer recurrence.

All patients with primary endometrial cancer seen at our institution from 1995 to the present were eligible for this institutional review board-approved study ($n = 1289$). Patients with synchronous ovarian primaries ($n = 17$) or incomplete follow-up ($n = 189$) were excluded. Records were reviewed retrospectively for diagnosis, treatment, CA-125 level and outcome. Recurrence was determined by physical findings or imaging studies and confirmed by biopsy.

Results: Of 1083 included patients, 743 had longitudinal CA-125 testing. Preoperative CA-125 was elevated in 89 patients, 46 of whom (52%) were found to have stage II or greater disease. Recurrence was detected in 96 of 1083 patients, 74 of whom had CA-125 testing results available. Of these 74, 47 (64%) had elevated CA-125 levels (true-positive) prior to or concordant with clinically confirmed recurrence, and 16 of 47 (34%) had elevated CA-125 levels with an average lead time of 127 days (range: 25–296) before recurrence was diagnosed. In contrast, only one of 96 recurrences was detected with Pap testing. CA-125 elevation was noted with recurrences at multiple anatomic sites including lung, abdomen and pelvis. The 27 of 74 (36%) with false-negative results had no apparent localization of disease that predicted failure of CA-125 to detect recurrence. In patients who recurred with true-positive CA-125, 45% had a normal preoperative CA-125, and 34% had stage I disease. False-positive results occurred in 31 of 660 (4.7%) recurrence-free patients. Of these 31, seven were attributed to new, nonendometrial primary cancers (lung, lymphoma, breast), and eight were associated with benign inflammatory conditions.

Conclusions: CA-125 shows utility as a marker of recurrence for endometrial cancer. CA-125 elevation may occur significantly before recurrence is clinically evident. CA-125 is a useful marker even if not elevated at the time of initial treatment and in patients with early-stage disease. CA-125 was more useful for detecting recurrence than accepted surveillance tests such as the Pap test.

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Clinical Trials - Phase I

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A phase I clinical trial of the mTOR inhibitor everolimus in combination with oral topotecan for patients with recurrent and advanced endometrial cancer

M. Abu-Khalaf, A. Santin, E. Ratner, D. Silasi, K. ElSahwi, L. Baker, M. Luther, M. Azodi, T. Rutherford, P. Schwartz
Yale University School of Medicine, New Haven, CT

Objective: Topotecan is an active agent in the treatment of advanced and recurrent endometrial cancers, with reported response rates of 20% in the first-line setting and 9% in the second-line setting. Everolimus is a Food and Drug Administration-approved mTOR inhibitor for treatment of advanced renal carcinoma. mTOR inhibitors have shown promising activity in advanced endometrial cancer. Preclinical data suggest that mTOR inhibitors potentiate the efficacy of topotecan.

Cohorts of three to six patients were enrolled and treated. Dose escalation comprised four dose levels (DLs) for oral everolimus (DL1 = 5 mg every other day, DL2 and DL3 = 5 mg daily, DL4 = 10 mg daily) in combination with oral topotecan (DL1 + DL2 = 1.9 mg/m^2, DL3 + DL4 = 2.3 mg/m^2 on days 1–5 of a 21-day cycle). Prior to the start of cycle 1, patients received "run ins" of topotecan for five days starting at day –21 and everolimus for seven days starting on day –14 for pharmokinetic sample collection (cycle 0). The primary aim was to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of topotecan + everolimus. Secondary aims were to evaluate pharmacokinetics and response rate by RECIST. Cycle 1 DLT was defined as drug-related nonhematologic toxicity ≥grade 3 (excluding alopecia, untreated nausea and vomiting), grade 4 thrombocytopenia, grade 4 neutropenia lasting >5 days, grade 4 febrile neutropenia requiring hospitalization, missing ≥1 dose of topotecan or ≥4 doses of everolimus in cycle 1 as a result of toxicity, and treatment delay of >2 weeks in starting cycle 2 as a result of unresolved toxicity.

Results: Nine patients (four serous, one adenocarcinoma, one endometrioid, two serous-clear cell, one adeno-clear cell) were treated and evaluable for toxicity. Six patients were treated in DL1 and three patients in DL2. Median age was 73 years (range: 42–79). Median number of prior lines of therapy was three. Median number of cycles completed on study (excluding cycle 0) was two (range: 0–10). DLT occurred in three patients: One patient on DL1 missed four doses of everolimus in cycle 1; one patient on DL2 developed grade 4 thrombocytopenia during cycle 0; one patient on DL2 developed grade 4 neutropenia/bacteremia and grade 4 thrombocytopenia during cycle 0. Other grade 3 nonhematologic toxic effects included hypokalemia, abdominal pain, thrombosis, nausea, neuropathy and dyspnea. No nonhematologic grade 4 toxicity occurred. Best response was stable disease in three patients (2, 4, and 10 cycles) and progressive disease in four patients; two patients were not evaluable for response.
Conclusions: The recommended dose for the phase II clinical trial is topotecan 1.9 mg/m^2 on days 1–5 in combination with everolimus 5 mg every other day in a 21-day cycle. Pharmacokinetic analyses are presented.

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Chemotherapy

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Is it more cost-effective to use bevacizumab in the primary treatment setting or at recurrence? An economic analysis

K. Fuh[1], J. Chan[1], B. Monk[2], R. Urban[1], L. Hu[1], D. Kapp[3], A. Caughey[1], X. Yu[4]
[1]*UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA,* [2]*Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, Phoenix, AZ,* [3]*Stanford University Medical Center, Stanford, CA,* [4]*University of Memphis, Memphis, TN*

Objective: Recent results from GOG 218 showed that the third arm, addition of maintenance bevacizumab (mB) to paclitaxel (P), carboplatin (C), and bevacizumab (B) improved progression-free survival (PFS) in advanced ovarian cancer. The results of the OCEANS trial on the addition of bevacizumab to gemcitabine (G) + C in recurrent ovarian cancer are pending. We propose comparing the cost-effectiveness of bevacizumab in the primary versus recurrent setting.

Cost of drugs, rates of complication, and PFS were derived from published data. Using the superior arm of GOG 218 (PCB + mB) as comparison, a cost-effectiveness analysis was performed to compare GCB + mB in the recurrent setting. An acceptable incremental cost-effectiveness ratio (ICER) per life-year saved (LYS) was established.
Results: The estimated cost of single-dose B (15 mg/kg) is $6450 for an average female weighing about 75 kg. Based on Medicare payment for administration of chemotherapy, the actual and estimated costs of treatment (for PCB + mB = [PC ($440) + B ($6450)]/cycle + $6450/maintenance cycle) plus the cost of potential complications were determined. In those with primary disease, the median PFS is approximately 16 months after combination chemotherapy. In the recurrent setting with platinum-sensitive disease, the median PFS is approximately eight months after combination chemotherapy. Assuming that the addition of B and mB improves PFS by six and three months in those with primary and recurrent disease, respectively, the estimated treatment cost per patient is $140,285 in the primary setting and $92,940 in the recurrent setting. The ICER of PCB + mB is $270,900 per LYS versus $361,100 per LYS in the primary versus recurrent setting.
Conclusions: In this economic model comparing bevacizumab in the primary versus recurrent setting, our data suggest that bevcizumab in the primary setting may be more cost-effective.

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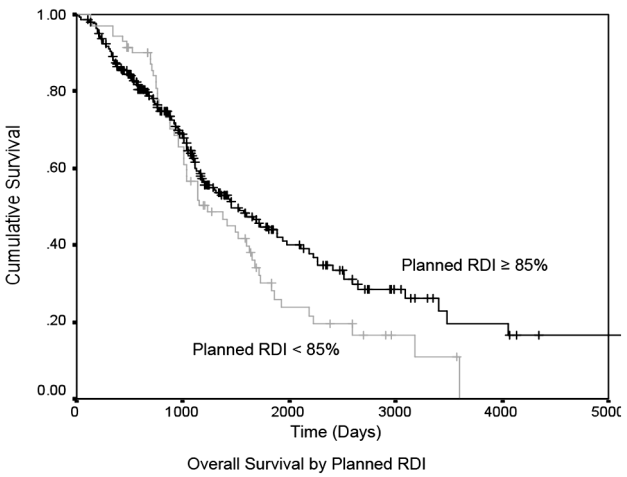
Predictors and effects of reduced relative dose intensity in women receiving their primary course of chemotherapy for ovarian cancer

R. Hanna[1], M. Poniwierski[2], R. Laskey[2], M. Lopez[2], A. Shafer[3], P. Gehrig[1], A. Alvarez-Secord[2], L. Havrilesky[2], G. Lyman[2]
[1]*University of North Carolina School of Medicine, Chapel Hill, NC,* [2]*Duke University Medical Center, Durham, NC,* [3]*Hartford Hospital, Hartford, CT*

Objective: The aims of this study were to identify (1) factors predictive of reduced relative dose intensity (RDI) and (2) the effect of reduced RDI on outcomes in women with advanced-stage ovarian carcinoma who are receiving their initial course of chemotherapy following surgery.

This multicenter retrospective study comprised women with surgical FIGO stage III/IV epithelial ovarian cancer treated postoperatively with multiagent intravenous chemotherapy between the years 1995 and 2008. Data were obtained from each institution's tumor registry and medical records to include the first four cycles of chemotherapy administered to each patient. Outcomes were: (1) delivered RDI, defined in comparison with standard ovarian cancer regimens as determined by literature review; (2) planned RDI, defined by physician's stated dosing plan at cycle 1 of treatment; and (3) overall survival. Reduced RDI was defined as <85% of standard dose. Statistical analysis was performed using SAS. The χ^2 test and Fisher's exact test were used for univariate and multivariate analyseis.
Results: Three hundred thirty-one patients met the inclusion criteria. In multivariate analysis, planned reductions in RDI were more common in obese women (BMI > 30) (OR = 2.63, 95% CI = 1.37–5.03, $P = 0.003$) and in those treated off research protocols (OR = 4.15, 95% CI = 1.86–9.28, $P = 0.001$). Reductions in actual delivered RDI were significantly more common in obese women (OR = 2.20, 95% CI = 1.20–4.03, $P = 0.011$), in those treated off research protocols (OR = 1.76, 95% CI = 1.03–2.99, $P = 0.038$), and in those receiving carboplatin-containing regimens (OR = 2.29, 95% CI = 1.03–4.66, $P = 0.042$). Patients with higher planned RDIs were more likely to experience chemotherapy-related side effects. Overall survival was associated with stage of disease (HR = 1.47, $P = 0.006$); race (HR = 1.29, $P = 0.016$); and planned RDI < 85% (HR = 1.38, $P = 0.052$).
Conclusions: Relative dose intensity is best maintained in nonobese women and in those who participate in research protocols. Women who receive planned reductions in RDI of primary chemotherapy for ovarian cancer have lower survival. To achieve optimal outcomes, women with ovarian cancer should be treated with target RDIs whenever possible.



Overall Survival by Planned RDI

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Therapeutic synergy and resensitization of drug-resistant ovarian carcinoma to cisplatin by HO-3867

K. Selvendiran[1], S. Ahmed[1], A. Dayton[1], M. Kuppusamy[1], T. Kálai[2], K. Hideg[2], P. Kuppusamy[1]

[1]Ohio State University, Columbus, OH, [2]Institute of Organic and Medicinal Chemistry, University of Pécs, Pécs, Hungary

Objective: Cisplatin (CP) resistance is a major cause of treatment failure in ovarian cancer. Drug combinations with multiple or complementary activities constitute a promising strategy to overcome this issue. We have developed a novel molecule, HO-3867, that has anticancer efficacy, with minimal cytotoxicity to noncancerous cells and tissues. In the present study we investigated the anticancer efficacy of HO-3867 used in combination with CP against chemotherapy-resistant human ovarian cancer cell lines and xenograft tumors.

A2780R, a CP-resistant human ovarian cancer cell line, was used. Cells were exposed to 1, 5, or 10 μM HO-3867 alone or in combination with CP (10 μg/mL) for 24 hours. Cell viability was determined by MTT assay, cell proliferation was measured by BrdU assay and cell cycle analysis was performed by FACS. Intracellular ROS levels were measured by DHE staining. Expression of cell cycle and STAT3 upstream regulatory proteins was determined by Western blotting. STAT3 overexpression studies were performed using transfected cDNA. In vivo studies using CP-resistant human ovarian cancer xenografts in mice were also conducted. Mice were given 100 ppm HO-3867 mixed with the feed and weekly injections of 4 mg/kg CP.

Results: Combined therapy using HO-3867 and CP significantly inhibited CP-resistant cell growth in vitro in a dosage-dependent manner. Combination therapy was associated with increased expression of p53 and p21 and decreased expression of cdk5 and cyclin D1. This combination treatment induced apoptosis by activating Bax and cytochrome c release, and stimulated cleavage of caspase-9, caspase-3, and PARP. Overexpression of STAT3 led to a decrease in HO-3867-induced apoptosis. The combination treatment significantly inhibited the growth of the CP-resistant ovarian xenograft tumors in vivo without any apparent toxicity, and produced a significant downregulation of pSTAT3 both in vitro and in vivo.

Conclusions: HO-3867, used in combination with CP, caused significant induction of cell cycle arrest and apoptosis in CP-resistant human ovarian cancer cells via downregulation of pSTAT3 and modulation of Bcl-2 family proteins. The cytotoxic effect of the combination treatment was significantly higher when compared with the sum of individual treatments, suggesting a therapeutic synergism. This combination regimen appears to be a potential means for treating recurrent and chemotherapy-resistant human ovarian carcinoma.

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Clinical Practice Issues

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Attrition of first-time faculty in gynecologic oncology: Is there a difference between men and women?

T. Rutledge[1], C. Muller[1], R. Schrader[1], Y. Gener[2], A. Fullilove[1], W. Rayburn[1]

[1]University of New Mexico, Albuquerque, NM, [2]Association of American Medical Colleges, Washington, DC

Objective: According to the Association of American Medical Colleges (AAMC), the departure from academic medicine (or attrition) is more common among women than men faculty in clinical departments. The objective of this long-term investigation was to determine whether this difference exists among faculty in gynecologic oncology.

In 1981, the AAMC Faculty Roster began collecting data about gynecologic oncology faculty prospectively from each medical school. Data were analyzed for each full-time physician employed at the 125 medical schools. Attrition rates at five and 10 years and fitted attrition (i.e., survival) curves were calculated for first-time faculty beginning their appointments during each of three decade periods (1981–1989, 1990–1999, 2000–2009) to compare probabilities of leaving.

Results: Women constituted 28% ($n = 89$) of full-time faculty in academic gynecologic oncology. Attrition rates from academia were similar for women and men by five years (20% vs 27%, $P = 0.23$) and much lower for women by 10 years (30% vs 47%, $P < 0.02$). Attrition curves demonstrate that the probability of leaving was lower in recent years, especially for women ($P < 0.01$). Women tended to leave as early as did men faculty.

Conclusions: Attrition of first-time faculty in gynecologic oncology is less common in recent years and is less common among women than men. Future studies will need to access reasons for attrition and how they may differ with gender.

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Clinical value and efficacy of surveillance in patients with early-stage endometrial cancer

R. Salani[1], E. Drennen[1], C. Nagel[2], R. Bristow[3]

[1]Ohio State University, Columbus, OH, [2]University of Texas Southwestern Medical Center, Dallas, TX, [3]UC Irvine Medical Center, Orange, CA

Objective: The aim of this study was to evaluate the recurrence patterns and the clinical and economic role of surveillance with vaginal cytology in women with low-risk endometrial cancer.

Patients undergoing primary surgery with final pathology consistent with a grade 1 endometrial cancer with disease confined to the endometrium (1988 FIGO stage IA) between September 1997 and December 2007 were retrospectively identified. Follow-up data for at least two years were also collected, including diagnosis of a recurrence, symptomatology at that time and method of detection. Costs for vaginal cytology were estimated using Medicare charge-to-cost ratios adjusted to 2010 costs.

Results: One hundred fifty-five patients met study inclusion criteria. The mean age was 54.4 years and the mean follow-up was 46.9 months. Four recurrences were detected, occurring 16–73 months after the initial diagnosis. During a scheduled visit, one patient was found to have an asymptomatic vaginal cuff recurrence, detected on physical examination. This patient underwent cuff brachytherapy and remains disease free. The remaining three cases were diagnosed at an unscheduled visit after the presence of symptoms (vaginal bleeding, abdominal pain, shortness of breath) prompted further evaluation. Two of these patients had distant disease and received systemic chemotherapy; one patient had extensive locoregional disease and received external-beam radiation therapy. One patient with distant disease responded and is without evidence of disease after 11 months; the remaining two have died of disease. In all, cytology detected no cases of recurrence and the estimated cost associated with cytology alone for all patients over the study time frame was $13,392 per year.

Conclusions: Patients with grade 1 endometrial cancer confined to the endometrium have a low risk of recurrence (2.6%) and were

detected on clinical findings alone. Emphasis should be placed on counseling patients on symptoms of recurrence and performing a thorough physical examination. The elimination of vaginal cytology for this select group of patients may be appropriate and result in a significant reduction in health care costs.

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Disparities in gynecologic oncologist care in patients with endometrial cancer in the United States

R. Ruskin[1], H. Deshmukh[1], D. Kapp[2], S. Ueda[1], L. Chen[1], T. Kiet[1], A. Husain[2], J. Chan[1]
[1]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, [2]Stanford University Medical Center, Stanford, CA

Objective: The aim of this study was to determine the demographic and clinical pathologic factors associated with the disparities in subspecialty care in the United States.

Data were extracted from a national database of patients diagnosed from 1991 to 2002. The χ^2 test was employed for statistical analyses.

Results: Among 18,338 patients, the median age was 71 years (range: 27–100). Three thousand two hundred ninety-seven patients saw gynecologic oncologists (GOs) compared with 14,411 who did not see GOs. Among older patients (>71 years), 23.4% saw GOs compared with 19.8% in the younger cohort ($P<0.001$). With respect to race/ethnicity, 28.0% of Asians received care by a GO compared with 25.6% of Hispanics, 25.9% of blacks, 21.9% of Native Americans or others,and only 21.1% of whites ($P<0.001$). In the Eastern, Central and Western states, 23.2, 20.4, and 19.4% received care by a GO. Over the three periods 1991–1994, 1995–1998 and 1999–2002, the proportion of patients who saw a GO increased from 10.7% to 23.6% to 27.5% ($P<0.001$). Based on clinical pathologic factors, of those who underwent primary surgery 21.4% saw a GO compared with 28.0% of those who did not receive primary surgery ($P<0.001$). With increasing stage of disease from I to IV, the proportion who receive care from a GO correspondingly increased from 19.8% to 27.2% to 32.6% to 25.9%, respectively ($P<0.001$). More patients with a poor histology diagnosis saw a GO (34.7% for serous and 32.2% for clear cell) than those (20.2%) with endometrioid uterine cancer ($P<0.001$). Increasing grade of disease was associated with a corresponding increase in subspecialty care at 16.4% versus 22.1% versus 27.0% for grade 1 versus grade 2 versus grade 3 ($P<0.001$). GO care was also associated with higher use of radiation at 25.7% versus 19.4% ($P<0.001$) and chemotherapy at 33.1% versus 19.4% ($P<0.001$) compared with non-GO care in the overall study group.

Conclusions: Older patients, Asians, residents in Eastern states, more recent diagnosis, more advanced stage and high-risk cell types were associated with a higher likelihood of receiving care by a GO. Further studies are warranted to determine the barriers to gynecologic oncology subspecialty care for patients with uterine cancer in the United States.

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Have PORTEC 1 and GOG 99 changed practice patterns in the United States?

E. Ko, M. Funk, W. Brewster
University of North Carolina, Chapel Hill, NC

Objective: The purpose of this study was to assess the practice of adjuvant radiation therapy (RT) for endometrial cancer in the United States since the publication of the PORTEC 1 and GOG 99 trials.

The NCI SEER database was used to identify women diagnosed with endometrial cancer. We conducted a retrospective cohort study comparing use of RT before and after publication of PORTEC 1 (1996–1999 vs 2000–2003) and GOG 99 (2000–2003 vs 2004–2007). Criteria for intermediate (IM) and high intermediate (HI) risk categories as defined by PORTEC 1 and GOG 99 were applied to identify patients for whom RT was indicated. χ^2 statistics and adjusted odds ratios (aOR) with 95% confidence intervals (95% CI) were estimated using SAS. Multivariate models were adjusted for age, stage, grade, U.S. census region and race. Two-sided P values <0.05 were considered statistically significant.

Results: On the basis of PORTEC 1 criteria, 2325 IM and 708 HI patients were identified from 1996 to 2003. Compared with the period before publication of PORTEC 1, the proportion of IM (30.5% vs 28.5%, $P=$NS) and HI (46.2% vs 47.7%, $P=$NS) patients receiving RT did not increase significantly after PORTEC 1. The adjusted estimates also indicated no increase in RT in either group (aOR IM = 0.85, 95% CI = 0.70–1.04; and aOR HI = 1.01, 95% CI = 0.71–1.42). On the basis of GOG 99 criteria, 11,996 IM and 5008 HI patients were identified from 2000 to 2007. Although lymph node dissection increased over time ($P<0.001$), the proportion of IM patients receiving radiation did not increase (32.1% vs 31.0%, $P=$NS). There was only a modest increase among HI patients (45.7% vs 48.5%, $P=0.05$). The adjusted estimates also indicated no increase in RT among IM patients (aOR = 1.02, 95% CI = 0.94–1.16) and a modest increase among HI patients (aOR = 1.14, 95% CI = 1.01–1.29). White women were more likely than others to receive RT (aOR IM = 1.16, 95% CI = 1.02–1.32; and aOR HI = 1.21, 95% CI = 1.00–1.46). Radiation was most frequent in the Northeast and least in the West in all four comparisons.

Conclusions: In the period postpublication of two key randomized clinical trials, fewer then half of women for whom RT was indicated actually received radiation. These findings suggest that physicians have not successfully incorporated the findings of PORTEC 1 and GOG 99 into the treatment of patients with intermediate and high intermediate risk, early-stage endometrial cancer. Additional efforts are urgently needed to disseminate and implement these findings into clinical practice.

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Incidence of venous thromboembolism after robotic surgery for gynecologic malignancy: Is dual prophylaxis necessary?

J. Embry[1], K. Davis[2], N. Mejia[2], S. Davidson[1], M. Kelly[1], K. Behbakht[1]
[1]University of Colorado, Aurora, CO, [2]Swedish Medical Center, Englewood, CO

Objective: Dual venous thromboembolism (VTE) prophylaxis with pharmacologic thromboprophylaxis (PTP) and sequential compression stockings (SCS) is well supported for laparotomy in gynecologic malignancies. Recent literature has reported a lower 1.2% incidence of VTE in laparoscopic surgery for gynecologic malignancy, raising doubts about dual prophylaxis recommendations. Dual prophylaxis for robotic surgery is also unclear. Our objective was to estimate the incidence of VTE after robotic surgery for gynecologic malignancies and compare complications of patients treated with and without PTP.

The medical records of women who underwent robotic surgery for gynecologic malignancy from September 2007 to September 2010 at

two institutions were examined for demographics, incidence of VTE, bleeding complications and minor (urinary tract and skin infections, abscess, urinary retention, lymphocysts and vaginal cuff dehiscence) and major (<6 weeks) perioperative complications. Variables were compared with the χ^2 test and Fisher's exact test.

Results: Records of 210 women were examined and cases were excluded if converted to laparotomy (43), if medical records were incomplete (16), or if age was >89 years (1). All 150 included patients had SCS and 42 (28%) received PTP. The median age was 59 years (range: 30–86), median body mass index was 29 kg/m^2 (range: 18–53), median estimated blood loss was 50 mL (range: 25–1200), and median operating time was 165 minutes (range: 62–280). The main pathologic diagnosis was endometrial cancer, and 81% had complex surgical procedures that included radical hysterectomy or pelvic and/or paraaortic lymph node dissection. Any PTP use was associated with increased rate of any complication ($P<0.001$) as well as increased bleeding complications ($P=0.005$) and minor complications ($P<0.001$), but was not associated with major nonbleeding complications. None of the 150 women developed a perioperative symptomatic VTE.

Conclusions: Use of PTP in women undergoing robotic surgery for gynecologic malignancy may be associated with greater bleeding and minor complications. The incidence of VTE among gynecologic cancer patients who underwent robotic surgery was 0% in this cohort, and the incidence of perioperative VTE is likely to be very low in this population. Until perioperative dual prophylaxis is prospectively evaluated, the risks and benefits should be considered when prescribing PTP.

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Is extended prophylaxis with low-molecular-weight heparin necessary in patients with endometrial cancer undergoing minimally invasive robotic surgery?

N. Neubauer, E. Chapman-Davis, R. Scott-Ram, J. Lurain, J. Schink, M. Lowe
Northwestern University/Prentice Women's Hospital, Chicago, IL

Objective: Women with a gynecologic oncologic malignancy are at high risk for venous thromboembolism (VTE). The method of VTE prophylaxis, duration of therapy, and need for therapy after minimally invasive surgeries remain to be proven. The aim of this study was to compare the rates of VTE (1) between women with endometrial carcinoma who underwent open abdominal hysterectomy and staging procedures and those who underwent robot-assisted staging procedures and (2) between women who underwent a minimally invasive procedure and received extended VTE prophylaxis postoperatively with low-molecular-weight heparin (LMWH) and those who did not.

After institutional review board approval, a retrospective chart review was performed from January 2007 to June 2010. Eligible patients underwent either an open abdominal or robot-assisted hysterectomy and staging procedure for endometrial carcinoma at a single academic institution. We obtained a comprehensive tumor history, method and duration of postoperative VTE prophylaxis, and presence or absence of postoperative VTE in each patient.

Results: One hundred fourteen patients underwent open abdominal hysterectomy and staging procedures, 100% of whom received prophylactic postoperative LWMH. Two hundred ten patients underwent robot-assisted hysterectomy and staging procedures for endometrial cancer. Of the 210 robotic patients, 101 patients (ROB-P) received extended postoperative VTE prophylaxis for two weeks, and 109 patients (ROB-NP) received no extended prophylaxis. A total of three patients (0.95%) were diagnosed with postoperative VTE, two from the open group (1.8%, 95% CI = 0.4–4.2%) and one from the ROB-P group (1.0%, 95% CI = 0.4–1.6%). No patient in the ROB-NP group experienced a VTE. Both of the patients in the laparotomy group with a VTE were diagnosed with a pulmonary embolus in the immediate postoperative period prior to discharge from the hospital. One patient in the robotic group was diagnosed with a deep vein thrombosis while on a two-week course of postoperative prophylactic LMWH (see table).

Conclusions: Patients in our institution with endometrial cancer who undergo robot-assisted hysterectomies and other staging procedures are at lower risk for VTE as compared with patients undergoing a laparotomy. As the VTE rate in our robotic population is even lower than the 1.7% reported in the literature and the cost of LMWH is on average $100 per day, extended postoperative prophylaxis with LMWH does not appear beneficial in this patient population.

	Open	ROB-P	ROB-NP	overall
n	114	101	109	
No. (%) VTEs	2 (1.8%)	1 (1.0%)	0 (0.0%)	0.53
Age				
Mean (SEM)	59.7 (1.2)	62.3 (0.9	56.7 (1.1)	
Median	59	61	56	0.0008
Body mass index				
Mean (SEM)	36.2 (1.1)	32.4 (0.9)	30.2 (0.7)	
Median	34	31	28	<0.0001
Stage				
IA	36	55	48	<0.0001
IB	24	22	35	
IC	5	5	7	
IIA	7	1	2	
2B	12	3	7	
IIC	2	0	0	
IIIA	6	11	6	
IIIB	1	0	0	
IIIC	5	4	2	
IV	14	0	2	
IVB	2	0	0	

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Management of complex pelvic masses using the OVA1 test: A decision analysis

G. Zsebik, K. Kim, J. Straughn, C. Landen
University of Alabama, Birmingham, AL

Objective: The purpose of this study was to assess the cost-effectiveness of the OVA1 test for the evaluation and treatment of women with complex pelvic masses.

A decision analysis model evaluated a hypothetical cohort of 25,000 patients who presented to their gynecologist with a complex pelvic mass requiring surgery. Three strategies were evaluated: (1) clinical assessment of whether the mass was malignant with subsequent referral to a gynecologic oncologist (GO) (CLINICAL); (2) utilization of the OVA1 test in addition to clinical assessment with triage of patients with a positive test to a GO (OVA1); or (3) referral of all patients to a GO (REFER ALL). Assignment of surgical costs assumed that patients under the care of the gynecologist underwent only a hysterectomy and bilateral salpingo-oophorectomy regardless of surgical findings and pathology, whereas a GO performed

appropriate surgical staging when the mass was malignant. Positive and negative predictive values of clinical assessment and the OVA1 test were estimated from reported data. A range of surgical probabilities and reoperation rates were estimated from published data. Actual payer costs of surgery were estimated for each strategy. Sensitivity analyses were performed on pertinent uncertainties.

Results: Using baseline assumptions, the CLINICAL strategy was least expensive with a cost of $288.2 million and resulted in 72% of patients receiving appropriate initial surgical staging. The REFER ALL strategy was more expensive at $290 million but resulted in 100% of patients receiving appropriate initial surgical staging. The OVA1 strategy was most expensive at $301.4 million, but resulted in 91% of patients getting appropriate initial surgical staging. Using conservative reoperation rates (10%), 142 patients would require a reoperation using the CLINICAL strategy, compared with 44 patients with the OVA1 strategy. Using aggressive reoperation rates (40%), 529 patients would require a reoperation using the CLINICAL strategy, resulting in an incremental cost of $4.7 million compared with 163 patients at $1.5 million with the OVA1 strategy.

Conclusions: Utilization of the OVA1 test in addition to clinical assessment would result in more patients being referred to a GO, higher rates of receiving the appropriate initial surgery, and lower rates of requiring reoperation, but at increased costs. Referral of all patients with a complex mass to a GO would allow the highest rates of appropriate management with the least cost.

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Relative impact of cost drivers on the increasing expense of inpatient gynecologic oncology care

S. Plaxe[1], L. Prellwitz[2]
[1]*UCSD Moores Cancer Center, La Jolla, CA,* [2]*University HealthSystems Consortium, Chicago, IL*

Objective: The goal of this study was to identify cost drivers (CDs) and quantify their impact on the rise of total inpatient per case cost (PCC) in gynecologic oncology care.

This was a retrospective, descriptive study of inpatients registered in the University HealthSystems Consortium (UHC) Clinical Database for 15 consecutive fiscal year (FY) quarters (fourth quarter of 2006 through second quarter of 2010). Scatterplots of FY quarter of discharge versus mean length of stay (LOS), PCC, and cost/case of each of 10 service group CDs were made. Plots were fitted to a linear trend line by least-squares regression. R^2, the coefficient of determination, was calculated. Rates of change in LOS, PCC, and cost/case of individual CDs, represented by the slope of each linear trend line, were computed. Only gynecologic oncology patients from hospitals contributing data for all quarters in the study period were included.

Results: Data from 57,087 patients, from 153 hospitals, were analyzed. Mean (95% CI) LOS was 4.88 (4.70–5.06) days in the initial quarter, and fell to 4.52 (4.36–4.68) days by the last quarter of the study. Mean (95% CI) PCC was $12,711 ($12,598–12,825) in the initial quarter, and rose to $16,417 ($16,296–16,539) by the last quarter of the study. An average of 44% of total PCC is attributable to surgical (including perioperative) services and supplies, 32% to accommodations, 11% to treatment and pharmacy, 9% to the lab and 4% to all other services. The scatterplot of mean LOS (y) versus quarter (x), fitted to a line described by the equation $y = -(0.03)x + 5.0$ ($R^2 = 0.58$), indicated a decrease of 0.03 day per quarter. In contrast, mean PCC (y) versus quarter (x), fitted to a line described by the equation $y = (283.18)x + 12{,}461$ ($R^2 = 0.92$), indicated an increase of $283 per quarter. The divergence of PCC from LOS suggests that factors other than LOS are important contributors to rising PCC. The main driver of increasing PCC was found to be cost of surgical services and supplies. The scatterplot of cost of services and supplies (y) versus quarter (x), fitted to a line described by the equation $y = (188.9)x + 5127.1$ ($R^2 = 0.97$), indicated that the cost of services and supplies rose $189/case per quarter. The increase in the cost of services and supplies accounts for two-thirds of the rise in PCC. By similar methodology, contributions to the increasing PCC of accommodations (18%), lab (8%), treatment and pharmacy (5%), and other services (<1%) were calculated.

Conclusions: Strategies focused on surgical and perioperative areas may afford opportunities to control hospital costs for gynecologic oncology patients.

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Repeat excisional cervical procedures in older women: Is there an age at which cold knife cone should be performed rather than in-office LEEP?

E. Nugent, C. Barr, K. Moxley, J. Strebel, K. Moore
University of Oklahoma, Oklahoma City, OK

Objective: The literature demonstrates an increasing proportion of severe cervical dysplasia in women greater than 35 years of age. Anatomic cervical changes, including recession of the cervical transformation zone into the endocervical canal, is also associated with increasing age and may reduce the effectiveness of loop electrosurgical excisional procedure (LEEP) or cold knife cone (CKC). Our objective was to examine rates of repeat excisional procedures in women greater than 30 years of age after colposcopic examination and LEEP.

Between January 2000 and December 2005 we identified 71 patients at our institution greater than 30 years of age requiring excisional cervical procedures. Multivariate analysis was performed to examine age and characteristics of excisional procedures required to effectively treat dysplasia. Cut point analysis was performed to determine an age recommendation for elimination of in-office LEEP.

Results: Median age was 42 (range: 33–65). Forty-five percent of patients were current smokers. The distribution of abnormal PAP tests leading to colposcopy and LEEP were 7% ASC-US, 15% ASC-H, 18% LSIL, 55% HSIL and 7% CIS, AIS or AGC. Seventeen percent of patients treated with LEEP in the cohort required a repeat excisional procedure. As patient age increased, endocervical curettage positive for dysplasia at the time of colposcopy and LEEP was noted ($P = 0.031$ and 0.029, respectively). Positive margins on LEEP specimens and performance of an excisional procedure were significantly associated with increasing age ($P = .010$ and 0.018, respectively). Only two patients less than 40 years of age required a repeat excisional procedure, and the overall likelihood of repeat excision in patients greater than 40 was approximately one in four.

Conclusions: Preliminary results suggest women greater than 40 years of age with dysplasia are at greater risk for local treatment failure and more frequently require a repeat excisional procedure. CKC rather than LEEP may be a preferable initial procedure in this cohort.

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The use of bevacizumab and cytotoxic and consolidation chemotherapy for the upfront treatment of advanced ovarian cancer: Practice patterns among medical and gynecologic oncology SGO members

J. Elder[1], M. Mattingly[1], A. Ferda[1], C. DeSimone[1], R. Ware[1], F. Ueland[1], J. van Nagell[1], J. Carlson[2], L. Seamon[1]
[1]*University of Kentucky, Lexington, KY,* [2]*Mercy Medical Center, Des Moines, IA*

Objective: Our objective was to determine the current practice patterns among members of the Society of Gynecologic Oncologists (SGO) regarding primary advanced ovarian carcinoma (OC) therapy and the utilization of CA-125 in recurrence evaluation.

A 29-item survey was sent via e-mail to the gynecologic and medical oncology members of SGO on three occasions in September 2010. The survey addressed the preferred chemotherapy regimens for primary advanced OC and the role of CA-125 in evaluating OC recurrence. Descriptive statistics and comparisons between groups were performed using χ^2 in STATA10 (College Station, TX).

Results: Of 1174 e-mail addresses obtained from the SGO, 258 surveys were completed (response rate 22%). Forty-nine percent of respondents practice in an academic setting, with the majority in institutions that have fellowship training programs ($n=107$, 42%). Sixty-six percent are board certified. Eighty-nine percent administer intraperitoneal chemotherapy in their practice. Those not administering intraperitoneal chemotherapy cited high toxicity relative to potential benefit as the primary reason. Although the majority of respondents ($n=133$, 52%) agree that clinical trials represent the best therapy, physicians in academia were more likely to recommend a clinical trial over other therapy options (65% vs 39%, $P<0.0001$). For patients treated off protocol, 57% of practitioners prefer an intraperitoneal taxane/platinum regimen, whereas 27 and 7% recommend 21-day platinum/taxane and platinum every 21 days/weekly taxane regimens, respectively. When stratified by practice setting, more physicians in academic centers chose intraperitoneal chemotherapy (48% vs 29%, $P=0.003$). The majority do not recommend bevacizumab in the upfront treatment of OC or administer consolidation paclitaxel outside of a clinical trial (92 and 87%, respectively). Although 69% agree that CA-125 should not be included as a progression-free endpoint in future clinical protocols, 72% use CA-125 to monitor recurrence and image based on rising levels, but would not treat based on rising CA-125 levels alone. Seventy-nine percent would continue to enroll patients in clinical protocols that include blinding CA-125 to participants and practitioners.

Conclusions: The majority of SGO member respondents agree that clinical trials offer the best therapy and prefer intraperitoneal chemotherapy off protocol. Most do not administer bevacizumab or consolidation paclitaxel outside of a clinical trial and believe that CA-125 should not be included as a progression-free endpoint in future clinical protocols.

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Three-dimensional power doppler angiography as a three-step technique for differential diagnosis of adnexal masses: A prospective study

M. Jurado, J. Alcazar, M. Auba, A. Ruiz-Zambrana
Clinica Universidad De Navarra, Pamplona-Navarra, Spain

Objective: The goal of this study was to assess the contribution of three-dimensional power doppler angiography (3D-PDA) for differential diagnosis of adnexal masses.

This prospective study (June 2008–January 2010) performed at one university tertiary care hospital comprised all women diagnosed as having a persistent adnexal mass and scheduled for surgery. All women were evaluated by ultrasound according to a predetermined protocol, following a three-step method. A B-mode morphological assessment was performed (first step). Those lesions thought to be benign according to gray-scale "pattern recognition" analysis were not further analyzed. Those tumors with solid components or that were questionable on B-mode ultrasound underwent two-dimensional power Doppler (2D-PDA) analysis of tumor blood flow location (second step). Those lesions without flow and where only peripheral blood flow was detectable were considered benign, whereas those tumors with central flow were considered malignant. The latter group underwent 3D-PDA analysis (third step). The vascularity index (VI) of the vascularized areas of the tumor was calculated offline by a single examiner. A tumor with VI $>1.556\%$ was considered malignant. All masses were surgically removed and a definitive histological diagnosis made. Sensitivity, specificity, positive (LR+) and negative (LR−) likelihood ratios, and global accuracy for each step were calculated and compared.

Results: Two hundred seventeen masses in 186 women (mean age: 44.3 years, range: 12–78) were evaluated during the study period. Sixty-one masses were malignant and 156 benign. The diagnostic performance of each method is outlined in the table.

Conclusions: Two-dimensional and three-dimensional power doppler angiography increased significantly the specificity of B-mode ultrasound. The probability of malignancy is significantly higher after 3D-PDA analysis than after B-mode and 2D-PDA assessment. Global accuracy is higher for the three-step method as compared with the one-step and two-step methods.

	Sensitivity	Specificity[a]	LR+	LR−	Accuracy
B-Mode	98.4%	75.6%	4.04	0.02	82.2%
2D-PDA (two-step model)	93.4%	91.7%	11.21	0.07	92.2%
3D-PDA (three-step model)	91.8%	95.5%	20.46	0.09	94.5%

[a]McNemar test: $P<0.001$ B-mode versus 2D-PDA and 3D-PDA. $P=0.016$ 2D-PDA versus 3D-PDA.

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Uterine leiomyosarcoma: Can locoregional recurrences be salvaged by surgery and additional therapies?

K. Levinson[1], E. Eisenhauer[2], P. Gehrig[3], A. Suri[3], M. Tenney[4], H. Frasure[5], L. Havrilesky[6], M. Lopez[6], A. Alvarez-Secord[6], A. Nickles Fader[1]
[1]*Johns Hopkins Medical Institutions, Baltimore, MD,* [2]*Ohio State University, Columbus, OH,* [3]*University of North Carolina School of Medicine, Chapel Hill, NC,* [4]*University of Oklahoma, Oklahoma City, OK,* [5]*University Hospitals of Cleveland, Cleveland, OH,* [6]*Duke University Medical Center, Durham, NC*

Objective: Uterine leiomyosarcoma (LMS) is a rare, aggressive malignancy, which often recurs. However, data informing the salvage of recurrences are limited. The objective of this study was to determine clinicopathologic variables associated with recurrence and survival in women with uterine LMS and the factors associated with salvagability of recurrences.

This multisite retrospective analysis comprised women with uterine LMS treated at five academic centers between June 1981 and August 2010. Clinical, pathologic and treatment data were collected. Adjuvant treatment groups were defined as observation (OBS), radiation therapy (RT) and chemotherapy (CT). Kaplan–Meier curves were constructed for progression-free survival and overall survival, and multivariate analyses using logistic regression and Cox hazards ratios were performed.

Results: One hundred eighty-one patients were identified. Median age was 55 years. One hundred twenty of 181 (66.3%) patients had stage I/II disease, 51 of 181 (28.2%) had stage III/IV disease, and 10 of 181 (5.5%) were not staged. All patients underwent primary surgery followed by OBS (31.5%), RT (25.4%), or CT (43.1%). With a median follow-up of 41 months, 109 of 181 (60.2%) patients recurred, and there was no difference between treatment groups ($P=0.212$). Recurrences were pelvic (26/109, 23.9%), distant (62/109, 56.9%), or pelvic and distant (18/109, 16.5%); 60% of distant recurrences were in the lung. Salvage was achieved in 36.7% of patients including 50% (13/26) of those with pelvic recurrences and 33.9% (21/62) of those with distant recurrences ($P=0.156$); 76.2% of patients with salvaged distant recurrences had lung recurrence only. Patients who recurred received a variety of therapies including surgery, CT, RT, and hormonal therapy. Of the 26 patients with pelvic recurrences, salvage was achieved in 7 who underwent surgery with or without additional therapy, in 8 of 9 who received CT with or without additional therapy, and in 4 of 4 who received both surgery and CT. For distant recurrences (lung and other), there was no difference in rate of salvage among different treatment groups ($P=0.764$). Median time from recurrence to death was 12 months, and median length of salvage was 23 months. Median progression-free survival and overall survival were 57 and 81 months.

Conclusions: Despite the biologic aggressiveness and lethality of LMS, our data suggest that a surprising number of recurrences were locoregional and amenable to salvage. Pelvic recurrences are more likely to be salvaged than distant recurrences. The role of surgery for isolated pelvic recurrences is less clear. Prospective studies are needed.

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Poster Area 4
Cervical Cancer, Cervical Cancer Clinical Trials, Gestational Trophoblastic Disease/Vulvar and Vaginal Cancers/Rare Tumors/Sarcomas and Public Health/Epidemiology: Abstracts 241–293
Sunday, March 6 – Tuesday, March 8, 2011
Exhibit Hall – Bonnet Creek Ballroom

Cervical Cancer

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2008 FIGO stage IIA1 and IIA2 cervical cancer: Does the new staging system predict survival and/or lymph node metastasis?

G. Garg[1], J. Shah[2], R. Morris[1]
[1]*Wayne State University/Detroit Medical Center, Detroit, MI,* [2]*Southern California Permanente Medical Group, Irvine, CA*

Objective: In 2008, the FIGO staging system for cervical cancer was revised, subdividing stage IIA cervical cancer into stages IIA1 and IIA2, based on tumor size ($\leq$4 cm and $>$4 cm, respectively). The objective of this study was (1) to determine the correlation of 2008 FIGO staging system with survival and lymph node metastasis in patients with stage IIA cervical cancer, (2) to elucidate the treatment patterns in stage IIA1 and stage IIA2 cervical cancer, and (3) to investigate whether radical hysterectomy or radiation influenced overall survival.

Data were extracted from the Surveillance, Epidemiology, and End Results database between 1988 and 2005. Statistical analysis used χ^2 test, Kaplan–Meier method, Cox regression, and logistic regression.

Results: Of the 560 women, 271 (48.4%) had stage IIA1 and 289 (51.6%) stage IIA2 cervical cancer. Stage IIA2 patients were younger than stage IIA1 patients (mean age: 49 years vs 54 years, $P=0.01$). Stage IIA1 and stage IIA2 differed significantly with respect to the administration of primary radiation (46.5% vs 64.4%, $P<0.001$) and adjuvant radiation (60.5% vs 77.5%, $P=0.006$). The incidence of adjuvant radiation following radical hysterectomy was high (48% [tumor size $\leq$2 cm] to 85% [tumor size $>$6 cm]). Five-year overall survival did not significantly differ between stages IIA1 and IIA2 (65.8% vs 59.5%, $P=0.2$). Although age ($P=0.004$), tumor size ($P=0.01$), and lymph node status ($P=0.001$) were all predictors of survival, only tumor size ($P=0.03$) was significantly associated with lymph node metastasis. The 2008 FIGO stage was an independent predictor of neither survival nor lymph node metastasis ($P>0.05$). Patients $<$65 years of age with tumors $\leq$2 cm of nonsquamous histology commonly underwent radical hysterectomy. When other contributing factors were controlled for, there was no significant difference in survival between patients treated by radical hysterectomy and those treated with primary radiation ($P>0.05$).

Conclusions: The 2008 FIGO staging criteria do not constitute an independent predictor of survival or lymph node metastasis in stage IIA cervical cancer. Given the equivalent efficacy of radical hysterectomy and radiation, attention should be paid to the high risk of adjuvant radiation in these patients.

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Adenocarcinoma as an independent risk factor for early-stage intermediate-risk cervical carcinoma

C. Mathews[1], S. Goodrich[2], R. Farrell[1], C. DeSimone[2], L. Seamon[2], L. Landrum[1]
[1]*University of Oklahoma, Oklahoma City, OK,* [2]*Lexington Gynecologic Oncology, Lexington, KY*

Objective: The observation arm of GOG 92 showed that the probability of recurrence was higher for cervical adenocarcinoma than for squamous cell cancer (SCC). Adjuvant radiation therapy appeared to benefit adenocarcinoma more than SCC, but the number of subjects with adenocarcinoma was small. This analysis will examine recurrence probability among subjects with IB adenocarcinoma who received no adjuvant treatment to determine whether histology should be considered as an intermediate-risk factor.

A retrospective review was performed of patients with stage IB cervical adenocarcinoma treated with hysterectomy and lymphadenectomy at two institutions between 1990 and 2007. Inclusion was limited to those with negative parametria, margins and lymph nodes who received no postoperative treatment. Subjects who met intermediate-risk criteria based on GOG 92 were also excluded. Subjects with one intermediate-risk (IR) factor, including positive lymphovascular space invasion (LVSI), tumor size $>$4 cm, or middle-/outer-third invasion, were compared with subjects with no risk (NR) factor. Fisher's exact test and the Cochran–Armitage trend test were used to compare recurrence risk among pathologic factors.

Results: We identified 91 patients with stage IB cervical adenocarcinoma with negative parametria, margins, and lymph nodes who did not receive postoperative treatment. The median age was 40 years, median follow-up was 3.1 years and 34 of 91 patients had an IR factor. The risk of recurrence was 5.9% (2/34) in the IR group and 1.7% (1/57) in the NR group (0.553). The relative risk of recurrence was 16.2

times higher (CI = 1.61–163.01, $P = 0.031$) among subjects with LVSI (2/10) than among those without LVSI (1/81). Only two subjects were identified with tumor size greater than four cm; neither recurred. There was no association between depth of invasion, categorized as <33, 33–66, and >66%, and recurrence ($P = 0.509$).

Conclusions: The overall risk of recurrence was small in our population compared with a 40% risk of recurrence in GOG 92 for patients with intermediate-risk cervical adenocarcinoma who received no postoperative treatment. The risk demonstrated in our population does not warrant the adverse effects associated with postoperative radiation, and we do not recommend considering adenocarcinoma as an independent criterion for intermediate-risk cervical cancer. Specific pathologic combinations, such as positive LVSI and adenocarcinoma, may confer a high risk of recurrence and be worthy of future consideration.

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Can LEEP replace cold knife conization for the management of cervical intraepithelial neoplasia in women with unsatisfactory colposcopic examination? A systematic review and a meta-analysis

S. El-Nashar, M. Hopkins, W. Cliby, A. Famuyide
Mayo Clinic, Rochester, MN

Objective: Unsatisfactory colposcopic examination in patients with cervical intraepithelial neoplasia (CIN) is associated with increased risk of occult invasive carcinoma. Traditionally, a cone biopsy using cold knife conization (CKC) has been recommended. Loop electrosurgical excision procedure (LEEP) is an alternative office procedure with fewer risks. We conducted a meta-analysis to compare LEEP with CKC for the treatment of CIN in patients with unsatisfactory colposcopic examination.

A MEDLINE and EMBASE database literature search through October 2010 was performed to identify published clinical trials and cohort studies comparing CKC with LEEP that included women diagnosed with CIN who had an unsatisfactory colposcopic examination. There was no restriction to language of publication. For each study, two reviewers independently assessed methodologic quality using validated scales and extracted outcome data. Agreement was evaluated using statistics. Funnel plots were used for the assessment of publication bias. Subgroups were specified a priori. Pooled relative risk (RR) and weighted mean difference (WMD) were used to report binary and continuous outcomes, respectively.

Results: The search identified 25 reports. The incidence of persistent and recurrent disease after LEEP was comparable to that after CKC (16.3% vs 12.4%, RR = 1.23, 95% CI = 0.96–1.57) (see figure). Subgroup analyses based on important baseline and outcome variables were conducted (see table). LEEP was less time consuming, was associated with less intraoperative bleeding, and resulted in shorter hospital stay (WMD: 9.5 minutes, 95% CI = 6.4–12.6; 42.4 cc, 95% CI = 21.3–106; and 1.5 days, 95% CI = 1.1–1.8, respectively). Compared with LEEP, cones were shallower with overall less volume and weight with CKC (WMD: 5.1 mm, 95% CI = 3.2–7.1; 2.6 cm^3, 95% CI = 0.6–5.7; and 2.6 g, 95% CI = 1.4–3.7, respectively). During follow-up, LEEP was associated with less cervical stenosis and unsatisfactory exam. However, this was not statistically significant (RR: 0.5, 95% CI = 0.1–1.5, and 0.7, 95% CI = 0.4–1.2, respectively).

Conclusions: LEEP appears to be an acceptable alternative to CKC in women with CIN and unsatisfactory colposcopy. There is a trend toward more recurrent CIN cases after LEEP compared with CKC. From previous data, CKC was associated with more preterm labor compared with LEEP. Patient counseling is important and close clinical follow-up remains necessary to enable prompt detection and treatment of persistent or recurrent disease.

Comparison	Number of studies	Number of articipants	Relative risk [95% CI]	Interaction testing *P* value
Early or late CIN disease during the follow-up				
Persistent disease (<6 months)	12	1579	1.04 [0.81, 1.35]	0.012[a]
Recurrent disease (>6 months)	6	986	1.89 [1.28, 2.79] [b]	
Type of study				
Clinical trials	6	718	2.17 [1.11, 4.24] [b]	0.083
Cohort studies	12	1847	1.14 [0.86, 1.52]	
Sampling strategy				
Based on diagnosis of CIN (only)	15	2226	1.36 [1.07, 1.71] [b]	0.111
Based on diagnosis of CIN and either positive margins in the cone biopsy or hysterectomy during the follow-up	3	339	0.82 [0.48, 1.39]	
Unsatisfactory colposcopy in >50% of patients vs <50%				
Studies with >50% of patients having unsatisfactory colposcopy	5	499	1.64 [0.77,3.48]	0.649
Studies with <50% of patients having unsatisfactory colposcopy	7	1108	1.31 [0.71,2.12]	
Unsatisfactory colposcopy at baseline in LEEP vs CKC				
Studies with more unsatisfactory colposcopy in LEEP	3	400	0.98 [0.59, 1.63]	0.027[a]
Studies with more unsatisfactory colposcopy in CKC	6	826	2.05 [1.37, 3.08][b]	
High grade dysplasia (CIN II and CIN III) at baseline				
Studies with more high- grade dysplasia in LEEP	7	801	1.04 [0.65, 1.66]	0.232
Studies with more high grade dysplasia in CKC	9	1314	1.45 [1.10, 1,92] [b]	

[a]Statistically significant interaction testing.[b]Statistically significant relative risk estimate for the subgroup in favor for CKC.

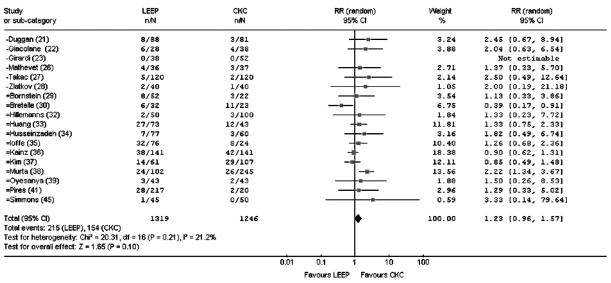

Figure . The rate of persistent or recurrent disease in large loop electrosurgical excision procedure compared to cold-knife conization women diagnosed with cervical intraepithelial neoplasia

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Chromosome 3q26 gain for identification of women less likely to progress from LSIL/CIN 1 to HSIL/≥CIN 2

A. Rodolakis[1], J. Biliatis[1,2], N. Thomakos[1,2]
[1]*University of Athens, Athens, Greece,* [2]*Alexandra Hospital, Athens, Greece, Athens, Greece*

Objective: The goal of this study was to determine whether 3q26 gain can predict which low-grade squamous intraepithelial lesions (LSIL) and atypical squamous cells of undetermined significance (ASCUS) will progress to higher-grade dysplasia (HSIL).

LSIL and ASCUS liquid cytology specimens from 73 women were examined using fluorescence in situ hybridization (FISH) for the detection of 3q26 gain. All women underwent colposcopy and biopsy at the initial visit. Our study population consisted of 40 women with the histologic diagnosis of cervical intraepithelial neoplasia 1 (CIN 1) or human papillomavirus (HPV) infection. Patients were reevaluated after a median follow-up of 17.5 months with liquid cytology, colposcopy and biopsy.

Results: A total of 40 cases were analyzed (31 LSIL, 9 ASCUS). Of those, eight (20%) were 3q26 FISH positive (six LSIL, two ASCUS), and 32 (80%) 3q26 FISH negative. Three of the eight FISH-positive women (38%) progressed to HSIL/≥CIN 2, whereas none of the 32 FISH-negative women did so. 3q26 gain could predict progression with a sensitivity, specificity, and positive and negative predictive values of 100, 86, 38, and 100%, respectively. In addition, FISH-positive women had a significantly lower regression rate compared with FISH-negative women ($P=0.009$).

Conclusions: In this first prospective study, 3q26 gain in LSIL/ASCUS cytology exhibited an impressive negative predictive value for progression to HSIL/≥CIN 2. Thus, 3q26 gain may be useful in stratifying patients' risk of progression and possibly alter management and reduce cost of follow-up.

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Completed versus aborted radical hysterectomy for node-positive stage I cervical cancer

A. Ziebarth[1], J. Durst[1], A. Subramaniam[1], N. Nguyen[1], H. Smith[1], E. Killian[1], K. Kim[1], C. Leath[2], J. Straughn[1], R. Alvarez[1]
[1]*University of Alabama, Birmingham, AL,* [2]*Brooke Army Medical Center, Ft. Sam Houston, TX*

Objective: Debate continues about the best management strategy for patients with operable, node-positive stage I cervical cancer. Our objective was to determine if progression-free survival (PFS), overall survival (OS) or complication rates are affected by radical hysterectomy in this cohort in the era of adjuvant chemoradiation.

Following institutional review board approval, all patients with cervical cancer diagnosed from 2000 to 2005 were identified. Demographics, therapy, clinicopathologic data, PFS, OS, and grade 3/4 complications were collected. Student's *t* test and Fisher's exact test were used for analysis.

Results: Between 2000 and 2005, 204 patients with cervical cancer were scheduled to undergo radical hysterectomy with lymphadenectomy. Of these, 25 (7.6%) had metastatic nodal disease at the time of surgery and underwent completion of radical hysterectomy and staging. Twenty (9.8%) other patients were found to have metastatic nodal disease based on frozen section and underwent pelvic and paraaortic lymphadenectomy without radical hysterectomy (aborted radical hysterectomy). Patients were similar in terms of age, body mass index, race, tobacco use, clinical stage, number of positive nodes and size of primary lesion. All 25 patients in the radical hysterectomy group received postoperative whole-pelvis radiation therapy (WPRT) with cisplatin chemotherapy; three (12%) patients required postoperative vaginal brachytherapy (BT) because of close or positive margins. In comparison, all patients undergoing aborted radical hysterectomy underwent WPRT and BT in combination with chemotherapy. There were no significant differences in urinary, gastrointestinal, or hematologic complications. At a mean follow-up of 46.1 months, there were no significant differences between those who underwent radical hysterectomy and those who underwent aborted radical hysterectomy in terms of rate of overall recurrence (36% vs 21%, $P=0.44$), local recurrence (16% vs 5.2%, $P=0.36$), or distant recurrence (20% vs 16%, $P=0.49$). When patients who underwent radical hysterectomy were compared with those who underwent aborted radical hysterectomy, there were there no differences in PFS (42.61 months vs 49.4 months, $P=0.29$) or OS (45.6 months vs 50.4 months, $P=0.44$).

Conclusions: The treatment of patients with early-stage cervical cancer found to have nodal metastases should be tailored at the time of surgery. Completion of radical hysterectomy and lymphadenectomy does not compromise safety or outcome in the era of adjuvant chemoradiation.

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Consequences of lengthening cervical cancer screening intervals on mammography rates

H. Dinkelspiel[1], T. Flanagan[2], W. Kinney[2], B. Fetterman[2], T. Lorey[2], P. Castle[3]
[1]*Kaiser Northern California, Sacramento, CA,* [2]*Kaiser Permanente Medical Center, Oakland, CA,* [3]*National Cancer Institute, Bethesda, MD*

Objective: The goal of this study was to characterize the relationship of cervical cancer screening intervals and rates with rates of compliance with Healthcare Effectiveness Data and Information Set recommendations for mammography.

Follow-up data were obtained from the databases of a large health maintenance organization, consistent with our institutional review board approval. Starting in 2003, combined Pap and human papillomavirus (HPV) co-testing was implemented. Healthcare Effectiveness Data and Information Set rates for mammography, which changed to cover ages 42–69 starting in 2006, are described.

Results: Prior to the implementation of co-testing, the median time to rescreening following a negative Pap test was approximately 15 months, and 65% of women who rescreened following a negative––currently "Negative for Intraepithelial Lesion and Malignancy"––Pap at the Regional Lab did so within 18 months ("annual screening"). By the end of 2008, the median interval to rescreening following a negative co-test between 2003 and 2008 was 30 months and rising each year. Compliance with Healthcare Effectiveness Data and Information Set mammography recommendations was 77% in 2006, 79% in 2007 and 82% in 2008.

Conclusions: Concern that doubling the cervical screening interval would negatively impact other cancer screening rates has not been substantiated in our population. Mammography rates remain excellent and have improved as cervical cancer screening intervals have lengthened. Therefore, decisions not to implement co-testing with increased cervical screening intervals based on concern about

adverse effects on compliance with other recommended cancer screening does not appear warranted.

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Effect of surgeon and hospital volumes on outcome for women undergoing radical hysterectomy for cervical cancer

J. Wright, S. Lewin, I. Deutsch, X. Sun, W. Burke, T. Herzog
Columbia University College of Physicians and Surgeons, New York, NY

Objective: Physician and hospital volumes have been shown to have an important influence on morbidity and mortality for a number of high-risk surgical procedures and medical conditions. For a number of oncologic procedures, outcomes are superior when the procedure is performed by high-volume surgeons at high-volume hospitals. Relatively little is known about the effect of volume on outcomes for cervical cancer. We analyzed the effect of surgeon and hospital volumes on perioperative morbidity and mortality for women with cervical cancer who underwent radical hysterectomy.

Women who underwent radical hysterectomy for invasive cervical cancer from 2003 to 2007 and were recorded in the Perspectives database were included. The primary endpoints for analysis were operative injuries, perioperative surgical complications, medical complications, transfusion, length of stay, ICU use and perioperative death. Surgeons and hospitals were stratified into volume-based tertiles based on the annual number of radical hysterectomies performed. Multivariable generalized estimating equations were used to examine the effect of surgeon and hospital volumes on morbidity and mortality while controlling for other clinical variables and surgeon and hospital clustering.

Results: A total of 1536 patients were identified. Hospital volume had no independent effect on any of the outcomes of interest. Patients treated by high-volume surgeons were less likely to have postoperative medical complications (22% low volume vs 15% high volume, OR = 0.55, 95% CI = 0.340.88) and had shorter lengths of stay (four days low volume vs three days high volume, OR = 0.49, 95% CI = 0.25−−0.98). Surgeon volume had no effect on the rates of operative injury (5% low volume vs 6% high volume, OR = 1.07, 95% CI = 0.56–2.06), perioperative surgical complications (3% low volume vs 2% high volume, OR = 0.64, 95% CI = 0.24–1.72), transfusion (14% low volume vs 7% high volume, OR = 0.59, 95% CI = 0.28–1.24), ICU use (4% low volume vs 2% high volume, OR = 0.71, 95% CI = 0.31–1.63), or readmission rates (1% low volume vs 3% high volume, OR = 1.72; 95% CI = 0.69–4.25). Neither surgeon nor hospital volume was associated with perioperative mortality.

Conclusions: Hospital volume has no effect on perioperative complication rates for women undergoing radical hysterectomy for cervical cancer. Although high-volume surgeons have lower rates of postoperative medical complications and shorter lengths of stay, these findings are modest compared with other high-risk surgical procedures.

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Genetic polymorphisms of the transporter associated with antigen processing are associated with cervical neoplasia in Korean women

N. Kim[1], S. Chung[1], S. Lee[2], W. Ju[1], S. Kim[1]
[1]*Ewha Womans University College of Medicine, Seoul, Republic of Korea,* [2]*Bundang Jaeseng Hospital, Kyunggido Sungnamsi, Republic of Korea*

Objective: Recent studies have determined that human papillomavirus (HPV) infection predisposes to cervical cancer and that other factors like host genetic polymorphisms may affect cancer susceptibility. The transporter associated with antigen processing is essential in assembling class I major histocompatibility complex (MHC-I) proteins. HPV evades immune recognition by decreasing MHC-I cell surface expression through downregulation of TAP1 levels. Consistent with heterogeneity in MHC-I expression is the individual variability in clearing detectable HPV infections. Genetic polymorphisms in TAP genes may affect protein structure, function, and ability to clear HPV infection and individual susceptibility to cervical neoplasia. In this study, we explored the association of genetic polymorphisms of TAP1 and TAP2 with cervical neoplasia in a nested case–control study of Korean women.

A total of 333 women (63 invasive cervical cancers, 124 cases of cervical intraepithelial neoplasia and carcinoma in situ, 145 cancer-free benign controls) who underwent surgery from November 2004 to May 2007 at the Department of Gynecology, Ewha Woman's University, Mokdong Hospital, were included in this study. To evaluate the role of TAP1 and TAP2 gene polymorphisms in cervical neoplasia, TAP1 I333V, TAP1 D637G, TAP2 I379V, and TAP2 T665A were selected. Unconditional logistic regression was used to estimate ORs and 95% CIs according to the TAP gene polymorphisms in cases and controls. Differences in allele and genotype distributions between cases of cervical neoplasia and controls for selected TAP polymorphisms were compared using Pearson's χ^2 test.

Results: Differences in allele distribution between women with cervical intraepithelial neoplasia and women with benign gynecologic disease were seen for TAP1 I333V ($P = 0.00$) and TAP1 D637G ($P = 0.10$). However, differences in allele distribution between women with cervical cancer and women with benign gynecologic disease were seen for TAP1 I333V ($P = 0.00$), TAP1 D637G ($P = 0.22$), TAP2 I379V ($P = 0.29$) and TAP2 T665A ($P = 0.08$). The odds ORs for cervical intraepithelial neoplasia and cervical cancer were significantly higher among CC homozygote carriers of the TAP1 I333V polymorphism (OR = 7.20, 95% CI = 3.28–15.83). TAP2 I379V C > T polymorphism carriers have a significantly lower risk than homozygote CC carriers (see table).

Conclusions: In addition to the downregulation of MHC-1 by oncogenic HPV, HPV pathogenesis might be facilitated by polymorphisms in the TAP proteins. TAP polymorphisms may potentially be used to identify women less susceptible to progression to cervical intraepithelial neoplasia and cervical cancer.

	Cases (*n*)	Controls (*n*)	OR (95% CI)
TAP1 I333V			
TT	82	101	1.00
CT	35	36	0.79(0.45–1.37)
CC	71	8	7.20(3.28–15.8)
CT + TT	117	137	0.69(0.47–1.02)
TAP1 D637G			
TT	126	104	1.00
CT	56	34	1.36(0.83–2.24)
CC	6	7	0.70(0.23–2.17)
CT + TT	182	138	1.09(0.77–1.53)
TAP2 I379V			
CC	116	144	1.00
TC	25	41	0.50(0.29–0.88)
TT	4	1	0.66(0.46–0.95)
TC + CC	141	185	0.63(0.45–0.88)
TAP2 T665A			
TT	65	51	1.00
CT	91	79	0.90(0.56–1.45)
CC	32	15	1.67(0.82–3.42)
CT + TT	156	130	0.94(0.61–1.45)

Distributions of selected TAP genotypes in CIS, cancer, and benign gynecologic disease.

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Implementation of surgical treatment for early-stage cervical cancer by Kenyan gynecologists in western Kenya

B. Rosen[1], O. Elkanah[2], P. Itsura[2], C. Giede[3], W. Jimenezfiedler[4], S. Sinasac[5], P. Cibulska[5], D. Miller[6], L. Elit[4], J. Dodge[5]
[1]University of Toronto, Toronto, ON, Canada, [2]Moi University, Eldoret, Kenya, [3]University of Saskatchewan, Saskatoon, SK, Canada, [4]Mcmaster University, Hamilton, ON, Canada, [5]University of Toronto, Toronto, ON, Canada, [6]University of British Columbia, Vancouver, BC, Canada

Objective: Cervical cancer is the number one cancer killer of women in Kenya. Most women present with advanced disease. Access to radiation treatment is severely resource limited (there is only one cobalt machine for treating cervical cancer for a population of 30 million), and very few women can afford either transportation to or expense of treatment. In 2009, a cervical cancer screening program using VIA was introduced into an HIV-affected population in western Kenya (prior to screening it was rare to identify a patient with early-stage cervical cancer). This screening program identified women with early-stage cancers who are potentially curable. The objective of this program was to determine if Kenyan gynecologists could learn to identify and surgically treat early-stage cervical cancer through a focused education program provided at their own hospital in Kenya.

A training module for radical hysterectomy was developed by a group of gynecologic oncologists. It consisted of PowerPoint presentations of the surgical procedure and complications, pre- and posttraining tests, and a detailed process of evaluation of the training surgeon following each case. In addition, there was a module on postoperative care, and the training included a database from which patient information could be prospectively collected for future analysis. At the end, the Kenyan gynecologists also evaluated the program.

Results: Two Kenyan gynecologists were trained to perform radical hysterectomy over two weeks. They completed all modules prior to operating and, with their mentor, performed six radical hysterectomies. The two gynecologists then completed a seventh radical hysterectomy on their own with the mentor in the room but not scrubbed. Five months after their training, the Kenyans completed another nine radical hysterectomies. Fifteen of 16 patients voided on their own five days after surgery. One patient had a hemmorhagic complication but lived. Seven of 16 had positive nodes. Two with positive nodes have received postoperative radiation and have been financially supported by the hospital.

Conclusions: Access to treatment of early-stage cervical cancer needs to be part of cervical cancer screening programs. In Kenya, where access to radiation is limited, radical hysterectomy becomes a feasible strategy to cure early-stage cancers. We used an organized educational strategy and a detailed evaluation process to teach this surgery to two Kenyan gynecologists. We found it is possible for them to learn this surgical procedure in a short time in their own country.

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Intraoperative detection of nodal metastasis in early-stage cervical cancer: A survey of the practice patterns of SGO members

G. Garg[1], J. Shah[2], E. Toy[3], J. Field[4], C. Bryant[5], R. Morris[6]
[1]Detroit Medical Center, Detroit, MI, [2]Southern California Permanente Medical Group, Irvine, CA, [3]University of Rochester, Rochester, NY, [4]William Beaumont Hospital, Detroit, MI, [5]M.D. Anderson Cancer Center, Orlando, FL, [6]Wayne State University, Detroit, MI

Objective: The purpose of this study was to determine the practice patterns of members of the Society of Gynecologic Oncologists (SGO) in different clinical situations involving the intraoperative detection of nodal metastases in early-stage cervical cancer.

A study questionnaire was mailed to the current members of SGO ($n=874$). Data were collected using an Internet survey database. Frequency distributions were determined, and nonparametric tests were performed.

Results: Thirty percent of SGO members responded ($n=274$). Only 38.6% routinely performed an intraoperative frozen section evaluation of the lymph nodes. Of these, most (80%) did not abort the radical hysterectomy (RH) for an isolated microscopically positive pelvic lymph node. The likelihood of aborting RH for microscopic nodal involvement increased, however, with number of positive pelvic lymph nodes (20% with one, 35% with two or three, and 55% with >3 positive pelvic lymph nodes), involvement of paraaortic lymph nodes (59%), or bilaterally positive lymph nodes (50%). Similarly, a large number of SGO members did not complete the RH if there was gross involvement of pelvic (45%) or paraaortic (69%) lymph nodes. Most (90%) completed the lymphadenectomy before aborting RH. When completing RH, the majority tailored its extent to perform a less radical resection. Variables significantly associated with the likelihood of completing RH in different clinical situations included: location of current practice (West), practice type (private), years in practice (>10 years) and number of cases seen per year (>10/month).

Conclusions: Practice patterns of SGO members are considerably diverse, which is reflective of the conflicting evidence available in the literature. Well-designed studies are required to determine the best overall approach.

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Is there a microinvasive cervical adenocarcinoma?

L. Spoozak, S. Lewin, W. Burke, I. Deutsch, X. Sun, T. Herzog, J. Wright
Columbia University College of Physicians and Surgeons, New York, NY

Objective: Women with microinvasive squamous cell carcinoma of the cervix have a favorable prognosis and are candidates for less radical, uterine-conserving surgery. Whether a microinvasive adenocarcinoma of the cervix exists and if conization is appropriate treatment are unknown. We examined the outcome of women with stage IA cervical adenocarcinoma and explored the safety of uterine-conserving surgery for these women.

Women with invasive squamous cell carcinomas and adenocarcinomas of the cervix with <5 mm of cervical stromal invasion diagnosed between 1988 and 2005 were analyzed. The demographic and pathologic characteristics were compared using the χ^2 test, and survival was examined using Cox proportional hazards models. The safety of conization and hysterectomy for women with adenocarcinoma was examined stratified by stage.

Results: A total of 3987 women including 988 (25%) with adenocarcinomas and 2999 (75%) with squamous cell carcinomas were identified. Stage IA1 tumors were noted in 554 (56%) of the women with adenocarcinomas and in 1610 (54%) of those with squamous neoplasms ($P=0.19$). Women with squamous cell carcinomas were more likely to undergo conization (26% vs 18%, $P<0.0001$) as definitive treatment. Nodal metastases were noted in 0.7% of women with stage IA1 adenocarcinomas compared with 3.3% of those with squamous tumors. Nodal disease was found in 0.8% of women with IA2 adenocarcinomas versus 2.8% of those with squamous carcinomas ($P=$ NS). In a multivariable model, adenocarcinomas were not associated with decreased survival for either stage IA1 (HR = 0.79, 95% CI = 0.21–2.94) or IA2 (HR = 0.51, 95% CI = 0.18–

1.47) carcinomas. Among women with stage IA1 adenocarcinomas, survival was equivalent for hysterectomy (five-year survival = 96.9%, 95% CI = 94.0–98.4%) and conization (five-year survival = 98.8%, 95% CI = 91.5–99.8%).

Conclusions: Survival for women with stage IA1 and IA2 cervical adenocarcinomas is favorable and similar to that of women with squamous cell carcinomas. A subset of women with microinvasive adenocarcinomas of the cervix may be candidates for less radical uterine-preserving treatment.

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Late toxicity of chemoradiotherapy: An underrecognized source of morbidity in survivors of locally advanced carinoma of the uterine cervix

K. Moxley, L. Syzek, J. Walker, K. Moore, L. Landrum, D. McMeekin, R. Mannel
University of Oklahoma, Oklahoma City, OK

Objective: The purpose of this study was to identify the incidence of treatment-related toxicity occurring more than six months from the completion of combination chemoradiotherapy in patients with cervical cancer.

Cervical cancer patients (stage IB2 and greater) treated at the University of Oklahoma from 1998 to 2006 with cisplatin-based chemotherapy in combination with radiation therapy were identified. Demographic data, treatment received and outcome data were abstracted from the medical records. Toxic effects occurring longer than six months from the completion of therapy, such as chronic pain, bladder and bowel dysfunction, lymphedema and fistula formation were recorded. Surgical interventions for palliation of therapeutic toxic effects were also documented.

Results: A total of 145 patients received concomitant chemoradiotherapy. Of these, 41% were enrolled in a clinical trial. The overall recorded late toxicity rate was 25%. Additionally, 20 patients had undergone radical hysterectomy prior to combined chemoradiotherapy, and the observed late toxicity rate in this subset was also 25%. In the entire cohort, 2% of patients required exenteration for palliation of their toxic effects, and there was a 25% recurrence rate across all stages.

Conclusions: There is significant toxicity associated with combined chemoradiotherapy. However, across the majority of contemporary oncologic studies, there are inconsistencies with the recording of late-onset toxic effects. This makes it almost impossible to ascertain the actual risk of encountering even high-grade late toxicity in our patients and makes it difficult to appropriately counsel them on the true risks of their therapy.

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Lifestyle modification in cervical cancer survivors: An ongoing need

M. Schlumbrecht, C. Sun, S. Westin, F. Zandstra, C. Tung, K. Denton, H. Rhodes, E. Garcia, C. Levenback, D. Bodurka
University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: With the introduction of multimodality therapy for cervical cancer, many women will be long-term survivors in need of comprehensive surveillance care. Lifestyle modifications are critical components of such care. Our goal was to evaluate patterns of obesity and smoking in a cohort of cervical cancer survivors, and to assess the potential influence of these comorbidities on subsequent follow-up.

We reviewed the records of patients treated for invasive cervical cancer at our institution from 2000 to 2003 who had no evidence of disease ≥ 3 years. Demographic and clinical data were collected, including smoking history and anthropometric measurements. BMI was categorized according to World Health Organization criteria. Logistic regression, Wilcoxon signed rank test, and χ^2 analyses were performed.

Results: Two hundred ninety-eight women had complete follow-up data at three years. The median age at diagnosis was 43.5 years (range: 17.6–87.1). Fifty-five percent (55%) were white, 30.2% were Hispanic and 12.1% were African-American. Sixteen percent (16%) were treated with surgery alone; the remainder received chemoradiation. At diagnosis, 32.4% had a normal BMI, 28.7% were overweight, and 35.2% were obese compared with 31.7, 21.1, and 45.2% at 3 years, respectively. Of the 51 women whose BMI categorization changed, 33 (64.7%) had weight gain and 18 (35.3%) had weight loss. No women initially classified as obese changed BMI categories. By paired analysis, increase in BMI was significant over the 3-year interval ($P < 0.001$). At the time of diagnosis, only 15 of 103 obese patients received nutrition consults. Fifty-two patients actively smoked at diagnosis. Smoking cessation was discussed with 23 patients, but only two patients accepted referral to a tobacco cessation program. Compared with nonsmokers, current smokers had a greater number of consults to the pain service ($P < 0.001$). Although not statistically significant, patients who continued to smoke after initial diagnosis appeared to be at increased odds of needing gastrointestinal consults (current smoker: OR = 1.90, 95% CI = 0.94–3.83. $P = 0.07$; ever smoker: OR = 1.58, 95% CI = 0.80–3.11, $P = 0.19$).

Conclusions: Obesity and smoking are significant comorbidities that may complicate care in cervical cancer patients during the survivorship phase of the cancer continuum. Preemptive counseling regarding lifestyle modifications is crucial to reduce the sequelae associated with these detrimental health habits.

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Liquid-based cervical cytology in the detection of recurrence after treatment for cervical cancer

B. Rimel[1], A. Ferda[2], J. Erwin[3], S. Dewdney[1], L. Seamon[2], C. DeSimone[2], F. Gao[1], W. Huh[3], L. Massad[1]
[1]Washington University School of Medicine, St. Louis, MO, [2]University of Kentucky, Lexington, KY, [3]University of Alabama, Birmingham, AL

Objective: Cervical cytology is a standard component of follow-up protocols for women with treated cervical cancer, but the frequency and proper management of women with borderline cytology results are unclear. Our objective was to evaluate the utility of liquid-based cytology in detecting recurrent cervical cancer and to determine the utility of colposcopy and biopsy done for patients with abnormal, but not frankly malignant Paps after treatment.

A retrospective multi-institution study evaluating all patients from three member institutions treated for cervical cancer from January 1, 2000 to January 11, 2009 was performed. Following institutional review board approval, patients were identified through local cancer registries and patient databases. Patients were included who had at least one posttreatment liquid-based cytology or colposcopy. Patients were excluded for lack of follow-up or incomplete treatment data. Descriptive statistics were performed using SAS (SAS Institutes, Cary, NC).

Results: Four thousand one hundred sixty-seven cervical cytology results from 929 women meeting inclusion criteria were identified. Six

hundred twenty-six Paps (15%) from 312 (34%) women were abnormal. Most abnormal results were ASCUS (296, 47% of abnormals) or LSIL (179, 28%), with ASC-H in 59 (9%), HSIL in 55 (9%), AGC in 14 (2%), and favor neoplasia in 41 (6%). Median follow-up was 24.9 months, with a mean of 4.5 Paps per patient. Abnormal Paps led to 200 colposcopies in 135 women. Only 45 women had CIN 2+, with CIN 3 in 25 and cancer in 12. Only five of 475 (1%) women with ASCUS/LSIL had CIN 3. Cancer recurred in 147 women, with 12 (8.1%) detected by Pap; all but one had Pap results of ASC-H or worse, while one patient with ASCUS + HPV had a visible lesion on return for assessment two months after Pap. Colposcopy for cytology less than HSIL without a visible lesion on exam did not detect any recurrence or CIN 3. Patients treated with radiation therapy had a higher incidence of abnormal Paps (19%), compared with those treated with surgery alone (9%, P = NS), but was not statistically significant.

Conclusions: A third of cervical cancer survivors will have abnormal cytology, but the low yield of colposcopy and biopsy for cytology less than ASC-H suggests that in the absence of a visible lesion, those with ASCUS/LSIL can be followed without colposcopy unless abnormalities persist. Women with ASC-H, HSIL and other severe abnormalities deserve further evaluation.

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Multicenter study on fertility-sparing laparoscopic radical trachelectomy

J. Nam[1], W. Joo[2], S. Chang[3], H. Yoo[2], J. Park[1], M. Jeong[4], D. Kim[1], J. Kim[1], Y. Kim[1], Y. Kim[1]

[1]Asan Medical Center/University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Ulsan University Hospital/University of Ulsan College of Medicine, Ulsan, Republic of Korea, [3]Ajou University School of Medicine, Suwon, Republic of Korea, [4]University of Kyung-Hee School of Medicine, Seoul, Republic of Korea

Objective: The purpose of this study was to assess the efficacy and safety of laparoscopic radical trachelectomy (LRT).

We enrolled woomen with early-stage cervical cancer who wanted to preserve fertility from four institutions. Surgical techniques of all institutions were identical because all the surgeons had been trained at Asan Medical Center in Seoul, Republic of Korea. Demographic, clinicopathologic, surgical and follow-up data were obtained from patients' medical records. All patients agreed to telephone interviews to assess their pregnancy outcomes.

Results: Fifty-nine patients were enrolled as candidates for LRT. In five patients, LRT was abandoned during the operation because of lymph node metastasis or parametrial involvement on frozen section. In one patient, a laparotomy was performed because of a large vessel injury. Therefore, 53 patients underwent LRT. The median age was 29 years (range: 22–44). The median tumor size was 1.8 cm in diameter (range: 0.4–4). Median length of surgery was 290 minutes (range: 120–520); and median estimated loss of blood was 300 mL (range: 50–1000). Perioperative transfusion was required in 15 patients. Six patients received adjuvant treatment. There was one vesicovaginal fistula after surgery. Median follow-up was 31 months (range: 7–70). There were two recurrences and one death from disease. Sixteen patients attempted to conceive. Eight patients succeeded in pregnancy, and three patients delivered healthy babies.

Conclusions: This large-scale multicenter study shows that LRT may be a safe and useful alternative to radical hysterectomy for women with early cervical cancer who want to preserve their fertility.

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Oncologic outcomes of radical trachelectomy at a single institution

C. Kim, N. Abu-Rustum, D. Chi, G. Gardner, M. Leitao, R. Barakat, Y. Sonoda

Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The aim of the study was to describe the oncologic outcomes of patients undergoing fertility-preserving radical trachelectomy for early-stage cervical cancer.

We performed a retrospective review of all patients with early-stage cervical cancer who underwent planned radical trachelectomy and pelvic lymphadenectomy at our institution from November 2001 to September 2010. Radical trachelectomy was performed by either an abdominal (RAT), vaginal (RVT) or robotic approach (RRT). Patient and pathologic characteristics were extracted.

Results: A total of 105 patients were identified who underwent attempted radical trachelectomy: 49 RAT, 52 RVT, and 4 RRT. The median age of all patients was 32 (range: 6–45). Overall, 76 (72%) did not require immediate radical hysterectomy and/or adjuvant therapy. Sixteen (15%) patients had a radical hysterectomy based on intraoperative findings. Thirteen (12%) patients had a trachelectomy but required adjuvant chemoradiation based on final pathology results. Preoperative stages included: 12 stage IA1 (12%), 12 stage IA2 (12%), and 81 stage IB2 (77%). Final histologies included 49 adenocarcinomas, one adenocarcinoma with neuroendocrine features, eight adenosquamous cancers, 45 squamous cancer, pne case of sarcoma botryoides, and one case of solitary fibrous tumor. The median follow-up was 29 months (range: 0.1–99.8). Of all patients who underwent a successful radical trachelectomy, one patient recurred and died of disease 24 months after surgery. Two patients expired from nononcologic causes. All other patients are alive and without evidence of disease. Nine (9%) of 105 patients required an intervention for perioperative complications.

Conclusions: Among patients who are offered radical trachelectomy, the majority are able to undergo the procedure successfully. These results provide additional evidence of the oncologic safety of this procedure. Radical trachelectomy should continue to be an option for patients with early-stage cervical cancer desiring fertility preservation.

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Oncologic outcomes of “cut through” radical trachelectomy for early-stage cervical cancer

Y. Sonoda, D. Chi, G. Gardner, M. Leitao, J. Carter, R. Barakat, N. Abu-Rustum

Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The aim of this study was to report the oncologic outcomes of patients who underwent a "cut through" radical trachelectomy (CTRT) with immediate completion radical hysterectomy (ICRH) for early-stage cervical cancer.

From November 2001 to October 2010, all patients who underwent an attempted fertility-sparing radical trachelectomy with lymph node dissection were identified. CTRT was defined when patients were intraoperatively found to have a positive endocervical margin on the trachelectomy specimen and underwent an ICRH. A positive endocervical margin was defined as the presence of invasive or in situ carcinoma. Patients were prescribed adjuvant chemoradiation if the final pathology revealed a positive lymph node, positive parametrial spread, or a positive parametrial or vaginal margin. Adjuvant therapy

was also prescribed based on final local tumor factors, namely, deep stromal invasion, lymphatic space involvement and tumor size.

Results: One hundred five attempted radical trachelectomies were performed during the study period. Ten (9.5%) patients were intraoperatively found to have a positive endocervical margin and underwent an ICRH. The median age was 32.5 years (range: 27–38). Nine (90%) were nulliparous, and one had one child. Nine (90%) patients were FIGO stage IB1, and one (10%) was IA2. Five patients had an attempted radical abdominal trachelectomy, and five had an attempted radical vaginal trachelectomy. Six (60%) patients had adenocarcinomas, two (20%) had adenosquamous carcinoma, and two (20%) had squamous carcinoma. Eight (80%) patients had invasive carcinoma at the endocervical margin, and two had adenocarcinoma in situ. Four (40%) patients were prescribed adjuvant therapy for the following reasons: two for a positive lymph node and two for final local tumor factors. With a median follow-up of 26 months (range: 3–48), all patients remain disease free.

Conclusions: Attempted radical trachelectomy with immediate completion radical hysterectomy did not appear to compromise oncologic outcomes in this patient population. These results may be useful when considering and counseling patients prior to radical trachelectomy.

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Outcomes of surgery for stage IB cervical cancer: Variations between squamous and adenocarcinoma histology

E. Tanner, A. Iasonos, A. Kostolias, W. Tew, Q. Zhou, K. Park, K. Alektiar, R. Barakat, N. Abu-Rustum
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The purpose of this study was to evaluate the impact of histology on outcomes in patients with surgically treated FIGO stage IB carcinoma of the cervix.

A prospectively maintained cervical carcinoma database was used to identify all patients with stage IB cervical carcinoma treated with primary surgery at our institution from January 1982 to January 2010. Age, stage, histology, grade, tumor size, parametrial extension, lymphovascular space invasion (LVSI) and adjuvant therapy were abstracted. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier method. Univariate analysis was performed using either the log-rank test for categorical variables or the Wald test based on Cox regression for continuous variables.

Results: We identified 409 patients with stage IB cervical carcinoma, 209 (51%) with squamous carcinoma (SC), and 200 (49%) with adenocarcinoma (AC). The median age was 42 years for SC versus 40 years for AC ($P=0.012$). Median tumor diameter (1.8 cm), stage (IB1 90%, IB2 10%), procedures performed (radical hysterectomy 80%, radical trachelectomy 18%, simple hysterectomy 2%), and median lymph nodes removed (pelvic 25, range: 0–71; paraaortic one, range: 0–69) were equivalent in patients with SC and those with AC. The proportion of positive lymph nodes was 16.3% in patients with SC versus 8.5% in patients with AC ($P=0.024$). The rates of poor prognosis features in patients with SC versus those with AC were as follows: grade 3 tumors, 38.6% versus 19.3% ($P<0.001$); deep one-third stromal invasion, 36.0% versus 23.4% ($P=0.008$); LVSI, 37.8% versus 23.5% ($P=0.002$); and parametrial extension, 7.2% versus 1.5% ($P=0.007$). Adjuvant pelvic radiation therapy (RT) (9.8%), pelvic RT with chemosensitization (17.6%), and chemotherapy alone (2.4%) were given equally to patients with SC and AC. Among patients with SC, 15.8% recurred versus 7.1% among patients with AC ($P=0.006$). Isolated pelvic recurrences occurred in 72.7% of patients with SC versus 46.2% of patients with AC ($P=0.088$). Pelvic and distant recurrences occurred in 6.1% of patients with SC versus 38.5% of patients with AC ($P=0.022$). The overall five-year survival rate for the entire cohort was 90%. Five-year PFS was 80% for patients with SC and 90% for patients with AC (HR = 2.63, 95% CI = 1.59–4.76). Five-year OS was 86.7% for patients with SC and 95.2% for patients with AC (HR = 3.23, 95% CI = 1.59–6.67).

Conclusions: Surgically treated stage IB cervical SC was associated with a greater proportion of high-risk features and reduced PFS/OS versus stage IB AC. The patterns of recurrence for stage IB SC and AC lesions also differ. This may have implications for the choice of adjuvant therapy modalities for different histologies as local control strategies may be selected for SC lesions and systemic control strategies for AC.

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Overall survival after pelvic exenteration for recurrent or persistent cervical cancer

S. Westin, V. Rallapalli, D. Urbauer, M. Frumovitz, L. Ramondetta, D. Bodurka, P. Ramirez, P. Soliman
University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: Historically, five-year survival after pelvic exenteration for cervical cancer has been reported to be as high as 50–60%. Given the significant improvement in upfront therapy for cervical cancer over the last 20 years, we hypothesized that survival after exenteration may have changed. The objective of this study was to determine overall survival after pelvic exenteration and evaluate factors impacting this outcome.

A retrospective review of all women who underwent pelvic exenteration at our institution between February 1993 and June 2008 was performed. Demographics, treatment details, pathologic information, and vital status were obtained from the medical record. Overall survival was defined as time from exenteration to date of death or last contact. Survival analysis was performed using the Kaplan–Meier method.

Results: Seventy-six patients with cervical cancer underwent pelvic exenteration during the study period. Median age was 49.8 years (range: 25–77); 60% of patients were white and 33% were Hispanic. Median body mass index was 27.6 kg/m^2, and median treatment-free interval was 18 months. Three patients who died of a surgery-related complication within the first 30 days were excluded from survival analyses. Overall five-year survival was 31.5%. Factors that negatively impacted overall survival included treatment-free interval less than 18 months ($P=0.003$), lymphovascular space invasion ($P=0.002$), perineural invasion ($P=0.05$), BMI <25 kg/m^2 ($P=0.033$), and primary tumor size >5 cm ($P=0.06$). Among patients treated with primary radiation therapy, concurrent chemotherapy was associated with lower overall survival compared with patients treated with radiation alone, although this did not reach statistical significance (20 months vs 53 months, $P=0.08$). In multivariate analysis, treatment-free interval <18 months and BMI <25 kg/m^2 retained a significant negative impact on survival.

Conclusions: Five-year survival after pelvic exenteration for recurrent cervical cancer was worse than previously reported. Multiple factors at the time of exenteration were associated with adverse survival outcome. Although changes in upfront treatment of cervical

cancer have improved survival, patients who receive chemoradiation may have a poor prognosis after pelvic exenteration.

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Oxygenation in cervical cancer and normal uterine cervix assessed using BOLD MRI: Initial experiences

J. Lea, R. Hallac, Y. Ding, Q. Yuan, R. McColl, D. Sims, P. Weatherall, R. Mason
University of Texas Southwestern Medical Center, Dallas, TX

Objective: Prognosis is particularly poor for patients with cervical cancer who present with large hypoxic tumors. Although tumor size can be assessed noninvasively, invasive electrodes have been required to measure oxygenation. A noninvasive assessment would be particularly attractive to patients and physicians and potentially could allow the design of personalized treatment regimes. BOLD (blood oxygen level-dependent) contrast MRI is a noninvasive technique sensitive to tumor vascular oxygenation. Deoxyhemoglobin causes T2* shortening, and the signal change accompanying an oxygen breathing challenge can indicate vascular oxygen dynamics. We sought to evaluate the feasibility of measuring cervical tumor oxygenation using a noninvasive technique with BOLD MRI.

A 3-T Phillips Achieva MR scanner and a multichannel phased-array surface coil were used to evaluate three normal volunteers and nine patients with stage IIB–IVA cervical cancer following institutional review board-approved consent. Dynamic T2*-weighted MRI and T2* maps were acquired using a multi-echo sequence, while subjects breathed air for two minutes followed by oxygen (15 L/min) and in some cases return to air. In addition, first-pass perfusion MR images were used to investigate tumor vascularity.

Results: BOLD MRI provided good-quality data both for patients ($n=9$) and for normal volunteers ($n=3$). T2*-weighted signal intensity (SI) was measured for iliacus muscle, normal uterus, normal cervix, and cervical tumor. Muscle showed a minimal response (ΔSI) to oxygen for both patients and healthy volunteers ($5.4\pm4.3\%$), whereas normal uterus showed a larger ΔSI ($18.1\pm10.3\%$). In addition, normal cervix showed a significant BOLD response ($18.7\pm11.5\%$). Baseline T2*-weighted signal intensity was stable in cervical cancers, but increased to variable extents (up to 20% ΔSI) on O_2 breathing.

Conclusions: This preliminary study demonstrates BOLD MRI is feasible for noninvasive examination of oxygenation changes in cervical cancer in response to hyperoxic gas breathing. Additional patients are currently being evaluated and followed clinically to assess the prognostic value of the observations. A noninvasive imaging technique to assess tumor hypoxia could help in selecting optimized treatment regimens in advanced cervical cancer.

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Preoperative neutrophil/lymphocyte ratio as a prognostic factor in patients with early cervical cancer treated with radical hysterectomy

Y. Lee, C. Choi, H. Park, T. Song, M. Kim, T. Kim, J. Lee, J. Lee, D. Bae, B. Kim
Samsung Medical Center, Seoul, Republic of Korea

Objective: This retrospective study evaluated the prognostic value of the neutrophil/lymphocyte ratio (NLR) in patients with early cervical cancer who were treated with radical hysterectomy.

Patients with clinically staged early cervical carcinoma (IB–IIA) who underwent type III radical hysterectomy and bilateral pelvic lymph node dissection with or without adjuvant therapy (radiation alone or concurrent chemoradiation) at Samsung Medical Center, Seoul, Republic of Korea, from 1996 to 2007 were retrospectively enrolled. We collected data from electronic medical records, including patients' basal characteristics, laboratory results and pathology reports.

Results: We enrolled 745 patients with early cervical cancer who had undergone radical hysterectomy in the present study. The cutoff value of NLR to stratify survival differences of the cohort was 2.0. When the cohort was divided according to this cutoff value, the higher NLR group (≥2.0) was younger in age and had larger tumors and lower incidence of positive resection margins than the lower NLR group (<2.0). There were no differences between the two groups based on stage, treatment, lymph node status, cell type, microscopic parametrial invasion, deep tumor invasion or lymphovascular space invasion. In multivariate analyses, preoperative NLR (≥2.0), stage, cell type and lymph node status were identified as independent risk factors for survival.

Conclusions: Preoperative NLR (≥2.0) was an independent predictor of survival after radical hysterectomy in patients with early cervical cancer and may be a cost-effective biomarker to stratify patients at high risk of recurrence and death in early cervical cancer as well as stage and lymph node status.

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Primary human papillomavirus screening with secondary VIA followed by cryotherapy

D. Starks[1], L. Nieves-Arriba[1], C. Enerson[2], S. Belinson[3], J. Brainard[1], A. Chiesa-Vottero[1], J. Belinson[1]
[1]The Cleveland Clinic, Cleveland, OH, [2]Prueba para la vida A.C, Morelia, Mexico, [3]Preventive Oncology International, Cleveland, OH

Objective: The aim of this study was to follow up the results of patients with high-risk human papillomavirus (HPV) who were subsequently triaged to secondary screening with VIA followed by cryotherapy in Mexican Cervical Cancer Screening Trial II (MECCS II). Our objective was to determine the effectiveness of triage VIA after primary HPV screening for prevention of undertreatment when performing cryotherapy prior to biopsy confirmation.

In MECCS II, participants were nonpregnant women aged 30–50, variable with no prior hysterectomy or pelvic irradiation. All obtained a self-sample using the fourth-generation POI/NIH brush. The sample was placed in PreservCyt for the high-risk HPV assays (HC-II and APTIMA). Two direct cervical samples were obtained for cytology, HC-II and APTIMA. Subjects positive on any test were recalled. At the second visit, triage VIA was used to identify preinvasive disease too large for the cryoprobe (greater than three-quadrant disease) or cancer. All patients then underwent colposcopy using the POI protocol of directed and random biopsies. All subjects eligible by VIA triage were treated with cryotherapy. Prior to cryotherapy, biopsies were obtained. All patients treated with cryotherapy were requested to return in 6 months. At six months, a direct sample was obtained for cytology, HC-II, and APTIMA. All subjects who had abnormal biopsies prior to cryotherapy or whose cervix appeared abnormal underwent colposcopy and were re-biopsied.

Results: Two hundred ninety-seven patients had cervical abnormalities detected by VIA and received cryotherapy. Two hundred twenty-nine patients were followed up at 6 months. The median age was 38.8 years (range: 30–53). Median parity wasthree3 live births (range: 0–14). Median number of sexual partners was one (range: 1–70). Twenty-one (9.1%) patients reported tobacco use. One hundred eighty-one (78.35%) were married. Eighty-eight (38.4%) patients reported no use of contraception. Prior to cryotherapy 30 patients (10%) had cervical intraepithelial neoplasia ≥ 2 ($\geq$CIN 2), 15 (50%) had a positive endocervical curettage (ECC), and two (6.7%) had three-quadrant or greater disease on VIA. At the six-month follow-up, only five (1.7%) patients had $\geq$ CIN 2 disease. Eleven of 15 (73%) patients with a positive ECC returned at six months after cryotherapy, two had been referred in the interim, one had a hysterectomy, and one patient was lost to follow-up. Two of 11 (40%) were ECC positive, and no patients had three-quadrant or greater disease.

Conclusions: VIA triage is not an effective method for evaluating the endocervix for high-grade lesions. Cryotherapy is a low-cost, effective means of treating high-grade cervical lesions in a low-resource setting.

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Prognostic value of metabolic tumor volume measured by FDG-PET/CT in patients with cervical cancer

H. Chung, J. Eo, K. Han, S. Kang, K. Kang, J. Kim, N. Park, Y. Song
Seoul National University College of Medicine, Seoul, Republic of Korea

Objective: The purpose of the study was to determine if preoperative metabolic tumor volume (MTV) measured by integrated [^{18}F] fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (FDG-PET/CT) imaging has prognostic value in patients with cervical cancer.

Patients with FIGO stage IB to IIA cervical cancer were imaged with FDG-PET/CT before radical surgery. MTV was measured from the attenuation-corrected FDG-PET/CT images using a standard uptake value (SUV)-based automated contouring program. We evaluated the relationship of MTV to disease-free survival.

Results: A total of 63 patients were included in the study. The cutoff value for predicting recurrence was determined using a receiver operating characteristic curve. MTV in this study was found to be correlated with lymph node metastasis, parametrial involvement, FIGO stage, and SUV_{max}. In univariate analysis, MTV $\geq$ 23.4 mL (HR = 1.017, 95% CI = 1.005–1.029, $P = 0.004$), $SUV_{max} \geq 9.5$ (HR = 5.198, 95% CI = 1.076–25.118, $P = 0.04$), lymph node metastasis (HR = 12.338, 95% CI = 1.541–98.813, $P = 0.018$), parametrial involvement (HR = 14.274, 95% CI = 1.785–114.149, $P = 0.012$), and lymphovascular space invasion (HR = 8.871, 95% CI = 1.104–71.261, $P = 0.04$) were related to disease-free survival. In multivariate analyses, age (HR = 0.748, 95% CI = 0.587–0.952, $P = 0.018$) and MTV $\geq$ 23.4 mL (HR = 49.559, 95% CI = 1.257–1953.399, $P = 0.037$) were determined to be independent prognostic factors of disease-free survival.

Conclusions: Preoperative metabolic tumor volume is an independent prognostic factor for disease-free survival in patients with cervical cancer treated with radical surgery.

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Prospective evaluation of PET/CT for lymph node status in FIGO stage IB–IIA cervical cancer

K. Lee[1], S. Lim[1], S. Cheon[1], S. Park[2], C. Park[1]
[1]Gil Medical Center/Gachon University of Medicine & Science, Incheon, Republic of Korea, [2]Gangnam Sacred Heart Hospital/Hallym University, Seoul, Republic of Korea

Objective: The goal of this study was to estimate the sensitivity and specificity of [^{18}F]fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) for detecting lymph node metastases in patients with FIGO stage IB–IIA cervical cancer before radical surgery.

Patients with newly diagnosed FIGO stage IB–IIA cervical cancer scheduled for radical surgery, including bilateral pelvic lymphadenectomy with or without paraaortic lymphadnectomy, were eligible. The imaging, operative and pathologic findings for each patient and each nodal site were compared.

Results: One hundred forty women were included in the study. Thirty-three (23.6%) patients had metastatic pelvic lymph nodes, and one patient with abmetastatic pelvic lymph node had abmetastatic paraaortic lymph node. The mean number of pelvic lymph nodes retrieved was 48.2 ± 17.8 (range: 23–100), and the mean number of paraaortic nodes was 9.7 ± 6.4 (range: 1–32). The overall patient-based sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FDG-PET/CT were 45.5, 87.9, 53.6, 83.9, and 77.9%, respectively. The histologically confirmed metastatic paraaortic lymph node of one patient was negative on FDG-PET/CT.

Conclusions: Pathologic validation of FDG-PET/CT imaging demonstrated its low sensitivity and high specificity in patients with early-stage cervical carcinoma.

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Regionalization of gynecologic cancer care for African-Americans with cervical cancer: Does it benefit this subset of patients?

D. English[1], K. Brookfield[1], E. Schroeder[2], M. Cheung[1], S. Schuman[2], L. Koniaris[1]
[1]University of Miami/Jackson Memorial Hospital, Miami, FL, [2]University of Miami Sylvester Cancer Center, Miami, FL

Objective: The literature describing the relationship between survival and hospital volume and teaching status for gynecologic malignancies has focused primarily on ovarian cancer. We sought to determine whether regionalization of cervical cancer care is associated with improved survival benefits for African-American women.

The 2007 Florida Cancer Data System (FCDS) data set was used to identify all incident cases of cervical cancer diagnosed in African-American women in the state of Florida from 1990 to 2000. Overall survival rates were calculated using the Kaplan–Meier method for patients undergoing surgical intervention at high-volume centers (HVCs), intermediate-volume centers (IVCs), low-volume centers (LVCs), teaching facilities (TFs) and nonteaching facilities (NTFs).

Results: Overall, we identified 1911 cases of cervical cancer in African-American women. Of these, 26.6% were being treated at TFs and 16.1% at NTFs. Overall five-year survival for African-American women with cervical cancer was 54.2%. Five-year survival for African-American women treated at TFs was 61.7% versus 49.8% for those at NTFs ($P < 0.01$). Five-year survival for African-American women treated at HVCs versus IVCs versus LVCs was 56.7% versus 55.7% versus 47.5% ($P < 0.01$).

Conclusions: African-American women with cervical cancer demonstrated improved five-year survival when treated at teaching facilities and high-volume centers.

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Risk factors for fistula formation in patients with cervical cancer treated with radiation therapy include postradiation biopsy

J. Feddock, C. DeSimone, M. Kudrimoti, L. Baldwin, H. Weiss, M. Randall
University of Kentucky Medical Center, Lexington, KY

Objective: The aim of this study was to review our institutional experience with patients with cervical cancer treated with radiation therapy (RT) to determine risk factors associated with fistula development.

A retrospective review was performed evaluating 495 patients treated for cervical cancer with surgery, chemotherapy, or radiation therapy at our institution between 1997 and 2010. Of the subset of patients treated with curative-intent radiation therapy, with or without chemotherapy, 24 were diagnosed with a fistula either at presentation, as a result of treatment, or in association with recurrent tumor.

Results: The median duration of follow-up was 55 months. Of the 24 patients who developed fistulas, two had enterovaginal fistulas, seven had vesicovagina fistulasl, eight had rectovaginal fistulas, and seven developed both vesicovaginal and rectovaginal fistulas. Six fistulas were present at the time of diagnosis, 12 were treatment related, and six were due to recurrent disease. The median age was 46; 58.3% or patients were smokers, 75% were white/Caucasian and 25% were African-American. All patients had bulky tumors, with 83.3% presenting with FIGO stage III/IV disease. High-grade histology and lymphovascular space invasion were present in 50 and 66.7%, respectively. The median radiation dose delivered to point A was 84 Gy, the median rectal dose was 66.8 Gy, and the median bladder dose was 70.25 Gy. Factors predictive of development of a fistula on multivariate analysis were high rectal dose >70 Gy ($P=0.022$), advancing tumor stage ($P=0.0009$), and African-American race ($P=0.033$). Among the 12 patients who developed a treatment-related fistula, nine (75%) underwent a negative biopsy preceding fistula development by a median 4.65 months. The median interval between treatment completion and development of fistula differed depending on whether the fistula was due to treatment toxicity, 13.1 months, or recurrent disease, 8.5 months.

Conclusions: Risk factors for fistula development identified in this series are similar to those reported in other published series. However, what is striking in our data is the frequency of biopsies prior to fistula development in patients with no tumor. Seventy-five percent of the patients who developed a toxicity-related fistula underwent a biopsy with no cancer seen within the six months preceding their fistula. Caution should therefore be taken when performing biopsies postradiation in patients with cervical cancer.

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The effectiveness of neodjuvant chemotherapy in cervical cancer stage IIB

B. Askandar, C. Santoso
Airlangga University Hospital, Surabaya, Indonesia

Objective: The goal of this study was to analyze the effectiveness of neoadjuvant chemotherapy in cervical cancer stage IIB in large samples.

All patients with cervical cancer stage IIB from 2006 to 2009 were collected. All patients had been given paclitaxel–carboplatin and PVB (cisplatin, vinblastine, bleomycin) for three cycles before being reexamined for operability. Operability was based on the evaluation of parametrium involvement. If the parametrium was free of tumor, the patient was categorized as operable.

Results: Four hundred seventeen patients were analyzed; 274 patients were given PVB and 143 patients were given paclitaxel–carboplatin. Forty patients in the PVB group became operable after three cycles (14.6%) and 32 patients in the paclitaxel–carboplatin group became operable after three cycles (22.4%); the difference was not significant ($P=0.063$). For small tumors (<4 cm), PVB and paclitaxel–carboplatin did not differ in effectiveness ($P=0.56$, χ^2). For large tumors (>4 cm), paclitaxell–carboplatin was more effective than PVB in making the tumor operable ($P=0.025$, χ^2).

Conclusions: Paclitaxel–carboplatin and PVB did not differ in effectiveness in cervical cancer stage IIB. Paclitaxel–carboplatin was more effective than PVB for large tumors (>4 cm).

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Type-specific Tem-PCR versus Hybrid-Capture II for the detection of human papillomavirus

E. Campian, B. Jarnagin, S. Mahadasyam, J. Tatalovich
Center for Pelvic Health, Franklin, TN

Objective: A novel Tem-PCR technology from Diatherix can detect and type 21 high-risk and 4 low-risk human papillomavirus (HPV) types in a single test. The objective was to evaluate Tem-PCR for the detection of type-specific HPV in the cervix as it compares with the Digene Hybrid Capture 2 assay (HC2).

Women at a community clinic, aged 16 years or older, who presented for routine Pap smear or colposcopy, were asked to participate in the study. Cervical swabs were analyzed for the presence of high-risk HPV by both Tem-PCR and Hybrid Capture II. The presence of high-risk HPV was correlated with Pap smear and biopsy results. Confirmatory DNA sequencing was performed on 21 Tem-PCR-positive high-risk HPV samples.

Results: Of the 151 women who had Tem-PCR samples, 143 had HC2 samples, 136 had Pap smear results, and 43 had cervical biopsies. Tem-PCR identified 57.58% more high-risk HPV samples than HC2 (52 samples vs 33 samples, $P<0.01$). Sensitivity of Tem-PCR for the detection of HGSIL was 84.62% (95% CI = 53.66–97.29%) with a negative predictive value (NPV) of 97.65% (90.96–99.59%). Sensitivity of HC2 for HGSIL was 84.62% (53.66–97.29%) with a NPV of 98.08% (92.55–99.67%). Sensitivity of Tem-PCR for the detection of cervical intraepithelial neoplasia (CIN) 3 and above was 100.00% (69.87–100.00%) with a NPV of 100.00% (67.86–100.00%). Sensitivity of HC2 for $\geq$ CIN 3 was 91.67% (59.75–99.56%) with a NPV of 95.00% (73.06–99.74%). Sensitivity of Tem-PCR for the detection of $\geq$ CIN 2 was 95.00% (73.06–99.74%) with a NPV of 90.91% (57.12–99.52%). Sensitivity of HC2 for the detection of $\geq$ CIN 2 was 90.00% (66.87–98.25%) with a NPV of 90.00% (66.87–98.25%).

Conclusions: Tem-PCR has a higher sensitivity for the detection of high-risk HPV than the Hybrid Capture 2 assay. Cervical sampling with Tem-PCR has an excellent sensitivity and negative predictive value for the presence of moderate and severe cervical dysplasia.

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Clinical Trials - Cervix Phase II/III

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MECCS II: Primary screening for cervical cancer with an mRNA human papillomavirus assay

L. Nieves-Arriba[1], S. Belinson[2], C. Booth[1], J. Brainard[1], A. Chiesa-Vottero[1], C. Enerson[3], A. Perez[3], Z. Sun[1], J. Belinson[1]
[1]*The Cleveland Clinic, Cleveland, OH,* [2]*Preventive Oncology International, Cleveland Heights, OH,* [3]*Prueba para la Vida, Morelia, Mexico*

Objective: The primary objective of Mexican Cervical Cancer Screening Trial II (MECCS II) was to design a highly sensitive and highly specific screening program able to be adapted to all socioeconomic levels in the state of Michoacán, Mexico. A secondary objectives was to determine the comparative sensitivity and specificity of primary human papillomavirus (HPV) screening using the Gen-Probe Aptima HPV Assay for the detection of high-grade precancer and cancer of the cervix.

The MECCS II trial was conducted in Patzcuaro and Zitacuaro, Michoacán, Mexico. Women aged 30–50 who were not pregnant, had varied histories of screening, and had no history of hysterectomy or pelvic irradiation participated. The sample was submitted to direct testing: cytology, HC-II, and Gen-Probe APTIMA HPV Assay (AHPV). Subjects positive on any test were recalled for further evaluation and treatment. This report focuses on the results of the direct testing (cytology, HC-II, and AHPV). Complete results were obtained for 2057 patients.

Results: Two thousand ninety-six patients have complete results. Mean age (SD) was 39.2, 8.6% were smokers, and 84.7% were married/cohabiting. Cytology results revealed >ASCUS in 7.7%; >LGSIL in 1.8%; and >HGSIL in 0.5%. Final biopsy revealed >CIN 2 in 2.1% and >CIN 3 in 0.77%. The sensitivity of ThinPrep ≥ASCUS, HC-II, and AHPV for >CIN 2 was 73.2, 81.4, and 76.7%, respectively (N.S). The specificity of ThinPrep >ASCUS, HC-II, and AHPV for >CIN 2 was 94.9, 92.6, and 93.8%, respectively (N.S.); for >CIN 3, specificity was 98.5, 91.0, and 93.0%, respectively (N.S.). The overall percentage of agreement among HPV assays (HC-II vs Aptima) was 97%. A receiver operating characteristic (ROC) curve comparing the accuracy of the two HPV tests (HC-II and Aptima) showed no difference in the area of clinical relevance. The ROC graph revealed no diagnostic differences in the performance of the assays.

Conclusions: These data demonstrate the diagnostic equivalence of the technologies reported.

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Phase II study of adjuvant chemotherapy following concurrent chemoradiation using paclitaxel and carboplatin in cervical cancer: A preliminary report

D. Suh[1], H. Kim[1], M. Kim[1], H. Chung[1], H Kim[1], J. Kim[1], S. Kang[1], T. Lee[2], H. Lee[3]
[1]*Seoul National University College of Medicine, Seoul, Republic of Korea,* [2]*Seoul National University Boramae Hospital, Seoul, Republic of Korea,* [3]*Konkuk University Hospital, Seoul, Republic of Korea*

Objective: We sought to determine the efficacy of adjuvant chemotherapy following concurrent chemoradiation (CCR) using paclitaxel and carboplatin in cervical cancer.

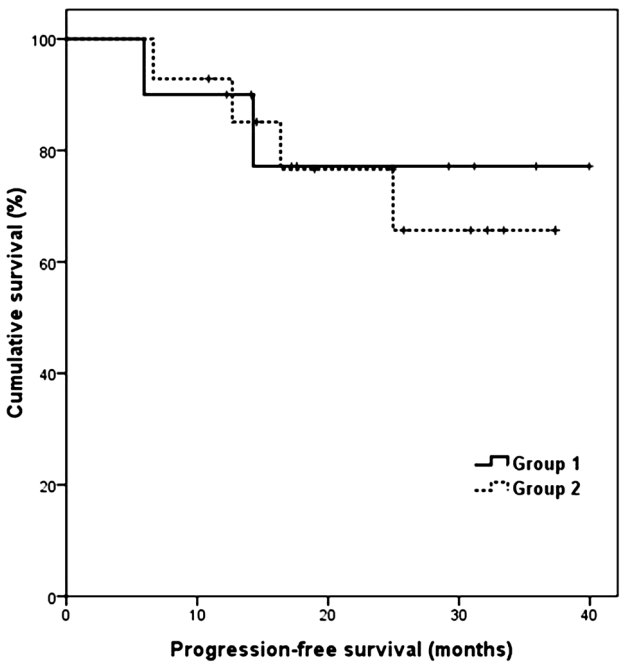
All 24 patients with FIGO stage IB1 to IVA cervical cancer were treated with CCR using paclitaxel (135 mg/m^2) and carboplatin (AUC 5.0) every three weeks. Then three cycles of adjuvant chemotherapy using paclitaxel (175 mg/m^2) and carboplatin (AUC 5.0) were administered every three weeks after CCR. Ten (group 1) and 14 (group 2) patients underwent primary surgery followed by CCR and primary CCR, respectively.

Results: Complete response rates were 100 and 71.4% in groups 1 and 2. Common grade 3 or 4 acute hematologic toxic effects were leukocytopenia (63.3 and 42.4%) and neutropenia (56.7 and 42.4%) in groups 1 and 2 among all cycles; these effects were manageable by supportive care. On the other hand, grade 3 or 4 acute nonhematologic toxic effects were peripheral neuropathy (6.7 and 10.2%) and constipation (8.3 and 1.7%) in groups 1 and 2. Moreover, grade 3 or 4 late complication rates were 10% (1/10) and 14.3% (2/14) in groups 1 and 2 (see table). The estimated three-year, progression-free survival rate was 77.1% (95% CI = 25.1–41.5%) and 65.7% (95% CI = 24.1–36.1%) in groups 1 and 2 (see figure).

Conclusions: Adjuvant chemotherapy after CCR using paclitaxel and carboplatin may be well tolerated and efficient despite the relatively common leukocytopenia and neutropenia, which can be controlled with conservative management. However, the efficacy of this treatment should be evaluated in large-scale clinical trials.

Grade 3 or 4 acute and late toxicity.

Toxic effect	Group 1 (60 cycles)	Group 2 (59 cycles)
Anemia	2 (3.3%)	5 (8.5%)
Leukocytopenia	38 (63.3%)	25 (42.4%)
Neutropenia	34 (56.7%)	25 (42.4%)
Thrombocytopenia	2 (3.3%)	2 (3.4%)
Nausea/vomiting	1 (1.7%)	1 (1.7%)
Hyponatremia	1 (1.7%)	0 (0%)
Hypokalemia	2 (3.3%)	1 (1.7%)
Diarrhea	2 (3.3%)	3 (5.1%)
Constipation	5 (8.3%)	1 (1.7%)
Fatigue	0 (0%)	1 (1.75%)
Peripheral neuropathy	4 (6.7%)	6 (10.2%)
Febrile illness	2 (3.3%)	1 (1.7%)



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Phase II study of belotecan (CKD-602) as a single agent in patients with recurrent or progressive carcinoma of the uterine cervix

J. Hwang, M. Lim, S. Seo, S. Park, S. Kang
Center for Uterine Cancer, Research Institute and Hospital, National Cancer Center, Goyang-si, Gyeonggi-do, Republic of Korea

Objective: A phase II trial was conducted to evaluate the efficacy and toxicity of belotecan (CKD-602), a topoisomerase I inhibitor, in persistent or recurrent carcinoma of the cervix.

Belotecan was administered at 0.5 mg/m^2/day for five consecutive days every 3-week cycle in patients with recurrent or progressive cervical carcinoma who were unsuitable candidates for curative treatment with surgery or radiotherapy.

Results: At the first stage of the trial, a total of 16 patients were entered on study. A median of three cycles were administered per patient (range: 1–7 cycles). Fourteen of 16 patients (87.5%) had received radiotherapy or chemotherapy prior to the study. The most frequently severe adverse events were anemia and neutropenia. Greater than grade 3 anemia and neutropenia were seen in 10 (23.8%) and 6 (14.3%) of 42 cycles, respectively. The incidence of nonhematologic toxicity was minimal. One patient died of treatment-related toxicity. There were no complete or partial responses to belotecan. The median overall survival was 12.38 months (95% CI = 9.71–15.04).

Conclusions: Belotecan was not active in the treatment of recurrent or progressive cervical cancer as a single agent. (ClinicalTrials.gov Identifier : NCT00430144).

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Gestational Trophoblastic Disease/Vulvar and Vaginal Cancers/Rare Tumors/Sarcomas

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A cost minimization analysis of first-line treatment strategies for low-risk gestational trophoblastic neoplasia

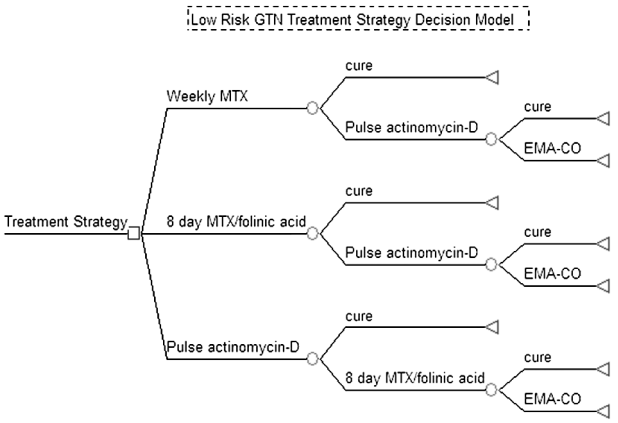
N. Shah, L. Barroilhet, R. Berkowitz, C. Feltmate, M. Muto, D. Goldstein, N. Horowitz
Brigham & Women's Hospital, Boston, MA

Objective: The aim of this study was to use decision modeling to determine the least costly first-line chemotherapy strategy for treating low-risk gestational trophoblastic neoplasia (GTN).

We created a decision analytic model of the three most commonly used first-line low-risk GTN treatment strategies, accounting for toxicity, response rates and need for second- or third-line therapy. These strategies included eight-day methotrexate (MTX)/folinic acid, weekly MTX and pulse actinomycin-D. Response rates, average number of cycles needed for remission and toxicity were determined by an extensive review of the literature. Costs of each strategy were examined from a societal perspective, including total treatment costs (medications, labs, professional fees), as well as lost production (foregone wages from work absence). Sensitivity analysis of these costs was performed using a cost minimization approach with the aid of decision tree software (TreeAge Pro 2009, TreeAge Inc).

Results: The relative costs of each strategy were influenced by average cycle number, response rate, and the associated inpatient stay required for administering second- or third-line multiagent chemotherapy. The average full societal costs of achieving cure are summarized in the table.

	Weekly MTX (30 –50 mg/m²)	8-day MTX (1 –1.5 mg/kg)	Pulse actinomycin-D (1.25 mg/m²)
Average number of cycles	6.15 (5.27 –8)	8.35 (5.5 –11.2)	4.4 (4 –4.8)
Response rate	68.2 (48 –81%)	85 (77.5 –90.6%)	86.2 (69 –100%)
Average cost of achieving cure	$8323	$3921	$5758



Conclusions: Over the range of experience regarding toxicity, required cycles, and response rates in the published literature, our model demonstrates that first-line treatment with eight-day MTX/folinic acid is consistently the least expensive strategy, and weekly MTX is consistently the most expensive. We recommend eight-day MTX/folinic acid as first-line treatment for low-risk GTN based on comparable efficacy rates and lower cost.

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Chemotherapy-based treatment in uterine carcinosarcoma

S. Rose, J. Spencer
University of Wisconsin, Madison, WI

Objective: The aims of this study were to compare overall survival and recurrence differences between patients with uterine carcinosarcoma who received chemotherapy-based treatment and those who received adjuvant radiation alone or no adjuvant therapy.

Following institutional review board approval, we conducted a retrospective chart review of all women seen in consultation at our institution with the diagnosis of uterine carcinosarcoma between 1987 and 2009. Data were collected on patient age, diagnosis date, primary surgery, FIGO stage, treatment details, dates of progression and death, and sites of first recurrence. Survival curves were generated using Kaplan–Meier analysis and compared using the log-rank test statistic.

Results: Seventy-five women with carcinosarcoma were identified. Three patients were excluded from the analysis (two for lack of follow-up and one for multiple, concurrent cancers). Of the remaining 72 patients, 30 (42%) had stage I, three (4%) had stage II, 19 (26%) had stage III, and 20 (28%) had stage IV disease. Thirteen (18%) patients received chemotherapy alone, 15 (20.5%) received chemotherapy in combination with radiation therapy, 30 (41%) received radiation alone, and 15 (20.5%) patients received no therapy. Of the 28 receiving chemotherapy-based treatment, 27 received platinum-based therapy and one received taxol alone. Interesting survival and progression-free trends favoring chemotherapy-based treatment were noted in stage I and stage III patients. No stage I patient who received chemotherapy-based treatment suffered a recurrence, and five-year survival for stage III patients receiving chemotherapy-based treatment was 44% versus 15% for those who did not. Overall survival and progression-free survival of the entire group, when adjusted for stage, revealed a significant advantage for those receiving chemotherapy-based treatment versus those receiving adjuvant radiation alone or no therapy ($P = 0.019$ and 0.006, respectively).

Conclusions: Our findings suggest that chemotherapy-based treatment benefits women with uterine carcinosarcoma. In particular,

further research into the role of chemotherapy in early stages of this disease is needed to better refine optimal treatment.

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Comparison of the new and old FIGO staging systems for vulvar carcinoma: A study of 4842 patients

A. Sultan[1], T. Kiet[1], R. Brooks[1], S. Ueda[1], L. Chen[1], D. Kapp[2], J. Chan[1]
[1]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, [2]Stanford University Medical Center, Stanford, CA

Objective: The purpose of this study was to validate the new FIGO staging for vulvar cancer.

Data from 1988 to 2007 were collected. Kaplan–Meier estimates and Cox regression models were used for statistical analyses.

Results: Of 4842 patients with vulvar cancer (median age: 70 years), whites, blacks and Asians constituted 88.8, 8.0, and 2.2% of patients. Using the new FIGO staging criteria, 56.4, 14.2, 21.9, and 7.6% had stage I, II, III, and IV disease. Grade 1, 2, and 3 tumors were found in 22.7, 42.0, and 18.7%, respectively. The five-year, disease-specific survival (DSS) was 72.2%. FIGO 2009 stage IB combined FIGO 1988 stages IB and II based on tumor size and stromal invasion. The five-year DSSs in FIGO 1988 stages IA, IB, and II were 97.1, 93.2, and 79.0%, compared with 97.1, 83.7, and 72.9% in FIGO 2009 staging ($P<0.001$). (see the table). Those with adjacent spread without nodal disease are now considered stage II rather than stage III, and those with adjacent spread and bilateral nodes are now stage III rather than stage IVA. With the limitations reported within our registry, the combined stage II, III, and IV survivals were 79.0, 62.4, and 30.3% using FIGO 1988 staging, compared with 72.9, 51.2, and 27.9% using FIGO 2009 ($P<0.001$). In stage III disease, the extent of nodal disease (1, 2, and ≥ 3 of positive nodes) predicted for worsened survival at 66.4% versus 49.1% versus 27.4%. On multivariate analysis, age, primary surgery, grade and stage were independent factors for improved survival.

Conclusions: Our data suggest that the FIGO 2009 criteria serve as better indicators of prognosis in subsets of patients with vulvar cancer. Stage, age, grade and surgery are independent prognosticators.

Patients with quamous cell vulvar cancer with complete staging data (i.e., stage, extension, lymph node, metastasis), $n=4842$.

	FIGO old, $P<0.001$		FIGO new, $P<0.001$	
	n (%)	5-Year DSS	*n* (%)	5-Year DSS
Stage I	1224 (25.3%)	94. ± 0.8%	2729 (56.4%)	86.0 ± 0.8%
IA	470 (9.7%)	97.1 ± 1.0%	470 (9.7%)	97.1 ± 1.0%
IB	754 (15.6%)	93.2 ± 1.2%	2259 (46.7%)	83.7 ± 0.9%
Stage II	1505 (31.1%)	79.0 ± 1.3%	687 (14.2%)	72.9 ± 1.9%
Stage III[1]	1570 (32.4%)	62.4 ± 1.4%	1061 (21.9%)	51.2 ± 1.8%
III(1)	– –	– –	504 (10.4%)	66.4 ± 2.4%
III(2)	– –	– –	232 (4.8%)	49.1 ± 3.9%
III(3)	– –	– –	325 (6.7%)	27.4 ± 3.1%
Stage IV	543 (11.2%)	30.3 ± 2.4%	365 (7.6%)	27.9 ± 2.8%
IV[2]	341 (7.0%)	37.3 ± 3.2%	163 (3.4%)	39.7 ± 4.5%
IVB	202 (4.2%)	17.9 ± 3.4%	202 (4.2%)	17.9 ± 3.4%

[1]Stage III divided based on node count (1, 2, ≥3). Data on size of lymph node metastasis not available.[2]Data on ulceration of LN not available.

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Disparities in treatment and survival between African-American and white women with vaginal cancer

H. Mahdi[1], S. Kumar[2], A. Munkarah[3], R. Hanna[4], D. Lockhart[1], H. Tamimi[1], R. Swensen[1], M. Doherty[5]
[1]University of Washington, Seattle, WA, [2]Mayo Clinic, Rochester, MN, [3]Henry Ford Health System, Detroit, MI, [4]University of North Carolina, Chapel Hill, NC, [5]Virginia Mason Medical Center, Seattle, WA

Objective: The purpose of this study was to compare the difference in treatment and survival between African-American and white women with vaginal cancer.

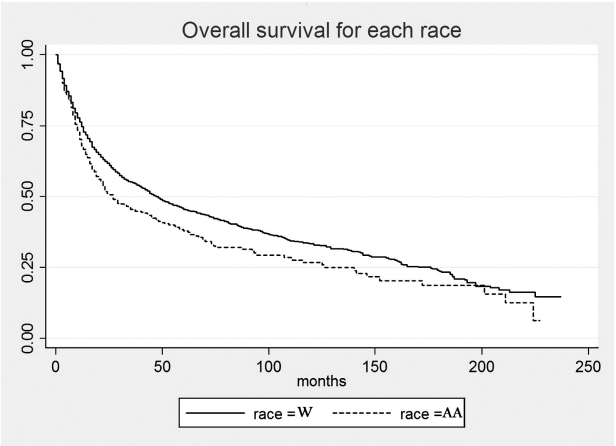
Patients with a diagnosis of invasive vaginal cancer were identified from the Surveillance, Epidemiology, and End Results Program (SEER) from 1988 to 2007, and were divided into white and African-American subgroups. Only patients with a diagnosis of squamous cell carcinoma (SCC) or adenocarcinoma (AC) were included. The Wilcoxon rank sum test, Kaplan–Meier survival methods and Cox regression proportional hazards were used for statistical analysis.

Results: A total of 2675 patients met the inclusion criteria, with the histologic distribution of 2190 (82%) SCCs and 485 (18%) ACs. There were 2294 (85.8%) white and 381 (14.2%) African-American women. Median age was 69 for white women and 65 for African-American women ($P<0.001$). SCCs and ACs were equally distributed between white and African-American women. Advanced-stage disease (FIGO III and IV) was more prominent in African-American than in white women (25.5% vs 19.5%, $P=0.019$). Radiation therapy was used equally in the two groups. However, surgical treatment alone or combined with radiation therapy was more frequent in white than in African-American women (27.67% vs 12.4%, $P<0.05$). The overall five-year survival was 45% for white and 39% for African-American women ($P=0.008$). In multivariate analysis, African-American women had significantly poorer survival compared with white women when controlling for age, histology, stage, grade, and treatment modality (HR = 1.2, 95% CI = 1.04–1.37, $P=0.02$) (see table and figure).

Conclusions: African-American women with vaginal cancer were more likely to present at a younger age and advanced stage and less likely to receive surgical treatment. Our data suggest that African-American race is an independent predictor of survival in patients with vaginal cancer.

Multivariate analysis displaying independent predictor of survival in patients with vaginal cancer.

Variable		HR	95% CI	*P* value
Age	>65	2.4	2.1–2.7	<0.001
Race	AA	1.2	1.04–1.37	0.016
Stage	II	1.5	1.3–1.7	<0.001
	III	2.1	2.1–2.7	
	IV	4.0	3.3–4.8	
Treatment	Radiation	0.6	0.5–0.7	<0.001
	Surgery	0.5	0.4–0.6	
	Combined	0.4	0.3–0.6	
Lymphadenectomy		0.7	0.6–0.9	<0.001
Nodal metastasis		2.1	1.5–2.95	<0.001



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Expression patterns of p53 and p21 cell cycle regulators and clinical outcome in women with pure gynecologic sarcomas

R. Voss, A. Suarez, R. Salani, D. Cohn, E. Eisenhauer
Ohio State University, Columbus, OH

Objective: Gynecologic sarcomas are aggressive malignancies associated with greater resistance to chemotherapy and poor prognosis. Trabectedin is an FDA-approved treatment for soft tissue sarcomas, and mutations in p53 and its downstream regulator p21 may be associated with increased effectiveness of this therapy. We set out to determine whether these p53 pathway mutations were associated with survival outcomes in patients with gynecologic sarcomas.

A retrospective review was performed to gather treatment and survival data on all patients receiving primary treatment for gynecologic sarcomas at our institution from 1991 to 2008. Patients with available sarcoma specimens were identified, and a tissue microarray (TMA) was created from these fixed embedded specimens that were randomly cored and selected. Specimens were stained with antibodies to p53 and p21 and scored for immunoreactivity by percentage of nuclear staining and staining intensity. Standard statistical tests were used to compare TMA results with clinical outcome, and hazard ratios were controlled for disease stage.

Results: Fifty-two patients had clinical data available, of whom 36 had pathologic specimens available for TMA. Stage was early in 21 of 36 (58%) and advanced in 15 of 36 (42%). With respect to histology, the specimens for TMA included 20 leiomyosarcomas (LMSs), nine endometrial stromal sarcomas, two adenosarcomas, and five undifferentiated or other sarcomas. There was no significant difference in p53 or p21 expression between LMSs and other sarcomas. However, p53 expression (p53+ tumors) was associated with higher rates of recurrence (HR = 2.7, 95% CI = 1.19–6.08) and death (HR = 2.5, 95% CI = 1.06–5.79). p21 expression trended toward more favorable disease-free and overall survival, but not to significance. Moreover, p53–, p21+ tumors were associated with the lowest risks for recurrence (HR = 0.2, 95% CI = 0.009–0.61) and death (HR = 0.3, 95% CI = 0.13–0.87). The median overall survival for patients with p53–, p21+ sarcomas was five years versus one year for patients with other expression patterns.

Conclusions: Dysregulation of cell cycle regulators p53 and p21 confers a worse prognosis in gynecologic sarcomas. Given that trabectedin may be more effective in this genetic phenotype, there is a biologic rationale for its further investigation in gynecologic sarcoma therapy.

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FIGO staging for carcinosarcoma: Can the new staging system predict overall survival?

T. Pradhan, E. Stevens, M. Ablavksy, G. Salame, Y. Lee, K. Economos, O. Abulafia
SUNY/Downstate Medical Center, Brooklyn, NY

Objective: The purpose of this study was to determine whether the revised FIGO 2009 staging of patients with carcinosarcoma can accurately predict patient survival, in comparison with previous FIGO staging.

From March 1988 until January 2010, patients with a diagnosis of carcinosarcoma were retrospectively identified from tumor registry records at two large teaching institutions. Data were collected via tumor registry data, medical chart records and social security death records. Patients were excluded if they had dual primary malignancies, if they did not undergo hysterectomy, and if data were missing. Patients were grouped in both broad stages (I–IV) and all FIGO substages to detect differences. Time-dependent receiver operating characteristic curves were generated to predict death before the end of the second year postdiagnosis for both the new and revised systems. Kaplan–Meier estimated median survival time was used to compare actual patient survival.

Results: Of 112 patients with carcinosarcoma, 37 (33%) had FIGO stage I disease, 15 (13.4%) had stage II disease, 36 (32%) were diagnosed as stage III, and 24 (21.4%) had stage IV disease. One hundred six of 112 (94.6%) patients underwent lymph node dissection (pelvic ± paraaortic); and of these 106 patients, 71 also underwent infracolic omentectomy and/or additional biopsies. Only four patients (3.6%) were downstaged when using broad staging criteria: Two patients were downstaged from stages II to I, and two patients were downstaged from stage III to stages I and II. When looking at substage, the area under the receiver operating curve was 0.67 for the old staging system, and 0.65 for the revised staging for carcinosarcoma. Kaplan–Meier estimated median survival time postdiagnosis was 610 days (95% CI = 478–930).

Conclusions: On the basis of our reclassification of 112 patients with uterine carcinosarcoma, the revised 2009 FIGO staging system does not predict survival more accurately than previous staging. On the basis of our analysis, carcinosarcoma has an overall poor prognosis and better indicators of survival are needed.

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Human papillomavirus genotype in patients who developed vaginal intraepithelial neoplasia after treatment for cervical neoplasms

C. Lai[1,2], A. Chao[1], T. Chen[1], H. Chou[1], C. Huang[1], H. Huang[1], M. Jao[1]
[1]Chang Gung Memorial Hospital, Taoyuan, Taiwan, [2]Chang Gung University, Gueishan, Taoyuan, Taiwan

Objective: The aim of this study was to compare the human papillomavirus (HPV) genotypes of cervical and vaginal neoplasms from women with incident vaginal intraepithelial neoplasia (VAIN) and a history of previous cervical neoplasms.

All VAIN cases diagnosed between 1999 and 2005 were retrieved from the tumor registry. A history of previous cervical intraepithelial neoplasia or cervical cancer was extracted from medical records. Those who had both a vaginal biopsy and cervical specimens in our hospital were eligible for analysis. HPV genotyping was performed on paraffin-embedded, formaldehyde-fixed specimens using PCR-based methods. Multiple HPV types were validated by type-specific PCR, direct sequencing and/or real-time PCR.

Results: Of the 454 VAIN cases with a confirmed diagnosis, 178 had a previous cervical specimen available. Of these 178 cases (mean age = 59.9 years, range: 30–91), 31 with poor DNA quality were excluded. HPV DNA was detected in 67.3% (99/147), and multiple HPV types were identified in 18% (18/99) of the samples. The leading HPV types were HPV16 (25%), HPV52 (10%), HPV58 (7%), HPV33 (7%), HPV39 (6%), and HPV42 (5%). HPV16 constituted 4.8% of low-grade and 32.3% of high-grade VAIN lesions. Fifteen cases

were HPV negative in both cervical and vaginal lesions, 33 had the same or shared HPV genotypes, and 99 (67.3%) had different HPV results.

Conclusions: We concluded that women with VAIN who have a history of cervical neoplasia might subsequently develop VAIN from acquisition of new HPV infections. Clarification of whether those types in VAIN lesions had been in vaginal epithelium at the time of previous cervical neoplasia requires prospective follow-up studies.

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Number of metastatic lymph nodes and locoregional control in vulvar cancer

S. Mahner, M. Choschzik, C. Eulenburg, M. Hager, F. Gieseking, J. Schwarz, F. Jaenicke, L. Woelber
University Medical Center Hamburg–Eppendorf, Hamburg, Germany

Objective: Lymph node metastases are the most important prognostic factor for recurrence and survival in vulvar cancer. Adjuvant radiotherapy is currently recommended for two or more metastatic lymph nodes according to National Cancer Institute (NCI) guidelines. This standard is based on small and heterogeneous patient populations. We therefore reanalyzed the impact of number of affected nodes for locoregional control in primary vulvar cancer in a large and homogenous patient cohort.

One hundred fifty-seven consecutive patients with primary squamous cell cancer of the vulva treated at our center were analyzed. All patients underwent primary surgery via triple incision resulting in complete tumor resection.

Results: Median age was 61 years; 44% had FIGO stage I, 20% stage II, 28% stage III, and 8% stage IV disease. Forty-nine patients (31%) had lymph node metastases; 21 patients had one, 13 had two, and 15 had more than two metastatic lymph nodes. In patients with only one affected lymph node, the size of the metastasis ranged between 1.5 and 70 mm, and 26% had extracapsular spread. Median follow-up was 23 months; 22 patients (14%) developed disease recurrence (77% vulva, 18% groin, and 5% both). There was a trend toward decreased disease-free survival in patients with more than two metastatic nodes compared with those with one or two ($P = 0.052$ and 0.057). However, compared with node-negative patients, survival of all patients with lymph node metastases was significantly inferior ($P < 0.001$, disease-free patients after two years: 88% in node-negative patients, and 59, 69, and 27% in patients with one, two, and more than two affected nodes, respectively). Thirty-one percent of the patients received adjuvant radiotherapy. There was no significant difference in disease-free survival between the node-positive groups who received and did not receive adjuvant radiotherapy.

Conclusions: Lymph node metastases remain the most important prognostic factor in patients with vulvar cancer. However, the detrimental effect of nodal involvement is already evident in patients with only one affected lymph node. Therefore, it might be justified to consider adjuvant radiotherapy of the groin even in these patients.

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Positive vulvar sentinel lymph node biopsy: A single-institution retrospective review

M. Tenney[1], E. Bishop[1], E. Nugent[1], L. Landrum[1], K. Moore[1], R. Mannel[1], J. Walker[1], M. Gold[2], D. McMeekin[1]
[1]University of Oklahoma, Oklahoma City, OK, [2]Vanderbilt University, Nashville, TN

Objective: Sentinel lymph node (SLN) biopsy in vulvar cancer has a high negative predictive value and has been shown to accurately identify patients with negative groin nodes. GOG 173 reported the false negative rate of SLN biopsy in squamous carcinoma of the vulva to be 4.4%. Less is known on how to manage patients with positive SLN biopsy. Options include completion inguinofemoral lymphadenectomy (IFLND), radiotherapy, and observation alone. We sought to determine the proportion of patients with a positive SLN with additional positive nodes following completion IFLND (SLN+/IFLN+) and to describe clinicopathologic features unique to these patients.

A retrospective review was performed for patients with vulvar cancer who underwent SLN biopsy followed by subsequent completion IFLN between 1999 and 2008. All patients had clinical stage II squamous cancers with >1 mm invasion, 2- to 6-cm tumor size, and no clinically suspicious lymph nodes. Charts were abstracted for clinicopathologic information including age, surgical findings, tumor size, presence of lymphovascular space invasion, lymph node count, survival and postoperative treatment. Patients with positive SLNs were then classified based on the presence of positive or negative residual nodes at completion IFLND, and groups were compared.

Results: We identified 50 patients who underwent SLN biopsy followed by completion IFLND. The median age of all patients was 65 years, and median tumor size was 3.3 cm. Twelve patients (24%) had a positive SLN. Three of these 12 patients (25%) had positive nodes identified on completion IFLND. In these three patients, median age was 84 years, and median tumor size was 5.0 cm, compared with the nine patients who were SLN+/IFLN– with a median age of 63 years and tumor size of 2.5 cm. The 40 SLN-negative patients had a median age of 62 years and median tumor size of 3.6 cm. Median progression-free survival in SLN +/IFLN+ patients was 15.9 months versus 30.8 months in SLN +/IFLN– patients.

Conclusions: In this population with a 24% baseline risk of nodal disease, the finding of a positive inguinofemoral lymph node following a positive SLN biopsy was relatively uncommon. Given the clinical significance of missing unrecognized but positive groin nodes in vulvar cancer, it is important to identify those who may benefit from completion IFLN following SLN biopsy. Our small series suggests that that younger patients with smaller tumors may be considered for SLN biopsy only regardless of nodal positivity. Studies involving a larger patient population are needed to identify clinicopathologic features unique to SLN+/IFLND– patients. This information may help guide appropriate operative and postoperative management of SLN-positive patients.

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Risk of second malignancies following extramammary Paget's disease

A. Karam, O. Dorigo
The David Geffen School of Medicine at UCLA, Los Angeles, CA

Objective: We sought to examine the prevalence, incidence, and survival of Paget's disease (EMPD) and whether the diagnosis was associated with a long-term risk of second malignancies.

We evaluated patients diagnosed with EMPD as well their outcome and risk of subsequent invasive primary cancers using data collected from the SEER program, between 1973 and 2007. Subsequent primary invasive cancers that were diagnosed more than two months after the initial EMPD diagnosis were included in the analysis. EMPD recurrences were not included in our analysis. We calculated the standardized incidence ratio (SIR) using the observed number of patients (O) divided by the expected number of patients (E) and estimated the excess absolute risk (EAR) per 10,000 person-years as ([O − E]×10,000)/PYR. We assumed a Poisson distribution of the observed tumors, and all statistical tests and 95% CIs were two-sided and based on an α level of 0.05.

Results: One thousand four hundred thirty-nine patients were diagnosed with EMPD; 965 were female and 474 were male. The median age at the time of diagnosis was 72 years and did not significantly differ between female and male patients. With respect to diagnoses, 72.1% had localized disease, 15.3% with locoregional spread and 2.2% with distant spread; the remaining 10.2% were unstaged. The cause-specific five-year survival was 95.9% for localized disease, 84.1% for regional disease, 0% for distant disease, and 93.3% for unstaged disease. The SIR for second malignancies in patients with EMPD was significantly elevated with an EAR of 124.5. The excess risk was in good part due to a significantly increased incidence of anorectal carcinomas with an O/E of 5.18 resulting in an EAR of 26.5. In female patients a significant proportion of the second malignancies were vulvar malignancies, with an O/E ratio of 27 and an EAR of 23.6. Correspondingly, male patients faced a significantly increased risk of second malignancies in the scrotum, with an O/E ratio of 300.3 and and EAR of 59.1. Patients with EMPD also appeared to be at risk of melanomas, with an EAR of 20.8. No significantly increased risk was noted for the occurrence of subsequent breast, ovarian, uterine and urologic malignancies, although a few additianal ovarian cancers were diagnosed during the first surveillance year.

Conclusions: Patients with EMPD are at increased risk of subsequent malignancies in the anus, rectum, skin, scrotum and vulva and should be indefinitely screened for these conditions after the original diagnosis.

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Survival following ovarian versus uterine carcinosarcoma

L. Seamon[1], I. Podzielinski[1], B. Huang[1,2], C. DeSimone[1], B. Shelton[1,2], M. Randall[1], R. Ware[1], J. van Nagell[1], M. Cibull[1], F. Ueland[1]
[1]University of Kentucky Medical Center, Lexington, KY, [2]Markey Cancer Center Biostatistics Unit and Kentucky Cancer Registry, Lexington, KY

Objective: A Gynecologic Oncology Group ovarian carcinosarcoma/malignant mixed mullerian tumor (MMT) study reported a response to platinum chemotherapy similar to that of historic uterine MMT controls. Because of the rarity of the disease, prolonged accrual to trials with limited power, and similar response to platinum chemotherapy, the investigators suggested that future ovarian MMT therapy should be extrapolated from uterine trials. There are inadequate data regarding the molecular biology and survival following ovarian versus uterine MMTs. Our objective was to compare the survival of early- and late-stage uterine versus ovarian MMTs.

By means of the SEER database, cases were identified from January 1995 to December 2007 using ICD codes for ovarian and uterine cancer. Inclusion criteria included carcinosarcoma or MMT histology, first primary, actively followed, and age ≥20 years. Death certificate- or autopsy-only cases were excluded. Outcomes of early (stages I and II) and advanced (stages III and IV) carcinosarcomas were compared between the two cancers using Kaplan–Meier curves, log-rank tests and Cox regression models.

Results: Two thousand eight hundred twenty-one patients met entry criteria (median: 212 cases/year, range: 181–253). Two thousand eighty-seven uterine MMTs were compared with 734 ovarian MMTs. The majority of women were Caucasian (73 and 83% for uterine and ovarian MMTs, respectively); however, more African-Americans were diagnosed with uterine versus ovarian MMT (20% vs 9%, respectively, $P<0.001$). Within early-stage MMTs, the two cohorts did not differ regarding age or number of cases undergoing surgical intervention. Although there was an imbalance in stage distribution, 79% of uterine MMTs were classified as stage I versus 49% of ovarian MMTs; there was no difference in overall survival (OS) between early-stage uterine MMTs and ovarian MMTs (Fig. 1). Median OS was 62 and 64 months, respectively ($P=0.86$), and there was no OS difference on Cox regression after controlling for race, age, stage, and treatment ($P=0.23$). Among the advanced-stage cohort, there was no difference in age group, stage distribution, or survival (Fig. 2). Median OS was 11 and 14 months, respectively ($P=0.39$), and OS survival was not different in a Cox regression model ($P=0.09$).

Conclusions: Early- or advance-stage ovarian and uterine carcinosarcomas demonstrate equally poor overall survival. Our data suggest that further investigation into the molecular biology of ovarian and uterine MMTs is worthwhile and, if similar, these cancers could be studied as the same disease.

Figure 1. OS for Stage I and II MMT

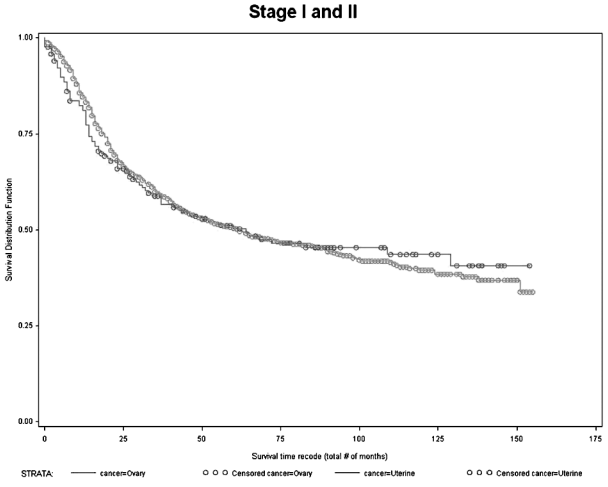
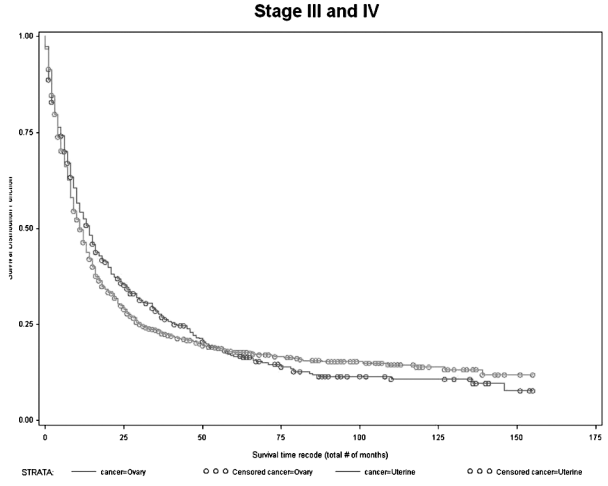


Figure 2. OS for Stage III and IV MMT



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The unique natural history of mucinous tumors of the ovary

M. Schiavone, T. Herzog, S. Lewin, I. Deutsch, X. Sun, W. Burke, J. Wright
Columbia University College of Physicians and Surgeons, New York, NY

Objective: Emerging data suggest that mucinous tumors of the ovary have distinct clinical characteristics and follow a different course than other epithelial ovarian tumors. We examined the clinical characteristics, natural history, and outcomes of women with mucinous tumors of the ovary in comparison to other epithelial histologic subtypes.

Women with invasive epithelial tumors of the ovary diagnosed between 1988 and 2007 and included in the SEER database were analyzed. Patients were stratified by histology, and the clinical and demographic characteristics were compared using the χ^2 test. Multivariable Cox proportional hazards models were developed to examine stage-specific survival while accounting for other clinicopathologic variables that influence outcome. Five-year survival rates were calculated by stage and histology, and survival was further analyzed using the Kaplan–Meier method.

Results: A total of 40,571 patients including 4811 (11.9%) with mucinous tumors were identified. Compared with serous tumors, women with mucinous tumors were younger (median age: 57 vs. 63), more often nonwhite, and more likely to have low-grade malignancies (28% vs 5% grade 1) ($P<0.0001$ for all). Mucinous tumors were more often diagnosed at an early stage; 55% of mucinous tumors were stage I compared with 11% of serous carcinomas ($P<0.0001$). In a multivariable Cox model among women with stage I neoplasms there was no difference in survival between mucinous and serous tumors (OR = 0.87, 95% CI = 0.74–1.04). However, survival was inferior for mucinous tumors for women with stage II (OR = 1.28, 95% CI = 1.03–1.60), stage III (OR = 1.55, 95% CI = 1.43–1.69), and stage IV (OR = 1.68, 95% CI = 1.54–1.83) neoplasms when compared with similar-stage patients with serous carcinomas. Five-year survival for stage III mucinous tumors was 25.7% (95% CI = 22.9–28.7%) compared with 33.6% (95% CI = 32.6–34.5%) for serous malignancies.

Conclusions: Mucinous tumors of the ovary have a distinct behavior and natural history. Although a large number of women have early-stage disease, for women with advanced-stage disease survival is inferior to that of serous carcionomas.

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Public Health/Epidemiology

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Charlson's index: A validation study to predict surgical adverse events in gynecologic oncology

S. Kondalsamy-Chennakesavan[1], S. Johnson[1], J. Nicklin[2], R. Land[2], A. Garrett[2], A. Obermair[3]
[1]University of Queensland, Brisbane, QLD, Australia, [2]Queensland Centre for Gynaecological Cancer, Brisbane, QLD, Australia, [3]Queen Alexandria Hospital, Portsmouth, United Kingdom

Objective: The risk of surgical adverse events (AEs) influences decisions on patient management. This study evaluated the usefulness of Charlson's index (Cha-I) in predicting AEs associated with major surgery for gynecologic cancer.

Patients who underwent a surgical intervention (laparotomy or laparoscopy) for proven or suspected gynecologic cancer in a tertiary referral center between January 2007 and July 2008 were included. The primary outcome was incidence of any AE (intra- or postoperative) within 30 days of surgery. Complexity of surgery was graded from 1 to 3, and Cha-I was calculated from 19 preexisting medical comorbidities according to Charlson et al. (J Chron Dis 1987;40:373–83). Uni- and multivariate logistic regression methods were used to assess the direction and strength of relationships between Cha-I and AEs.

Results: Patients' ($n=311$) mean age (SD) was 55.9 (14.3) years, and 192 patients (61.7%) had surgery for a malignancy. Sixty percent of patients had a laparotomy, and 67% were overweight or obese. Eighty-three patients (26.7%) developed at least one AE. On univariate analysis, Cha-I, age, obesity, complexity of surgery, and abnormal liver function tests were associated with the risk of AEs. After adjustment for age, complexity of the surgery, surgical approach (open vs laparotomy), overweight and presence of malignancy, Cha-I as well as overweight retained statistical significance (see table).

Conclusions: Charlson's index has not been validated in detail, in this subspecialty. This study has shown that it is an independent predictor of adverse outcomes among patients who require surgery for gynecologic cancer.

Covariate	Odds ratio	95% CI		P
Age	1.01	0.99	1.03	0.400
Laparotomy vs laproscopy	1.11	0.56	2.21	0.768
Charlson's index	1.18	1.06	1.32	0.004
Surgical complexity				
Grade 2 vs grade 1	1.40	0.63	3.11	0.413
Grade 3 vs grade 1	2.21	0.60	8.08	0.230
Overweight or obesity	2.70	1.35	5.42	0.005
Malignancy	1.16	0.60	2.23	0.658
Abnormal liver function tests	1.80	0.76	4.29	0.182

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Clinical performance of a self-sustaining cervical cancer screening clinic in Nairobi, Kenya: The PAPS Team experience

Y. Lin[1], K. Matsuo[1], E. Yoo[1], M. Titus[2], G. Webley[3], G. Spears[3], L. Muderspach[1], N. Mugo[4], E. Thomas[3]
[1]University of Southern California, Los Angeles, CA, [2]Loma Linda University Medical Center, Loma Linda, CA, [3]The PAPS Team International, Redlands, CA, [4]Kenyatta National Hospital, Nairobi, Kenya

Objective: This study evaluates the clinical performance and patient characteristics of an innovative multidisciplinary cervical cancer screening clinic.

Over nine days, 1598 women were prospectively registered into a cervical cancer screening program in Nairobi after clinicians completed intensive classroom didactics. Demographic and clinical information was collected by questionnaire and a clinician-administered interview. Conventional Pap tests were performed and followed with colposcopy and/or loop electrosurgical excision procedure (LEEP), as indicated. Uni- and multivariate analyses were performed, and histologic diagnoses were correlated with cytologic diagnoses and clinical information.

Results: Among registrants, 1570 (98.2%) completed questionnaires, underwent Pap testing, and were evaluable for analysis. The mean ($\pm$SD) age was 37($\pm$11) years. Sixty-four percent were married; 71% were sexually active; 66% used some form of contraception; 50% reported a prior sexually transmitted disease diagnosis. This was the first Pap test for 64% of patients. Within the tested population, 143 (9.1%) subjects had abnormal Pap results (ASCUS 19.6%, AGUS 1.4%, LSIL 46.9%, HSIL/CIS 28%, and invasive cancer 5.6%). On univariate analysis, age <25 years ($P=0.04$), unmarried partner status ($P<0.001$), history of an abnormal Pap test ($P<0.001$), current sexual

activity ($P=0.047$), any contraceptive use ($P=0.002$), any condom use ($P=0.005$) and HIV seropositivity ($P<0.001$) were significantly associated with an abnormal Pap test during this period. Sixteen percent of patients <25 years of age had an abnormal Pap. Fourteen percent of unmarried women, 33% of those with a prior abnormal Pap smear, 10% of sexually active women, and 12 and 13% of those women reporting contraceptive and condom use, respectively, had an abnormal test during this clinic period. Multivariate analysis revealed that having a previous abnormal Pap test was statistically significantly associated with an abnormal Pap result in this population of self-referred women ($P=0.01$). Colposcopic findings correlated well with Pap results ($P<0.0001$) during this period.

Conclusions: This study reports the feasibility of a multidisciplinary cervical cancer screening clinic with didactics followed by clinical and laboratory training of local caregivers to perform reliable pelvic exams and proficiently render cytological diagnoses, thereby supporting such multipronged international collaborations for cervical cancer prevention.

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Cost-effectiveness of extended postoperative venous thromboembolism prophylaxis in gynecologic pncology patients

S. Uppal, V. Dandolu, E. Hernandez
Temple University Hospital, Philadelphia, PA

Objective: The purpose of this study was to investigate the cost-effectiveness of prolonged prophylaxis with enoxaparin in high-risk surgical patients with gynecologic cancer.

A Markov decision analytic model was used to estimate the costs and outcomes associated with the prolonged use of enoxaparin in patients undergoing gynecologic surgery for malignancy. We estimated incremental cost per quality-adjusted life-year (QALY) saved by the addition of postdischarge prophylactic anticoagulation for an additional three-week period. Probability estimates for various outcomes and efficacies were obtained from the literature, using data specific for gynecologic surgery patients when available. Crude survival rates from the SEER database were used for calculation of yearly outcome probabilities.

Results: In the base case scenario, cost-effectiveness estimates for an extended period of prophylaxis varied from $136 per QALY saved for a 35-year-old patient with IB cervix cancer to $1103 per QALY saved for a 65-year-old patient with stage IIIC ovarian cancer and $21 per QALY saved for a 50-year-old with IA uterine cancer. Sensitivity analysis indicated that variation of the marginal cost of low-molecular-weight heparin and the marginal effectiveness to extremes did not change the conclusions of the statistical model.

Conclusions: In this cost-effectiveness analysis, the strategy of extended enoxaparin remained a highly cost-effective method of thromboprophylaxis in patients undergoing surgical management of common gynecologic malignancies.

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High incidence of anal disease diagnosed from screening HIV-infected women with anal cytology and triage to high-resolution anoscopy

J. Hou, D. Smotkin, S. Isani, H. Smith, O. Ben-David, G. Goldberg, M. Einstein
Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

Objective: With increasing use of antiretroviral therapy (ARVs) in patients with HIV, there has been a decrease in nearly all AIDS-related malignancies. However, the incidence of anal cancer has been increasing, particularly in patients with HIV, even in those on ARVs. Since March 2007, the NY State Department of Health has recommended visual inspection and screening for anal disease in high-risk individuals. We have initiated widespread anal disease screening of HIV-infected women (and men) since March 2008 and present the initial results of this anal cancer screening cohort of women.

Screening with an anal Pap test was initiated in all HIV-infected patients by primary care providers starting March 2008. All women with abnormal anal Pap test results were referred for high-resolution anoscopy (HRA) and biopsy of abnormal lesions. All cytology and histology results were tabulated. Association of high-grade disease with HIV status was performed using χ^2 analysis.

Results: Anal cytology was performed in a total of 530 women during this 18-month period, with greater than 95% of the cytology performed in women with documented HIV infection. Seventy-two of 530 (14%) had an anal Pap cytology diagnosis of "atypical," ASCUS, LSIL, or HSIL that preceded HRA. Histologically proven high-grade anal intraepithelial neoplasia (AIN) was identified in 24 of 72 (33%) with HRA-directed biopsies. In women with a new abnormal anal Pap, the correlation between preceding anal cytology and biopsy-proven histology is outlined in the table. Women with CD4 T-cell counts <200 (19/23) were significantly more likely to have high-grade histology than women with CD4 counts >200 ($P<0.001$).

Conclusions: There is a disturbingly high rate of high-grade anal dysplasia (33% of all abnormal anal cytology) in a screening population of HIV-infected women, predominantly in those women with CD4 counts <200. During this initiation of routine anal cancer screening at a single institution that serves a community with a high prevalence of HIV, there is a poor correlation between anal cytology and HRA-directed histology. Twenty-two of 72 (31%) histologically proven high-grade AIN lesions identified with HRA had an anal cytology interpretation of "atypical," ASCUS, or LGSIL. There is a clear need for a better understanding of the natural history and screening for anal disease and anal cancer. HRA, particularly in the setting of poorly controlled HIV patients, should be performed with any atypia on anal cytology to maximize the identification of occult high-grade AIN or worse.

Correlation between preceding anal cytology and HRA-directed histology in HIV-infected women.

Preceding cytology	Normal HRA	Anal/ perianal warts	AIN1	High-grade AIN	Total
Atypical	5	0	0	3	8
ASCUS	1	2	1	4	8
LGSIL	17	3	17	15	52
HGSIL	1	0	1	2	4
Total	24(33%)	5(8%)	19(26%)	24(33%)	72

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Racial disparities in ovarian cancer surgical care: A population-based analysis

O. Ibeanu[1], M. Zahurak[1], R. Bristow[2]
[1]Johns Hopkins Medical Institutions, Baltimore, MD, [2]UC Irvine Medical Center, Orange, CA

Objective: The aim of this study was to investigate differences with respect to racial classification in the frequency of ovarian cancer-related surgical procedures and in access to high-volume surgical providers among women undergoing initial surgery for ovarian cancer.

The Maryland Health Services Cost Review Commission database was accessed for women aged >18 years undergoing a surgical procedure that included oophorectomy for a malignant ovarian neoplasm between July 1, 2001 and June 30, 2009. Multivariate logistic regression analyses were used to evaluate for differences in the likelihood of selected surgical procedures and access to high-volume surgical providers (surgeons≥10 cases/year, hospitals≥20 case/year) on the basis of racial classification.

Results: A total of 2487 patients were identified who underwent a primary surgical procedure that included oophorectomy for a malignant ovarian neoplasm: whites = 1884 (75.4%), African-Americans = 400 (16.1%) and other/unknown = 203 (8.2%). Compared with white patients, African-American patients were significantly younger (mean age: 55.4 years vs 59.9 years, $P<0.0001$) and less likely to have commercial insurance (28.5% vs 39.5%, $P<0.0001$). Compared with white patients, African-American racial classification was associated with a statistically significant and independent lower likelihood of hysterectomy (OR = 0.53, 95% CI = 0.42–0.66, $P<0.0001$), colon resection (OR = 0.65, 95% CI = 0.48–0.87, $P=0.004$), lymphadenectomy (OR = 0.67, 95% CI = 0.50–0.91, $P=0.01$) and surgery by a high-volume surgeon (OR = 0.55, 95% CI = 0.44–0.69, $P<0.0001$).

Conclusions: Among women undergoing initial surgery for ovarian cancer, African-American patients are significantly less likely to be operated on by a high-volume surgeon and to undergo important ovarian cancer-specific surgical procedures compared with white patients.

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Rapid high-risk human papillomavirus test shows excellent agreement with standard Hybrid Capture 2 when used onsite in rural northern Tanzania

J. Young[1], B. Badman[2], G. Lazenby[1], A. Nyanga'nyi[3], M. Stoler[2], P. Taylor[2]
[1]Medical University of South Carolina, Charleston, SC, [2]University of Virginia, Charlottesville, VA, [3]Qiagen, Gaithersburg, MD

Objective: With the knowledge that human papillomavirus (HPV) testing is the only cervical cancer screening modality known to decrease mortality in low-resource settings, we sought to determine the validity of the careHPV test (Qiagen, Gaithersburg, MD) as compared with Hybrid Capture 2 testing for use as a screening tool in rural Africa.

Women aged 30–60 with no prior history of cervical cancer screening were recruited from villages surrounding Selian Lutheran Hospital in Arusha, Tanzania. After consent was obtained via local nurse-translators, the women underwent a gynecologic exam including liquid-based cytology, careHPV specimen collection and visual inspection with acetic acid (VIA). Biopsies were obtained for any VIA-positive women. CareHPV specimens were run onsite after training local laboratory technicians. All specimens were shipped back to the University of Virginia for cytologic analysis. After confirmation of cytologic diagnosis, all specimens were shipped to Qiagen for Hybrid Capture 2 testing (HC2) and HPV genotyping of specimens positive for HPV DNA on HC2.

Results: In June 2010, 324 women were enrolled in this study. These women averaged 42 years in age (range: 30–60), with the majority reporting monogamous marital relationships. Most women were multiparous and 21% were postmenopausal. HC2 was positive in 42 of 324 women (12.8%). Of these, six were Pap or biopsy positive for cervical intraepithelial neoplasia grade 2/3 (CIN 2/3), and one patient was diagnosed with adenocarcinoma in situ (7/42, 16.7%). No cancers were found in the study group. One patient was biopsy positive for CIN 3 but negative for high-risk HPV DNA by careHPV and HC2. Otherwise, careHPV showed excellent agreement with HC2, with positive agreement in 94% (95% CI = 80.4–98.3), negative agreement in 99.3% (95% CI = 97.4–99.8) and total agreement in 98.7% (95% CI = 96.8–99.5). HPV16 was the most common genotype (6/42, 14.3%), with HPV31, -35 and -56 also found frequently. Only one patient tested positive for HPV18.

Conclusions: careHPV rapid HPV testing shows excellent agreement with Hybrid Capture 2 high-risk HPV DNA testing and is a viable option for cervical cancer screening in Africa and other low-resource settings.

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Stage IC ovarian cancer: Tumor rupture versus ovarian surface involvement

N. Barrena Medel, S. Lewin, I. Deutsch, Y. Qiao, X. Sun, W. Burke, T. Herzog, J. Wright
Columbia University College of Physicians and Surgeons, New York, NY

Objective: Stage IC ovarian cancer is found in a heterogenous group of patients including women with ovarian surface involvement and patients with tumor rupture. The prognostic importance of tumor rupture has long been debated. We examined women with stage IC ovarian cancer and compared the outcomes of patients with ovarian surface involvement with those of patients with tumor rupture.

Women with invasive epithelial tumors of the ovary diagnosed between 2004 and 2007 and registered in the SEER database were analyzed. Patients with stage IC or IIIC tumors with only occult nodal metastasis were included. Patients were stratified into three groups: ovarian surface involvement, tumor rupture and both surface involvement and rupture. The demographic and clinical characteristics of the group including the risk of nodal metastasis were compared using the χ^2 test. Multivariable Cox proportional hazards models were developed to estimate cancer-specific survival.

Results: A total of 1203 patients were identified. The cohort included 270 (22.4%) women with ovarian surface involvement, 873 (72.6%) with tumor rupture, and 60 (5.0%) with surface involvement and rupture. Women with serous tumors were more likely to have ovarian surface involvement than patients with other histologic subtypes ($P<0.001$). Patients with tumor rupture (OR = 0.54, 95% CI = 0.31–0.93) were less likely to have lymph node metastases than women with ovarian surface involvement. Among women with stage IC tumors, cancer-specific survival for patients with tumor rupture (HR = 1.82, 95% CI = 0.96–3.44) or with surface involvement and rupture (HR = 1.31, 95% CI = 0.29–5.91) was similar to that of patients with ovarian surface involvement alone. Three-year survival was 88.9% (95% CI = 80.9–93.4%) for patients with ovarian surface involvement, 83.5% (95% CI = 79.7–86.6%) for women with tumor rupture and 86.8% (95% CI = 62.2–95.9%) for patients with surface involvement and rupture.

Conclusions: Among women with apparent stage IC ovarian cancer, ovarian surface involvement carries a greater risk of nodal metastasis than capsular rupture. For women with stage IC ovarian cancer,

survival is similar for women with ovarian surface involvement and those with tumor rupture.

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Television and Internet sources of information negatively associated with human papillomavirus vaccination among college-age women

J. Young[1], A. Brown[2], L. Carr[2], J. Korte[1], S. Modesitt[2]
[1]*Medical University of South Carolina, Charleston, SC,* [2]*University of Virginia, Charlottesville, VA*

Objective: We sought to evaluate the frequency of human papillomavirus (HPV) vaccination among college women as well as factors associated with choosing to receive the vaccine in this population.

An Internet survey tool was used to survey 2456 randomly selected college women attending the University of Virginia. All students were e-mailed a cover letter which included the consent and a link to the Internet questionnaire. No compensation was provided, and all survey responses were completely anonymous. The 30-item questionnaire was based on previously validated studies using the Health Belief Model and Theory of Planned Behavior.

Results: Nine hundred fifty-three women responded to this survey for a response rate of 38.8%. Most respondents were between ages 19 and 21, sexually active and nonsmokers. The majority were white (78%), with the remainder being black (5.6%), Hispanic (3.9%) and other race (12.4%). Ninety-eight percent of respondents had heard of the HPV vaccine, and 61.4% had received at least one HPV injection. Vaccinated individuals were significantly more likely to use physicians (66.8% vs 49.7%, $P<0.0001$) and parents (62.5% vs 32%, $P<0.0001$) as a source of vaccine information. In comparison, unvaccinated individuals more frequently reported television (76% vs 60%, $P<0.0001$) and the Internet (25% vs 11.5%, $P<0.0001$) as their sources of vaccine information. Being sexually active, having received a Pap smear, and white race were also associated with HPV vaccination. Racial disparities in vaccination rates exist, with whites having higher vaccination rates (64%) compared with blacks (41.2%, OR = 0.52 95% CI = 0.28–0.96), Hispanics (45.7% OR = 0.34, 95% CI = 0.16–0.71) and other minorities (36.4%, OR = 0.44, 95% CI = 0.28–0.71). On logistic regression, only race and source of information were retained in the final model, with physician source of information twice as likely to result in vaccination (OR = 2.11, 95% CI = 1.57–2.84) compared with television (OR = 0.53, 95% CI = 0.38–0.73) and Internet (OR = 0.46, 95% CI = 0.31–0.69), which were negatively associated with HPV vaccination.

Conclusions: Television and Internet sources of information are negatively associated with choosing HPV vaccination. Racial disparities in HPV vaccination exist even among a population of women with ready access to care.

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The clinical and financial implications of MRI of pelvic masses

E. Ratner, S. Cross, P. Schwartz, S. McCarthy
Yale University School of Medicine, New Haven, CT

Objective: Ovarian and uterine pathology constitutes a vast fraction of female morbidity accounting for a large amount of health care costs and resources. The pressure to decrease health care expenditures continues to increase as the portion of the federal budget allocated to health care approximates 7%. High-technology diagnostic imaging techniques are often a target, although these costs are a small amount of the total health care expenditure. Our objective was to evaluate cost-effectiveness and clinical benefits of MRI as it stands out as a relatively expensive modality with little research in technology assessment.

The radiologic records at Yale New Haven Hospital from 1997 to 2005 were reviewed. Four hundred ten patients who underwent ultrasonographic or CT evaluation followed by MRI for evaluation of a pelvic mass were randomly selected. A minimal follow-up of 42 months was employed with a mean follow-up of 80 months (range: 42–144).

Results: In 34% of patients, the first modality was determined to have worrisome findings, but the MRI findings were not concerning (0.26, 0.43). In 6% of patients, MRI findings confirmed a concerning diagnosis made on the basis of the first modality (0.028, 0.12). In 50% of patients, both the first modality and MRI did not reveal concerning findings (0.41, 0.59). In the remaining 10% of patients, the first modality did not reveal suspicious findings, whereas MRI demonstrated worrisome results (0.05, 0.16). Clinical management of the patient was altered secondary to MRI findings in 91% of cases. Surgery was avoided in 43% of cases (0.35, 0.52), and was changed to an appropriate method (suitable abdominal incision, involvement or not involvement of a gynecologic oncologist) in an additional 20% (0.13, 0.28). In 13% of cases, MRI did not reveal any masses that were demonstrated on prior imaging (0.08, 0.21). In an additional 7% of cases, MRI served either to provide or to confirm a diagnosis of benign origin, allowing conservative management. Nine percent of cases were not influenced by MRI findings (0.05, 0.16).

Conclusions: We have demonstrated that MRI is highly accurate in diagnosing the etiology of pelvic masses. Gynecologic MRI saves health care dollars when compared with laparoscopy and laparatomy. Our results demonstrate that unlike other modalities, MRI changed clinical management in 91% of patients, avoiding surgical intervention in 43% and, thus, providing significant cost benefit.

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Weighing the risks: The ecological relationship between obesity and early-onset endometrial cancer

R. Salani, J. Fisher, J. McLaughlin, E. Paskett, D. Cohn
Ohio State University, Columbus, OH

Objective: The incidence of endometrial cancer has steadily increased from 27,000 cases in 1975 to more than 43,000 cases in 2010. Concurrently, the prevalence of obesity has doubled over the last 40 years. We evaluated the relationship between the proportion of endometrial cancers diagnosed in women younger than age 50 and obesity.

Using data from the SEER Program of the National Cancer Institute (nine original registries, years 1975–2006) we calculated incidence rates for invasive "corpus uterus" and "uterus, NOS" (hereafter referred to as endometrial) cancer according to year of diagnosis. Incidence rates were calculated per 100,000 women and were age adjusted to the 2000 U.S. standard population (using 19 age groups). Data from the National Health Examination Survey and National Health and Nutrition Examination Survey (NHANES) were used to assess rates of obesity in the United States over similar intervals.

Results: In 1975, women younger than 50 years of age accounted for approximately 6% of all endometrial cancer cases. In 2005, the proportion of endometrial cancer cases in women under 50 increased to more than 12%. During this same interval, the prevalence of obesity in women also rose, increasing from 16.1% in the 1970s to 35.5% in 2008, directly correlating with the rate of endometrial cancer cases.
Conclusions: The rate of endometrial cancer in women younger than age 50 is rapidly increasing and may be associated with a precipitous rise in the rate of obesity in this population. Future research about this potential association is warranted. Based on data showing a large increase in the proportion of endometrial cancers diagnosed in women younger than age 50, continued surveillance for the disease, even in younger women, appears necessary. Furthermore, education regarding the association between endometrial cancer and obesity, as well as prevention strategies, is imperative.

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Poster Area 5
Surgical Techniques/Robotics/Minimally Invasive Surgery: Abstracts 294–313
Sunday, March 6 – Tuesday, March 8, 2011
Exhibit Hall–Bonnet Creek Ballroom

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Clinical and economic impact following the introduction of robotics for endometrial cancer staging
Z. Vaknin[1,2], S. Lau[1,2], R. Agnihotram[1], N. Drummond[1,2], D. Halliday[1,2], R. Gotlieb[1,2], J. How[1,2], E. Franco[1], W. Gotlieb[1,2]
[1]McGill University, Montreal, QC, Canada, [2]Jewish General Hospital, Montreal, QC, Canada

Objective: The purpose of this study was to analyze the surgical outcome and economic implications following the introduction of robotics for the surgical treatment of endometrial cancer.

This study was a prospective evaluation of all consecutive robotic surgeries performed for the treatment of endometrial cancer since the introduction of a robotics program in December 2007, compared with the entire historic cohort of patients who underwent surgery, laparotomy or laparoscopy between March 2003 and December 2007. Collected data included demographics, clinical data, intraoperative variables, perioperative outcome and cost analysis. Comparison between groups was based on the $\chi 2$ and Mann–Whitney tests and logistic regression for selected outcomes.
Results: A total of 143 consecutive patients underwent robotic surgery between December 2007 and March 2010, and were compared with 160 consecutive patients who underwent laparotomy or laparoscopy between March 2003 and December 2007. Following the introduction of robotics, the rate of minimal invasive surgery (MIS) increased from 17% (laparoscopies) to 66% after one year and reached 95% after two years (robotics). Patient characteristics, stage, grade and histology were comparable for both groups, but the body mass index was higher in the robotics group (median 29.8 kg/m^2 vs 27.6 kg/m^2, $P<0.005$). Patients undergoing robotics suffered fewer adverse events (13% vs 42%, $P<0.0001$) with an adjusted odds ratio of 0.27 (95% CI = 0.14–0.51), and lower estimated median blood loss (50 cc vs 200 cc, $P<0.0.0001$), but longer operating times (233 minutes vs 206 minutes, $P<0.0001$). Median hospital stay was significantly shorter in the robotics group than in the laparotomy/laparoscopy group (one day vs five days, respectively, $P<0.0001$) with an odds ratio of 0.06 (95% CI = 0.03–0.16). The overall direct and indirect hospital costs, excluding the initial installation cost, were significantly lower for robotics than for the laparotomy/laparoscopy group (7644 CND vs 9704 CND, respectively, $P<0.0001$), with an odds ratio of 0.26 (95% CI 0.13–0.53). This benefit remained, albeit lower, when including acquisition and maintenance cost, as long as five to 10 surgeries were performed per week.
Conclusions: Introduction of robotics for uterine cancer staging increases the proportion of patients benefiting from minimal invasive surgery, improves short-term outcomes and results in lower hospital costs.

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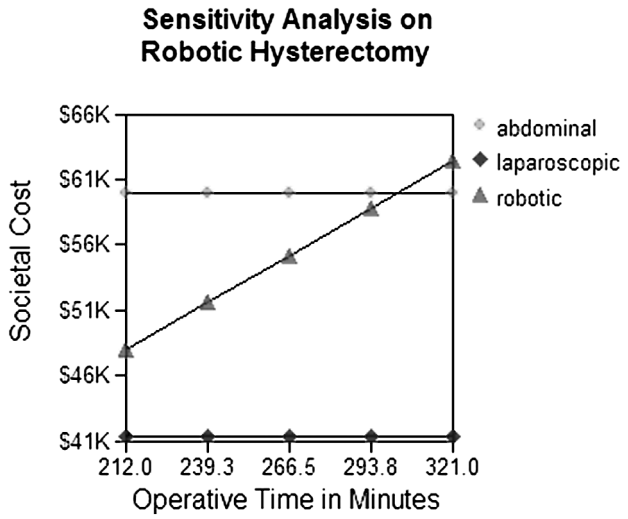
Comparing robotic hysterectomy with alternate operative strategies for endometrial cancer: A feasibility analysis of cost equivalence from the societal perspective
N. Shah, K. Wright, G. Jonsdottir, S. Jorgensen, J. Einarrson, M. Muto
Brigham & Women's Hospital, Boston, MA

Objective: Based on our institutional experience, we sought to determine the conditions under which robotic hysterectomy for endometrial cancer is cost equivalent from the societal perspective to abdominal or traditional laparoscopic hysterectomy.

We performed a retrospective cohort analysis of patient characteristics, operative times, complication rates, and hospital charges for 234 consecutive cases of patients who underwent a hysterectomy for endometrial cancer by any method in the year 2009 at Brigham & Women's Hospital in Boston, MA. Costs of robotic, abdominal and laparoscopic methods of hysterectomy were examined from the societal perspective, including total hospital charges (operative cost and inpatient stay) and lost production (foregone wages from work absence). Sensitivity analysis of these costs was performed using a cost-minimization model with the aid of decision tree software (TreeAge Pro 2009, TreeAge Inc.).
Results: Of 234 hysterectomies for endometrial cancer in 2009, 40 (17.1%) were robotic, 91 (38.9%) were abdominal, and 103 (44.0%) were laparoscopic. The conversion rate to open procedure for the robotic approach was 0%, whereas the conversion rate for traditional laparoscopy was 6.8%. The rate of intraoperative hemorrhage (estimated blood loss [EBL] >1000) was 0% for robotic, 2.3% for abdominal, and 1.0% for laparoscopic (Table 1). Ninety-six and three-tenths percent of the variation in operative cost between patients was predicted by operative time ($R=0.963$, $P<0.001$). Mean operative time for robotic hysterectomy was significantly longer than for other methods ($P<0.001$) (Fig. 1). The patient characteristics high body mass index and presence of adhesions influence the method of hysterectomy and independently predict increased operative time ($P<0.001$). On average, we estimate the costs to society are $54,062 for robotic hysterectomy, $59,997 for abdominal hysterectomy, and $41,339 for laparoscopic hysterectomy. The relative costs of each method were robust to sensitivity analysis of conversion and hemorrhage rates, as well assumptions regarding return to work. The threshold in operative time that makes robotic hysterectomy cost equivalent to an abdominal approach is within the range of our experience. By contrast, there is no operative time in our experience that makes robotic hysterectomy cost equivalent to traditional laparoscopy.
Conclusions: Although traditional laparoscopy is the least costly method to society for most patients, in select patients for whom this method is not feasible, robotic surgery may be the least costly.



	Robotic	Laparoscopic	Abdominal
N	40 (17.1%)	103 (44.0%)	91 (38.9%)
conversion rate	0%	6.8%	N/A
EBL > 1000	0%	2.3%	1.0%
median operative time	242 min	187 min	195 min
average societal cost	$54,062	$41,339	$59,997

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Comparison of robot-assisted and standard laparoscopic procedures in patients with endometrial cancer

M. Leitao, G. Gardner, G. Briscoe, K. Santos, E. Jewell, N. Abu-Rustum, C. Brown, D. Chi, Y. Sonoda, R. Barakat
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The purpose of this study was to compare outcomes of robot-assisted laparoscopic (RBT) and standard transperitoneal laparoscopic (LSC) procedures in patients with endometrial cancer.

All cases with a preoperative endometrial cancer diagnosis scheduled for RBT among nine surgeons were prospectively captured from May 1, 2007 to June 19, 2010. A consecutive cohort of cases scheduled for LSC for endometrial cancer during the same period among seven surgeons were retrospectively identified. All surgeons were experienced LSC surgeons. Fellow involvement was gradually increased for the RBT group over time. Fellow involvement was constant in the LSC group. Operating room time (ORT) was measured from patient arrival in the OR to exit. Operative time (OT) was measured from skin incision to full closure. Appropriate statistical tests were used.

Results: We identified 271 cases planned for RBT and 278 planned for LSC. Median body mass index was 28.6 kg/m^2 (range: 18.6–66) and 28.2 kg/m^2 (range: 16.9–57.2), respectively. Conversion to laparotomy was necessary in 32 RBTs (12%) and 34 LSCs (12%) ($P = 0.9$). Pelvic and paraaortic lymphadenectomy was performed in 110 of 239 (46%) completed RBTs and 112 of 244 (46%) completed LSCs ($P = 0.8$). Median ORT was 301 minutes (range: 142–613) and 253.5 minutes (range: 133–532), respectively ($P < 0.001$). Median OT was 217 minutes (range: 99–533) and 184.5 minutes (range: 80–445), respectively ($P < 0.001$). ORT and OT for RBTs varied among surgeons; more experienced RBT surgeons had significantly shorter ORTs. After 40 cases per surgeon, the median times for RBT equaled those for LSC. Median pelvic, paraaortic and total nodal counts for RBTs were 14 (range: 3–34), six (range: 0–22), and 21 (range: 7–48) compared with 16 (range: 3–48), five (range: 1–21), and 22.5 (range: 6–57) for LSCs (P = NS for all). Median length of hospital stay (LOS) was one day (range: 1–5) for RBTs (71% discharged on postoperative day one) and two days (range: 1–15) for LSCs (27% discharged on postoperative day 1) ($P < 0.001$). Median estimated blood loss was 50 mL (range: 0–400) for RBTs and 100 mL (range: 0–900) for LSCs ($P < 0.001$).

Conclusions: Robotic and LSC approaches are both feasible, and both result in good outcomes in patients with endometrial cancer. RBT was associated with longer ORT and OT compared with LSC in a well-established and experienced LSC program. However, ORT and OT were equal after 40 RBT cases per surgeon. Patients who underwent an RBT had a shorter LOS. LOS may be related to surgeon preferences and initial clinical pathways.

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Criteria for the safety of less radical trachelectomy in early-stage cervical cancer: A multicenter study

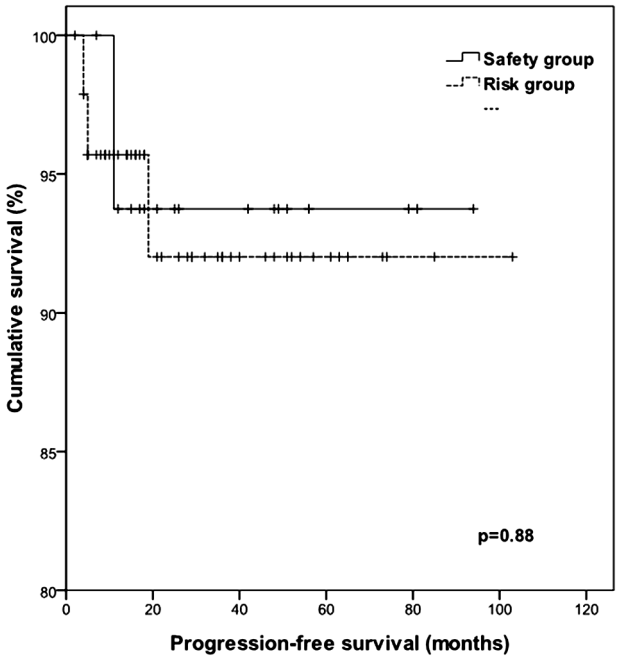
M. Kim[1], H. Kim[1], Y. Jeon[2], Y. Kim[2], T. Kim[3], M. Lim[4], C. Choi[5], S. Chang[6], S. Park[4], B. Kim[5], J. Kim[1]
[1]Seoul National University College of Medicine, Seoul, Republic of Korea, [2]Seoul National University Bundang Hospital, Seongnam, Republic of Korea, [3]Kwandong University College of Medicine, Seoul, Republic of Korea, [4]National Cancer Center, Goyang, Republic of Korea, [5]Samsung Medical Center, Seoul, Republic of Korea, [6]Ajou University School of Medicine, Suwon, Republic of Korea

Objective: We sought to identify the safety criteria for use of less radical trachelectomy in FIGO IA1–IB1 cervical cancer.

We reviewed medical records and pathologic slides of 65 patients with FIGO stage IA1–IB1 cervical cancer from six tertiary medical centers between November 2001 and March 2010. No parametrial involvement and lymph node metastasis were considered for defining the safety of less radical trachelectomy. The criteria for no parametrial involvement and lymph node metastasis were determined using the receiver operating characteristic (ROC) curve, and we compared clinicopathologic outcomes between safety and risk groups for less radical trachelectomy.

Results: The median age of all patients was 31 years (range: 22–44 years), and their diseases consisted of FIGO stage IA1 ($n = 6$), IA2 ($n = 5$), and IB1 ($n = 54$) cervical cancer. Mean stromal invasion and tumor size were 4.2 ± 3.68 mm and 1.8 ± 1.1 cm. The ROC curve showed that with a stromal invasion ≤ 5 mm and tumor size ≤ 10 mm, less radical trachelectomy could be safe. When we compared clinicopathologic outcomes between the safety (stromal invasion ≤ 5 mm and tumor size ≤ 10 mm) and risk (stromal invasion > 5 mm and tumor size > 10 mm) groups, the safety group showed no parametrial involvement and lymph node metastasis (see table). On the other hand, there was no difference in progression-free survival between the two groups (see figure).

Conclusions: These findings suggest that less radical trachelectomy may be safe in patients with cervical cancer with stromal invasion ≤ 5 mm and tumor size ≤ 10 mm.



Clinicopathologic outcomes in the safety (stromal invasion ≤ 5 mm and tumor size ≤ 10 mm) and risk (stromal invasion > 5 mm and tumor size > 10 mm) groups for less radical trachelectomy.

	Safety group($n=17$)	Risk group($n=48$)	P value
Age, median (range)	32 (23–39)	31 (22–44)	0.84
FIGO stage			<0.01
IA1	8 (47.1%)	0 (0%)	
IA2	5 (29.4%)	0 (0%)	
IB1	4 (23.5%)	48 (100%)	
Histology			0.29
Squamous carcinoma	15 (88.2%)	34 (70.8%)	
Adenocarcinoma	1 (5.9%)	11 (22.9%)	
Adenosquamouscarcinoma	1 (5.9%)	3 (6.35%)	
Type of operation			0.49
Abdominaltrachelectomy	2 (11.8%)	11 (22.9%)	
Vaginaltrachelecotmy	15 (88.2%)	37 (77.1%)	
Extent of radicality			0.66
Type I	1 (5.9%)	5 (10.4%)	
Type II	13 (76.5%)	31 (64.6%)	
Type III	3 (17.6%)	12 (25.0%)	
No. of resected lymph node, median (range)			
Pelvic lymph node	21 (8–44)	19 (0–47)	0.69
Paraaortic lymphnode	0 (0–0%)	0 (0–9)	0.40
Lymphovascular spaceinvasion	2 (11.8%)	21 (43.8%)	0.02
Parametrial involvement	0 (0%)	1 (2.1%)	1.00
Lymph node metastasis	0 (0%)	3 (6.3%)	0.56
Positive vaginalresection margin	1 (5.9%)	1 (2.1%)	0.46
Duration of follow-up	26 (7–94)	27 (2–103)	0.30

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Endometrial cancer as a platform for training residents in robotic hysterectomy techniques

M. Finan[1], R. Rocconi[2]
[1]University of South Alabama Mitchell Cancer Institute, Mobile, AL, [2]University of South Alabama, Mobile, AL

Objective: The robotic approach has been implicated as a cause for declining resident surgical experience in training programs nationwide. We describe our results and outcomes over a four-year period in training residents in robotic hysterectomy techniques in patients undergoing robotic surgery for endometrial cancer.

From August 1, 2006 through July 31, 2010 a method of training residents in robotic surgical techniques was developed; this included a dry lab that closely simulates the specific tasks of TRH. This was accompanied by resident observation of robotic surgery, and followed by progressive involvement of residents in the robotic console, focusing on TRH while the attending focused on teaching as well as performing lymphadenectomy when indicated. The resident training culminated in their completion of dozens of TRH, with careful supervision during these endometrial cancer cases. Data were analyzed with SPSS using χ^2, ANOVA and logistic regression analysis.

Results: Twenty residents completed the dry lab, and 302 robotic cases were performed. We excluded 115 cases of radical hysterectomy, staging or bilateral salpingo-oophorectomy only, and those nonendometrial cases, leaving 187 in our study group. Of these, 164 (87.7%) had some level of resident involvement, with 115 of 187 (61.5%) cases having residents operating in the console. In 67 cases (35.8%) the resident was able to complete the TRH. When resident cases were compared with attending cases, the two groups were similar with respect to: age, body mass index, number of prior surgeries, stage, and performance of lymphadenectomy. The attending group had a higher mean uterine weight, 125.3 versus 95.8 ($P=0.018$), and a lower mean patient age, 59.4 versus 63.1 ($P=0.027$), when compared with the resident group. The mean time for resident TRH was 45.95 minutes compared with 43.42 minutes for attending cases ($P=0.465$). Mean console time for resident cases was 98.03 minutes versus 98.34 minutes for attending cases ($P=0.956$). Total operating room times were also similar ($P=0.272$) as were complications ($P=0.143$) and length of stay ($P=0.643$).

Conclusions: Using endometrial cancer cases to train residents in TRH does not significantly add to the time of TRH, console time, overall procedure time, hospital stay, or complication rate; measurable outcomes were similar in the two groups. Increased resident participation in the console resulting in completion of robotic hysterectomy training is safe and feasible in patients undergoing robotic surgery for endometrial cancer and should be encouraged.

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Fertility-sparing surgery for treatment of early-stage cervical cancer: Open versus robotic radical trachelectomy

A. Nick, M. Frumovitz, K. Schmeler, P. Soliman, P. Ramirez
University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: The goal of this study was to compare open (ORT) and robotic (RRT) radical trachelectomy with pelvic lymphadenectomy and to provide outcome data on a large series of patients.

We retrospectively identified patients who underwent ORT or RRT at a single institution between September 2005 and June 2010. Tumor characteristics as well as perioperative, operative and obstetric outcomes were analyzed. The Mann–Whitney rank sum test and Fisher's exact test were used to compare surgical endpoints.

Results: Twenty-eight of 32 patients with early-stage cervical cancer (18 with IB1, 10 with IA2, and 4 with IA1 with lymphovascular space invasion/poorly differentiated histology) who desired future fertility underwent successful completion of radical trachelectomy. Four patients (one open/three robotic) underwent conversion to radical

hysterectomy secondary to close (<5 mm) endocervical margin. The median age at diagnosis was 28.9 years (range: 21.4–37.2), and 24 women (75%) were nulliparous. On preoperative exam, nine of 28 had a visible lesion ranging from 1 to 3 cm. Twenty-one patients (75%) underwent ORT and seven (25%) underwent RRT. RRT was associated with significantly less blood loss compared with ORT (median estimated blood loss: 75 cc vs 300 cc, $P=0.002$) and decreased length of postoperative stay (median: two days vs four days, $P<0.001$). There was no significant difference in operative time or postoperative complication rate. Median number of lymph nodes removed was 18 (range: 7–50) with no significant difference between surgical modality. One patient had a positive parametrial lymph node and received postoperative chemoradiation. The majority of patients (18/21 or 56%) had no residual disease in the cervix on final pathology. Common short-term morbidities included fever (14%) and urinary tract infection (UTI) or retention (25%). Common long-term morbidities were cerclage erosion (18%), cervical stenosis (14%), and irregular menstrual bleeding (11%). Ten (36%) patients are actively attempting or have attempted pregnancy, and of these two are currently pregnant, one delivered at 33.1 weeks EGA, one had two spontaneous abortions, and four are undergoing infertility evaluation or treatment. The median follow-up is 17.8 months (range: 0.95–57.9 months). There are no documented recurrences.

Conclusions: Radical trachelectomy is an oncologically safe procedure with low morbidity in appropriately selected patients with early-stage cervical cancer. RRT results in less blood loss and decreased postoperative stay compared with ORT.

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Integration of and training for robot-assisted surgery in a gynecologic oncology fellowship program

M. Leitao, G. Gardner, G. Briscoe, K. Santos, E. Jewell, C. Brown, D. Chi, R. Barakat
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The aim of this study was to assess the feasibility and outcomes of integrating robot-assisted surgery into a gynecologic oncology fellowship program.

We identified all cases planned for a robot-assisted procedure for various indications from the start of our robotics program May 15, 2007 to September 28, 2010. Various procedures for benign and malignant gynecologic indications were performed during this period. Time points were prospectively captured intraoperatively as part of an ongoing quality assessment program. All cases were performed with a gynecologic, surgical, or urologic oncology fellow. Fellow time spent on the surgeon console performing some or all of the procedure was captured intraoperatively for cases that were not converted to laparotomy. Total operating room time (ORT) was determined from patient arrival to exit in the operating room. Total operating time (OT) was determined from skin incision to completion of skin closure. Time periods were compared as follows: first year (Y1) = 2007/2008, second year (Y2) = 2009, third year (Y3) = 2010. Complications were assessed within 30 days of surgery. Appropriate statistical tests were used.

Results: Seven hundred seventy-five cases were scheduled for a robot-assisted procedure during our study period (162 in Y1, 331 in Y2, 282 in Y3). Median age, median BMI and malignancy as an indication for surgery were similar for all three periods (P = NS). Conversion to laparotomy occurred in 23 of 162 (14%) Y1 cases, 29 of 331 (9%) Y2 cases, and 18 of 282 (6%) Y3 cases ($P=0.02$). In cases not converted to laparotomy, fellows sat at the surgeon console in 17 of 139 (12%) Y1 cases, 151 of 302 (50%) Y2 cases, and 183 of 264 (69%) Y3 cases ($P<0.001$). The median ORT was 298 minutes (range: 116–670) for Y1, 249 minutes (range: 104–659) for Y2, and 225 minutes (range: 79–584) for Y3 ($P<0.001$). The median OT was 218 minutes (range: 58–533) for Y1, 169 minutes (range: 34–562) for Y2 and 148 minutes (range: 39–496) for Y3 ($P<0.001$). In the cases not converted to laparotomy, intra- and postoperative complications occurred in 25 of 139 (18%) Y1 cases, 27 of 302 (9%) Y2 cases, and 15 of 264 (6%) Y3 cases ($P<0.001$).

Conclusions: Robot-assisted surgery can be safely and efficiently integrated into a gynecologic oncology fellowship program. Despite significant increased fellow participation on the surgeon console, there were continued overall improvements in operating room time, operating time, rate of conversion and complication rates.

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Outcomes of patients with gynecologic malignancies undergoing video-assisted thorascopic surgery and pleurodesis for malignant pleural effusion

J. Whitworth, A. Bryant, R. Cerfolio, K. Schneider, J. Fauci, J. Straughn
University of Alabama, Birmingham, AL

Objective: We sought to evaluate the indications and outcomes of patients with known gynecologic malignancies who underwent video-assisted thorascopic surgery (VATS) and pleurodesis for malignant pleural effusion.

A retrospective study of patients with gynecologic malignancies who underwent planned VATS/pleurodesis between January 2000 and July 2010 was performed. Abstracted data included demographics, diagnosis, disease status, treatment history, indication for VATS, complications and outcomes.

Results: Forty-two patients with a gynecologic malignancy underwent VATS/pleurodesis. Median age was 63 years. Twenty-nine patients (69%) had ovarian cancer, 10% had endometrial cancer, 7% had cervical cancer, and 7% had peritoneal cancer. Fifty-seven percent had recurrent disease at the time of VATS. Fifty-seven percent of patients were undergoing chemotherapy at the time of VATS. Eight patients (19%) underwent perioperative VATS to improve pulmonary status; three patients were already intubated at the time of VATS. Seven patients (17%) underwent palliative VATS. Sixty-nine percent of patients had undergone at least one prior thoracentesis; 19% had previously required a chest tube. The median length of stay was seven days (range: 1–53). Two patients (5%) went to the ICU postoperatively. Twenty-five patients (60%) had right VATS, 13 (31%) had left VATS and four (10%) had bilateral VATS. Sixty-two percent had gross disease noted at the time of VATS, 52% had positive biopsy results and 52% had positive cytology. A mean of 1650 cc was drained at the time of surgery (range: 300–4500) and the majority (88%) of patients had a talc pleurodesis performed. Chest tubes remained for a median of two days (range: 1–7). Seven patients (17%) were readmitted within 30 days, six for complications unrelated to their VATS. One patient was readmitted with hospital-acquired pneumonia and died during readmission. Seventy-four percent of patients are dead of disease. Median time to death after VATS was 104 days. Patients who underwent a perioperative VATS had the longest survival (845 days), whereas those who underwent palliative VATS had a median time to death of 50 days.

Conclusions: Patients with gynecologic malignancies may require VATS/pleurodesis for symptomatic pleural effusions. Based on readmission rates, postoperative complications and subsequent pulmonary interventions, this procedure appears to be safe and effective. This

procedure should be used in the perioperative period and in the setting of recurrent disease to palliate symptoms.

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Perioperative and pathologic outcomes following robot-assisted laparoscopic versus abdominal management of ovarian cancer

G. Feuer, M. Burrell, S. Salmieri, P. Hernandez
Southeastern Gynecologic Oncology, LLC, Atlanta, GA

Objective: The goal of this study was to evaluate the feasibility and efficacy of robot-assisted management of ovarian cancer as compared with an abdominal approach.

Preoperative patient characteristics and perioperative outcomes and pathology were recorded for ovarian cancer cases between January 2008 and August 2010. Each case presented with ovarian cancer requiring initial staging, a pelvic mass with an intraoperative diagnosis of ovarian cancer, or exploration and staging following neoadjuvant chemotherapy. Lymph node dissection was performed when indicated. An abdominal approach ($n=25$) was used for masses >16 cm and for all emergency surgeries. A robotic ($n=39$) approach was used for all other cases. Data for the robotic and abdominal groups were compared using two-tailed t tests for continuous variables and χ^2 tests for percentages.

Results: Patient characteristics for the two groups were equivalent. Operative time for the robotic group was 129.4 minutes, which was 30 minutes longer than for the abdominal group (95.6 minutes, $P=0.0005$). A greater number of patients in the robotic group underwent neoadjuvant chemotherapy (1 (4%) vs 10 (25.6%), $P=0.0252$). Intraoperative complications included a splenic tear and a cystotomy in the abdominal group and a vaginal tear in the robotic group that did not require a conversion to laparotomy. Major complication rates were similar (7 (28.0%) vs 7 (17.9%), $P=0.13426$), with one reoperation in the robotic group to repair anastomosis leakage. There was less blood loss (460.4 cc vs 71.3 cc, $P=0.0001$) and a shorter hospital stay (7.2 days vs. 1.9 days, $P=0.0004$) in the robotic group. There were no differences in the number of nodes removed (9.1 nodes vs 10.2 nodes, $P=0.5179$) or days to chemotherapy (33.5 days vs 35.7 days, $P=0.7392$).

Conclusions: Robot-assisted management of ovarian cancer is feasible and effective, with reasonable perioperative and pathologic outcomes as compared with an abdominal approach. This suggests that gynecologic oncologists should consider a robotic approach in cases of interval staging, early-stage disease, or advanced-stage disease after neoadjuvant chemotherapy.

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Postoperative analgesic and antiemetic requirements after minimally invasive surgery for early cervical cancer: Is the robot better?

P. Soliman[1], G. Langley[1], R. dos Reis[2], M. Frumovitz[1], K. Schmeler[1], A. Nick[1], P. Ramirez[1]
[1]*University of Texas M.D. Anderson Cancer Center, Houston, TX,* [2]*Universidade Federal do RGS, Porto Alegre, Brazil*

Objective: Women with early-stage cervical cancer undergoing radical hysterectomy and pelvic lymphadenectomy using minimally invasive surgery (MIS), including both laparoscopy and robotic surgery, have been shown to have decreased blood loss and a shorter hospital stay when compared with women undergoing the same procedure using an open approach. It remains unclear if robotic surgery provides any benefit for the patient when compared with traditional laparoscopy. We sought to compare the postoperative analgesic and antiemetic requirements of the two MIS approaches.

After institutional review board approval, the medication administration records of all patients who underwent MIS radical hysterectomy and pelvic lymph node dissection at a single institution were reviewed. The surgical approach was based on surgeon preference, and all cases included in the analysis were performed concurrently. The type and amount of analgesics and antiemetics used by each patient during the hospital stay were recorded. Descriptive statistics and nonparametric tests were used to compare the groups undergoing laparoscopy (LRH) and robotic surgery (RRH).

Results: Between April 2004 and August 2010, 92 patients underwent MIS for early cervical cancer: 62 by LRH and 30 by RRH. Median age was higher in the RRH group (42 years vs 52 years, $P=0.02$). There was no difference in median BMI between the groups (27 kg/m^2 vs 26.7 kg/m^2, $P=0.58$). Length of hospital stay was significantly shorter in the RRH group (two days vs one day, $P=0.002$). Total intravenous opioid requirements were significantly higher in the LRH group (26.1 mg morphine sulfate) compared with the RRH group (10.7 mg morphine sulfate) ($P<0.001$). However, there was no difference in oral opioid, nonopioid analgesic, or antiemetic requirements between the two groups.

Conclusions: Our data suggest that the robotic approach to radical hysterectomy and pelvic lymphadenectomy results in a significant decrease in length of hospital stay and intravenous opioid requirements, potentially providing added benefit over total laparoscopic radical hysterectomy.

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Postoperative pain medication requirements in patients undergoing robotically assisted and standard laparoscopic procedures for newly diagnosed endometrial cancer

M. Leitao, G. Gardner, G. Briscoe, P. Dholakiya, K. Santos, E. Jewell, N. Abu-Rustum, Y. Sonoda, R. Barakat, V. Malhotra
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The purpose of this study was to compare postoperative pain medication use in patients undergoing robot-assisted (RBT) and standard laparoscopic (LSC) procedures for newly diagnosed endometrial cancer.

All cases with a preoperative endometrial cancer diagnosis scheduled for RBT or LSC from May 1, 2007 to June 19, 2010 were identified. A standardized postoperative pathway includes routinely offering all patients intravenous (IV) patient-controlled analgesia (PCA). Various IV PCA data points were retrospectively abstracted from the electronic medical record for patients who did not require conversion to laparotomy and had an IV PCA started postoperatively. All medication doses were converted to equivalent fentanyl doses using institutional conversion guidelines. The total fentanyl dose was calculated. The total fentanyl dose was then divided over the total number of hours the patient had access to the PCA to calculate the hourly fentanyl dose (HFD).

Results: We identified 239 RBT and 244 LSC cases that were not converted to laparotomy. Baseline patient characteristics were similar. IV PCA was used in 206 RBTs (86%) and 217 LSCs (89%) ($P=0.2$). Ketorolac was given concurrently in 77% of cases in both groups

($P=0.9$). Fentanyl was used in 196 of 206 RBTs (95%) and 195 of 217 LSCs (90%) ($P=0.02$). A basal infusion was used in 3 (1.5%) and 21 (10%), respectively ($P<0.001$). The median number of patient attempts was 14 (range: 0–372) for RBT and 21 (range: 0–349) for LSC ($P<0.001$). The median number of hours with access to a PCA was 14.9 (range: 0–51) for RBT compared with 16.8 (range: 7–180) for LSC ($P<0.001$). The median number of additional medication boluses needed was 1 (range: 1–5) for RBT and 2 (range: 1–6) for LSC ($P=0.03$). The total fentanyl dose received for RBT cases was 242.5 μg (range: 0–2705 μg) compared with 367.5 μg (range: 0–2625 μg) for LSC ($P<0.001$). The median HFD was 16.7 μg (range: 0–51 μg) for RBT compared with 22.7 μg (range: 0–132.4 μg) for LSC ($P=0.01$). Simultaneous multiple regression analysis further demonstrated that RBT was independently associated with a lower total fentanyl dose compared with LSC ($P=0.04$).

Conclusions: The use of the robotic platform is independently associated with significantly lower postoperative pain medication requirements compared with standard laparoscopy.

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Predictive risk factors for prolonged hospitalizations after gynecologic laparoscopic surgery

B. Zand[1], A. Nick[2], H. Sangi-Haghpeykar[1], M. Frumovitz[2], P. Soliman[2], K. Schmeler[2], P. Ramirez[2]

[1]Baylor College of Medicine, Houston, TX, [2]University of Texas M.D. Anderson Cancer Center, Houston, TX

Objective: The goal of this study was to evaluate perioperative factors that may result in prolonged hospitalization after gynecologic laparoscopic surgery.

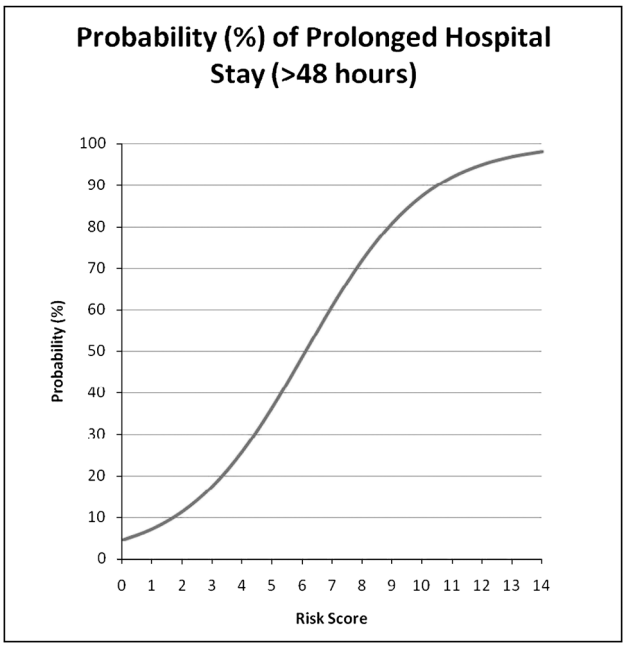
All patients who underwent gynecologic laparoscopic surgery for benign or malignant diagnosis at a single academic institution from January 2000 to January 2009 were evaluated. Patients were grouped as either short length of stay (<48 hours) or prolonged length of stay (>48 hours). Intraoperative characteristics analyzed included complexity of surgery, blood loss, operative time, malignant or benign indications and intraoperative complications. Low-complexity procedures included diagnostic and second-look laparoscopy. The intermediate group comprised such procedures as simple hysterectomies and oophorectomies. High-complexity surgeries included radical procedures/lymph node dissections. Postoperative adverse events were any complication that occurred within 30 days. Logistic regression analysis was done to assess significant predictors. Sensitivity/specificity analysis was performed for identification of cutoffs for risk factors continuous in nature. A risk score was created from the coefficients of the multivariate analysis to predict the probability of prolonged length of stay.

Results: A total of 902 patients met criteria for evaluation. The median BMI was 26.5 kg/m^2 (range: 16.8–72.3) and the median age was 49 years (range: 12–88). There were 509 (56.4%) patients who underwent surgery for benign indications and 393 (43.6%) for malignant indications. The number of cases that were of low, medium, and high complexity were 84 (9.3%), 708 (78.5%), and 110 (12.2%), respectively. A total of 344 (38.1%) patients had a prolonged stay. Independent predictors of prolonged stay were age >50 years ($P<0.0001$), blood loss >80 mL ($P=0.003$), operative time >170 minutes ($P<0.0001$), blood transfusion ($P=0.001$), surgery for endometrial cancer ($P=0.0008$), medium/high-complexity surgery ($P=0.0007$) and postoperative complications ($P<0.0001$). BMI, prior surgical history and medical comorbidities were not independent predictors of prolonged stay. A model including the significant variables was used to compute a risk score (RS) (see table) and describe probability of prolonged stay (see figure).

Conclusions: Our study showed that only age >50, blood loss >80 mL, operative time >170 minutes, blood transfusions, medium/high-complexity surgery and postoperative complications increase the risk of prolonged hospital stay after laparoscopic surgery.

Variable	Value	Coefficent	Odds ratio	Risk point (RP)
Age	≥ 50 years	0.521	1.684	1
Blood loss	≥ 80 mL	0.6648	1.944	1
Operative time	≥ 170 min	0.9078	2.479	2
Complexity	Medium or high	1.024	7.592	2
Transfusion	Yes	2.0271	2.109	4
Diagnosis	Endometrial cancer	0.7462	2.784	2
Postoperative complication	Yes	0.8315	2.297	2
Constant coefficent		–3.0571		

Figure 1. Probability (%) of prolonged hospital stay (>48 hours) after gynecologic laparoscopic surgery. The graph given by the formula 100/(1+ e^(3.0571-(RS/2)). RS = risk score= sum of risk points (RP)



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Robot-assisted laparoscopic hysterectomy is superior for endometrial cancer in the morbidly obese

A. Maddock[1], R. Pierre[1], T. Ford[1], D. Kredentser[2], T. McElrath[2], T. Morrissey[2], P. Timmins[2]

[1]Albany Medical Center, Albany, NY, [2]Women's Cancer Care Associates, Albany, NY

Objective: The aim of this study was to demonstrate the feasibility of robot-assisted laparoscopic hysterectomy (RALH) for the surgical management of endometrial cancer (EC) in obese women.

A data set including 1034 RALHs performed by four surgeons between March 2007 and January 2010 was evaluated. One hundred ninety-three patients with EC were abstracted from this database based on WHO BMI criteria. One hundred four were obese, 67 were morbidly obese and 22 extremely morbidly obese. Contemporary

consecutive cohorts including 44 laparotomies (XLAPs) and 57 total laparoscopic hysterectomies (TLHs) were used for comparison. Preoperative demographics including age, BMI, parity and prior abdominal surgery were evaluated. Peri- and postoperative metrics including operative time (OT), node dissection (ND), estimated blood loss (EBL), uterine weight (UWt) and length of hospital stay (LOS) were also compared. Continuous variables are reported as means $\pm$SD. All comparisons of continuous variables across cohorts were analyzed using a two-sample Student t test. Two-tailed P values <0.05 were considered significant.

Results: The preoperative demographics were statistically similar in all groups. Major and minor complication rates were similar in each cohort. The RALH and TLH cohorts were statistically similar in relation to UWt, ND, and LOS. However, OT (137 ± 43 minutes vs 150 ± 47 minutes, $P = 0.05$) and EBL (80 ± 85 mL vs 206 ± 206 mL, $P < 0.001$) were lower in the RALH group. In contrast, UWt (378 ± 364 g vs 115 ± 77 g, $P < 0.001$), number of nodes (19.1 ± 12.0 vs 12.0 ± 11.5, $P = 0.001$), EBL (389 ± 415 mL vs 80 ± 85 mL, $P < 0.001$), and LOS (4.0 ± 1.5 days vs 1.3 ± 1.1 days, $P < 0.001$) differed between the XLAP and RALH groups. XLAPs were quicker than RALHs (115 ± 33 minutes vs 137 ± 43 minutes, $P < 0.001$). And 2.6% of RALHs (5/193) were converted to open surgery, compared with 15.8% of TLHs (9/57).

Conclusions: The TLH and RALH cohorts were statistically identical in every pre-, peri- and postoperative metric except OT and EBL. On the basis of UWt, however, it is clear that XLAPs are reserved for patients with a higher suspected clinical stage of disease and should not be in the same comparison group. Much has been made in the literature of the additional OT associated with RALH. However, this study shows a statistically significant decrease in operative time with RALH as compared with TLH. The overall findings of this study support the assertion that RALH facilitates the use of a minimally invasive approach and should be strongly considered for surgical treatment of EC in the obese population.

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Robot-assisted surgery for gynecologic cancer: A systematic review

D. Lu[1], G. Shi[1], Z. Liu[1], D. Liu[2], X. Zhou[2]
[1]West China Second University Hospital/Sichuan University, Chengdu, China, [2]West China School of Medicine, Sichuan University, Chengdu, China

Objective: Robotic surgery is the latest innovation in the field of minimally invasive surgery, and its use in endometrial cancer (EC) and cervical cancer (CC) has been reported. The aim of this Cochrane systematic review was to evaluate the evidence for and against robot-assisted surgery in gynecologic cancers.

We searched the electronic databases (CENTRAL, MEDLINE, EMBASE) comprehensively and the citation lists of relevant publications. All randomized controlled trials (RCTs) comparing robot-assisted surgery with laparoscopic or open surgery were included. As no RCTs were available, controlled clinical trials (CCTs) were included. We assessed risk of bias and extracted data from included studies.

Results: Seventeen CCTs involving patients with EC (1640 patients) and CC (652 patients) were identified. When compared with laparoscopic surgery for EC, robotic surgery was associated with comparable length of stay and perioperative complication rate, but with significantly lower estimated blood loss (EBL) and conversion rate. When laparotomy was performed for EC, the intraoperative complication rate was comparable, but the postoperative complication rate and EBL were significantly lower than in the robotic surgery group. When compared with laparoscopic surgery for CC, robotic surgery was associated with a comparable perioperative complication rate and disease-free and overall survival, but with a significantly lower EBL. When laparotomy was performed for CC, the intraoperative complication rate and disease-free and overall survival were comparable, but length of stay and postoperative complication rate were significantly lower in the robotic surgery group (see table).

Conclusions: Evidence from CCTs supports the use of robot-assisted surgery for EC and CC. Additional well-designed RCTs are warranted to confirm or refute the current evidence.

Robot-assisted surgery for endometrial and cervical cancer.

Outcome	Robot vs. laparoscopy MD/ RR [95% CI]	Robot vs. laparotomy MD/ RR [95% CI]
Endometrial cancer		
Length of stay (day)	-0.20 [-0.44, 0.04]	Null
Intraoperative complication rate	0.57 [0.19 , 1.66]	0.97 [0.19, 4.99]
Postoperative complication rate	0.80 [0.57, 1.12]	0.30 [0.21, 0.44]
Estimated blood loss (ml)	-75.21 [-98.97, -51.45]	-160.09 [-203.93, -116.24]
Transfusion rate	0.58 [0.24, 1.40]	0.28 [0.12, 0.63]
Conversion rate	0.42 [0.24, 0.72]	Null
Cervical cancer		
Disease-free survival rate	0.98 [0.90, 1.08]	1.13 [1.04, 1.24]
Overall survival rate	0.99 [0.91, 1.08]	1.02 [0.97, 1.07]
Length of stay (day)	Null	-1.81 [-2.45, -1.16]
Intraoperative complication rate	1.17 [0.32, 4.33]	0.64 [0.21, 1.99]
Postoperative complication rate	1.43 [0.77, 2.66]	0.68 [0.53, 0.87]
Estimated blood loss (ml)	-76.60 [-132.7, -20.49]	Null
Transfusion rate	3.56 [0.58, 21.76]	0.27 [0.12, 0.62]

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Robotic radical hysterectomy: Extent of tumor resection and operative outcomes compared with laparoscopy and exploratory laparotomy

G. Gardner, M. Leitao, M. Carreras, E. Jewell, Y. Sonoda, D. Levine, N. Abu-Rustum, C. Brown, D. Chi, R. Barakat
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The aim of this study was to evaluate the radicality of resection and operative outcomes for patients undergoing surgery for newly diagnosed cervical cancer with the robotic platform (RBT) compared with standard laparoscopy (LSC) and laparotomy (LAP).

All radical hysterectomies performed for newly diagnosed cervical cancer from May 1, 2007 to July 6, 2010 were identified. Patient demographics, operative time, estimated blood loss (EBL), length of stay (LOS), operative conversions and complications were identified. Nodal counts, length of vaginal margin (VM) and size of parametria resected (width of parametria [WP] and total area of parametria [TP]) were determined. TP was defined as a volumetric unit of width, length and thickness of parametrial tissue resected. SPSS Version 15.0 was used to analyze for differences between the surgical groups. Medians were compared with the Kruskal–Wallis test. Dichotomous groups were compared with the χ^2 test; when P was <0.05 for the three-group test, two-group analyses were performed: RBT versus LSC and RBT versus LAP.

Results: Seventy-eight radical hysterectomies were identified: 45 LAP, 27 RBT, and six LSC. There was no difference in age, parity, BMI, prior pelvic surgery, or other comorbidities between the surgical groups. Median total room times for RBT (366 minutes, range: 228–659) and LSC (383 minutes, range: 307–445) were similar, but longer than that for LAP (273 minutes, range: 164–431) ($P < 0.001$). EBL for RBT was 100 cc (range: 50–300), compared with 200 cc (range: 100–

350) for LSC ($P=0.02$) and 300 cc (range: 100–900) for LAP ($P<0.001$). Median LOS for RBT was two days, compared with three days for both LSC and LAP ($P<0.001$). With respect to the extent of parametria resected, median left WP was four, 4.5, and 3.5 cm ($P=0.53$); median right WP was four, 4.2, and 3.95 cm ($P=0.74$); median left TP was 8.75, 9.04, and 6.6 cm^3 ($P=0.78$); and median right TP was 8.55, 10.28, and 7.65 cm^3 ($P=0.63$) for RBT, LSC, and LAP, respectively. Median VM was 2.5, 1.6, and 2.55 cm ($P=0.57$) for RBT, LSC, and LAP, respectively. Median number of pelvic nodes was 18, 25, and 23 ($P=0.27$), and median number of paraaortic nodes was five, three, and four ($P=0.75$) for RBT, LSC, and LAP, respectively. There were no operative conversions from RBT to LSC or LAP. There was no difference in complication rate between the three groups ($P=0.58$).
Conclusions: Irrespective of surgical approach, the degree of radicality as identified by extent of parametrial resection, length of vaginal margin, and nodal counts was similar for all cases. Robotic cases were associated with lower EBL and shorter LOS than LSC and LAP. There was no difference in the rates of intraoperative or postoperative complications across the surgical groups.

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Surgery–adjuvant therapy interval in women with endometrial cancer staged with robot-assisted laparoscopy versus laparotomy

E. Simons, L. Huang, S. Messing, E. Toy
University of Rochester Medical Center, Rochester, NY

Objective: The purpose of this study was to determine the interval between surgical staging procedure and initiation of adjuvant therapy in patients with endometrial cancer staged by a robotic procedure versus laparotomy.

Adult women who underwent comprehensive surgical staging and adjuvant radiation or chemotherapy for endometrial cancer in Rochester, NY, between January 2004 and December 2009 were eligible for the study. One hundred eighty-two patients met inclusion criteria, of whom 121 were staged by laparotomy and 61 robotically. A retrospective chart review collected information on demographic characteristics, past medical history, length of hospital stay during surgical admission and perioperative adverse events. Tumor histology, grade and surgical stage were also recorded. The surgery–adjuvant therapy interval ("STAT interval") was calculated as the number of days between the date of surgical staging and the date of first adjuvant treatment.
Results: Baseline characteristics including age, race, insurance status, body mass index and significant medical history were similar for the groups. Histologic subtypes and grade also did not significantly differ; however, patients in the laparotomy cohort were more likely to have advanced-stage disease on final pathology ($P=0.03$). Length of hospital stay during the surgical admission was significantly shorter in the robotic group (2.7 days vs 4.8 days, $P<0.001$). The overall STAT interval did not significantly differ between the two groups. However, the variance was much larger in the laparotomy group. In patients undergoing adjuvant chemotherapy, the STAT interval was significantly shorter in the robotic cohort (29 days vs 37 days, $P=0.03$). For those receiving adjuvant radiation therapy, the STAT interval did not significantly differ between the two groups.
Conclusions: In this study, patients who received adjuvant chemotherapy after robotic staging for endometrial cancer had a significantly shorter surgery–adjuvant therapy interval than those staged by laparotomy. As the decision to start adjuvant chemotherapy often hinges on a patient's postoperative recovery, this finding may reflect improved postoperative functional status in patients who undergo robotic staging procedures. This study therefore suggests that for women who may ultimately require adjuvant chemotherapy, robotic staging procedures may allow earlier initiation of treatment in the postoperative period.

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Surgical outcomes of robot-assisted surgical staging for morbidly obese (BMI >40) patients with endometrial cancer: Technique for morbidly obese patients

P. Singhal[1], H. Haque Aziz[2], G. Tyler[3], D. Marchetti[1]
[1]Gynecologic Oncology Associates of WNY, Buffalo, NY, [2]State University of New York, Buffalo, NY, [3]Marshfield Clinic, Marshfield, WI

Objective: The purposes of this study were to evaluate the surgical outcomes of a robot-assisted endometrial cancer staging procedure for morbidly obese patients (BMI >40) and to describe "hand-assisted technique."

We prospectively collected single-surgeon, single-institution robot-assisted endometrial cancer staging outcomes of 52 morbidly obese patients with BMI >40.0 kg/m^2 (range: 40–70). These patients underwent total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO) and/or bilateral pelvic (PLND) and periaortic (PaLND) lymph node dissection. We also describe hand-assisted robotic surgery (HARS) for supermorbidly obese patients (BMI >60). Major intraoperative and postoperative complications, or conversion to laparotomy, were measured. Secondary outcomes including operative time, blood loss, transfusion rate, number of lymph nodes retrieved and length of hospitalization were also measured.
Results: Fifty-two patients with BMI >40 were identified as undergoing robot-assisted endometrial cancer staging. Of 52 patients, 45% had undergone previous laparotomy. The majority of these patients (85%) had major medical problems. Median operative time was 255 minutes (range: 195–450). Four patients underwent HARS. The median operative time for HARS was 188 minutes (range: 155–210). Three patients were converted to laparotomy. There were no blood transfusions. Median estimated blood loss was 109 mL (range: 25–400). There were no intraoperative complications. The median length of stay was 1.76 days (range: 1–3.5). One patient was readmitted for thromboembolism and was diagnosed to have heparin-induced thrombocytopenia. The median number of total lymph nodes removed was 22 (range: 6–41).
Conclusions: Robot-assisted endometrial cancer surgery is feasible among morbidly obese patients. Furthermore, we have started using hand-assisted port among morbidly obese patients to decrease intraoperative time. We caution that surgery in these obese patients is technically more difficult and should be preceded with caution.

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Surgical volume and its effect on morbidity and mortality for endometrial cancer

S. Lewin, T. Herzog, I. Deutsch, X. Sun, W. Burke, J. Wright
Columbia University College of Physicians and Surgeons, New York, NY

Objective: Surgical volume is an important determinant of outcome for a number of high-risk surgical procedures. Patients operated on by high-volume surgeons and at high-volume hospitals have decreased morbidity and mortality. Little is known about the association between volume and outcome for endometrial cancer.

We examined the effect of surgeon and hospital volume on perioperative morbidity and mortality for women who underwent hysterectomy for endometrial cancer.

Patients who underwent abdominal hysterectomy with or without lymphadenectomy by a gynecologic oncologist for endometrial cancer from 2003 to 2007 and were recorded in the Perspectives database were analyzed. The primary endpoints for analysis were operative injuries, perioperative surgical complications, medical complications, transfusion, length of stay, ICU use and perioperative death. Surgeons and hospitals were stratified into volume-based tertiles based on the annual number of hysterectomies performed. Multivariable generalized estimating equations were used to examine the effect of surgeon and hospital volume on morbidity and mortality while controlling for other clinical variables and surgeon and hospital clustering.

Results: A total of 6015 patients were identified. Volume had no effect on the rates of intraoperative injury. Patients operated on by high-volume surgeons were less likely to experience perioperative surgical complications (12% vs 15%, OR = 0.57, 95% CI = 0.38–0.85), to have medical complications (22% vs 31%, OR = 0.57, 95% CI = 0.37–0.88), and to require ICU admission (4% vs 9%, OR = 0.47, 95% CI = 0.28–0.80). Surgeon volume had no effect on transfusion requirements, length of stay, or rates of readmission. Patients operated on at high-volume hospitals were less likely to require ICU admission (4% vs 9%, OR = 0.44, 95% CI = 0.25–0.77). There was no association between hospital volume and postoperative medical or surgical complications. Neither surgeon volume nor hospital volume influenced perioperative mortality.

Conclusions: Patients treated by high-volume gynecologic oncologists have lower rates of perioperative surgical complications and medical complications. The effect of surgical volume on outcomes for women with endometrial cancer operated on by gynecologic oncologists is modest compared with that for other high-risk surgical procedures.

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Two-port access staging laparoscopy for endometrial cancer: A case–control study

G. Yim[1], S. Kim[1], J. Paek[1], E. Nam[1], Y. Kim[1], S. Lee[1], M. Lee[1], J. Kim[2]
[1]Severance Hospital/Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Kwandong University College of Medicine, Goyang, Republic of Korea

Objective: The purpose of this study was to compare surgical outcomes of two-port access (TPA) and conventional laparoscopy in surgical staging of endometrial cancer.

This was a case–control study of 15 and 33 patients who underwent TPA and conventional staging laparoscopy for endometrial cancer. The TPA system consisted of a single multichannel port at the umbilicus and an ancillary 5-mm port in the suprapubic area.

Results: Patient data in terms of operative morbidity and surgical outcomes were evaluated. All surgical procedures were completed laparoscopically with no conversion to laparotomy. The TPA group had significantly longer operative time (240 ± 47 minutes vs 181 ± 63 minutes, $P = 0.002$), less blood loss (142 mL vs 221 mL, $P = 0.025$), larger number of retrieved paraaortic lymph nodes (18 vs 6, $P < 0.001$), shorter postoperative hospital stay (6.1 ± 2.1 days vs 7.8 ± 1.7 days, $P = 0.004$) and less postoperative pain (6 hours: 3.3 vs 4.1; 24 hours: 2.6 vs 3.2; 48 hours: 2.5 vs 2.8, $P = 0.035$). There were no postoperative complications requiring further management.

Conclusions: Two-port access staging laparoscopy using a single multichannel port system could be a feasible procedure in selected endometrial cancer patients with only minimal skin incisions. Prospective randomized trials will permit the evaluation of the potential benefits of this minimally invasive surgical technique.

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Utilization of specialized postoperative services in a comprehensive surgical cytoreduction program

K. Long, E. Tanner, R. Brightwell, K. Shih, Y. Sonoda, M. Leitao, N. Abu-Rustum, R. Barakat, D. Chi
Memorial Sloan–Kettering Cancer Center, New York, NY

Objective: The objective of this study was to evaluate the use of specialized postoperative services in the care of patients undergoing surgical cytoreduction for serous ovarian carcinoma.

Demographic, surgical, and perioperative data were collected for all patients with advanced-stage serous carcinoma of the ovary, fallopian tube or peritoneum who underwent primary or interval cytoreductive surgery at our institution from December 2000 to December 2009. The postoperative services evaluated included: nutrition, respiratory therapy, physical therapy, the wound care team, the lymphedema prevention team, interventional radiology, anesthesia/pain and integrative medicine. Extensive upper abdominal surgery (EUAS) was defined as surgery involving the liver, diaphragm, spleen, pancreas, gallbladder, stomach, porta hepatis or celiac axis. Patients without EUAS were classified as the "standard" surgical group. Standard two-sided statistical analysis was used.

Results: Of the 510 patients identified, EUAS was performed on 43.3%. Patients with EUAS had increased rates of optimal cytoreduction ($P < 0.001$) and complete gross resection ($P < 0.001$). They also had longer procedures ($P < 0.001$), higher blood loss ($P < 0.001$), longer hospital stays ($P < 0.001$), and more complications ($P = 0.001$) than patients in the standard group. Utilization of nutrition services and care by a dedicated wound team did not significantly differ between the EUAS group and the standard group ($P = 0.83$ and 0.84, respectively). Interventional radiology was required in 26.7% of the EUAS group versus 11.8% of the standard group ($P < 0.001$). Physical therapy was consulted for 38% of the EUAS group versus 21.8% of the standard group ($P < 0.001$). Respiratory therapy was consulted for 48.4% of the EUAS group versus 29.8% of the standard group ($P < 0.001$). In the EUAS group, utilization of the lymphedema prevention team ($P = 0.016$), anesthesia/pain ($P = 0.006$), and integrative medicine ($P = 0.035$) was significantly increased compared with the standard group.

Conclusions: Since 2001, there has been a change in the surgical paradigm at our institution to incorporate EUAS into surgical cytoreduction. This change has led to improved cytoreductive outcomes but also increased complications, necessitating greater use of specialized postoperative care services. This information may be useful for institutions contemplating implementing a similar comprehensive surgical cytoreduction program.

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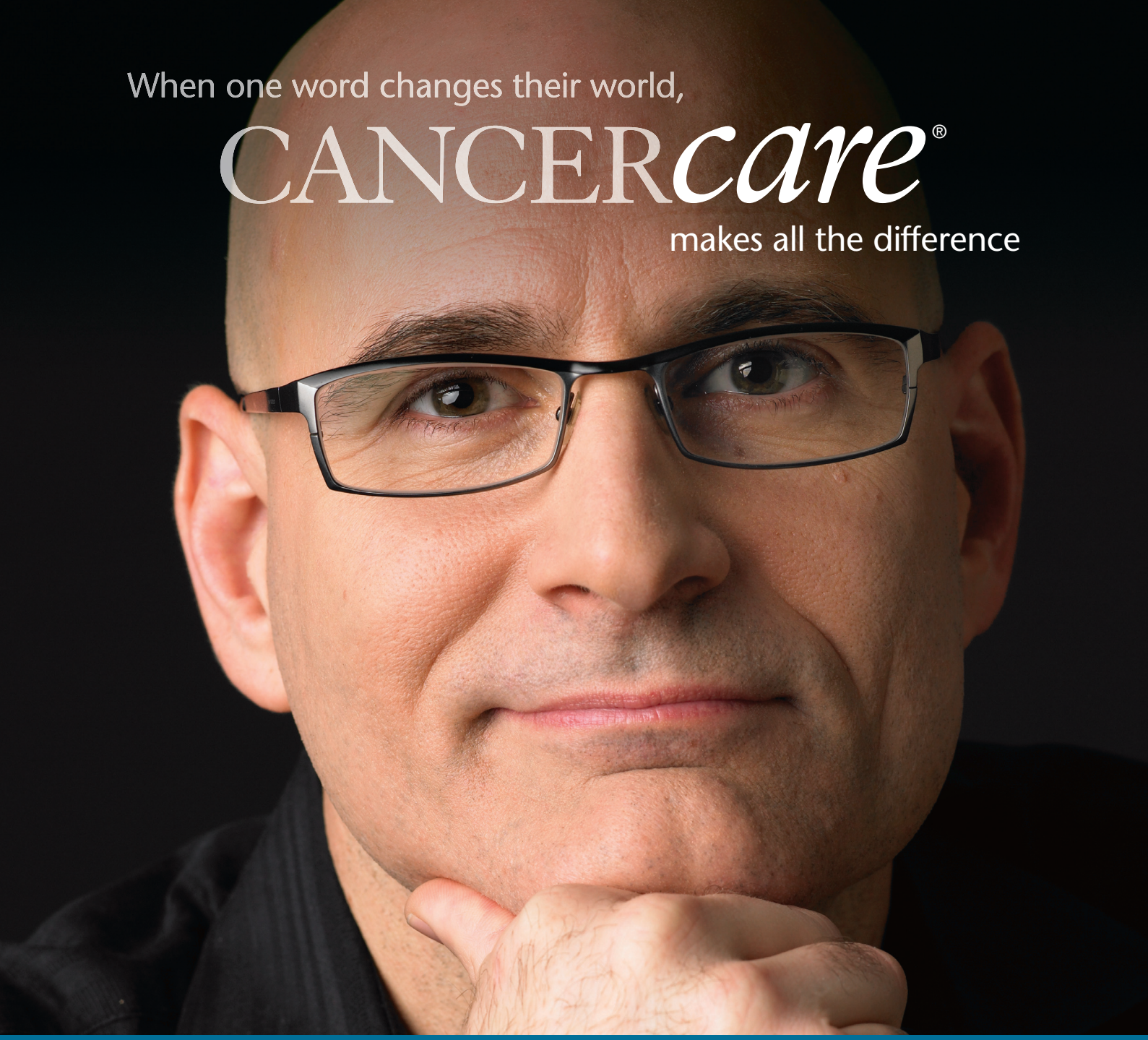

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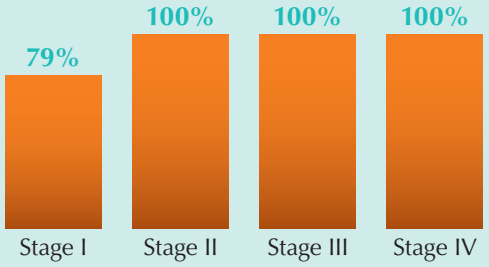

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