In compliance with ACCME regulations, the American College of Surgeons, as the accredited provider of this activity, must ensure that anyone in a position to control the content of the educational activity has disclosed all relevant financial relationships with any commercial interest. Members of the program committee were required to disclose all financial relationships and speakers were required to disclose any financial relationship as it pertains to the content of the presentations. ACS defines a “commercial interest” as any proprietary entity producing health care goods or services consumed by, or used on patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests. The ACS considers “relevant” financial relationships as financial transactions (in any amount) occurring within the past 12 months that may create a conflict of interest.

ACS is also required, through our joint sponsorship partners, to manage any reported conflict and eliminate the potential for bias during the activity. The program committee members (if applicable) and speakers were contacted and the conflicts listed below have been managed to our satisfaction. However, if you perceive a bias during a session, please report the circumstances on the session evaluation form.

Please note we have advised the speakers that it is their responsibility to disclose at the start of their presentation if they will be describing the use of a device, product, or drug that is not FDA approved or the off-label use of an approved device, product, or drug or unapproved usage.

The requirement for disclosure is not intended to imply any impropriety of such relationships, but simply to identify such relationships through full disclosure, and to allow the audience to form its own judgments regarding the presentation.

<table>
<thead>
<tr>
<th>NAME</th>
<th>NOTHING TO DISCLOSE</th>
<th>DISCLOSURE (Company &amp; Role)</th>
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</thead>
<tbody>
<tr>
<td>Carol Aghajanian, MD</td>
<td>Sanofi Aventis/BiPar- Ad board and Honorarium, IMER- Speaker Honorarium   Watermark Research- Honorarium</td>
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<tr>
<td>Ronald Alvarez, MD</td>
<td></td>
<td>GSK, Eli Lilly, Ortho Biotech - Honorarium</td>
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<td>(Planning Committee member)</td>
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<tr>
<td>Philip J. DiSaia, MD</td>
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<td>Merck, Ortho Biotech- Honorarium- Speaker</td>
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<td>(Planning Committee)</td>
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<tr>
<td>Mark Einstein, MD</td>
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<td>BMS- Advisory Board, Honorarium</td>
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<tr>
<td>John Farley, MD</td>
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<td>(Planning Committee)</td>
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<td>Martee Hensley, MD</td>
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<td>Neil Horowitz, MD</td>
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<td>D. Scott McMeekin, MD</td>
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<td>Kathleen Moore, MD</td>
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<td>David S. Miller, MD</td>
<td>Sanofi Aventis, Marshall Edwards Pty Limited, Genentech, GlaxoSmithKline, Fujirebo Diagnostics, Inc.- Grant funding, Genentech, Amgen, Abraxis Bioscience, Ortho Biotech- Advisory Board and Honorarium, Ortho Biotech-Speaker</td>
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<tr>
<td>Bradley Monk, MD</td>
<td>Johnson &amp; Johnson, GSK, Eli Lilly, Merck, Genzyme – Research Funding, Honorarium, Speaker</td>
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<tr>
<td>David Mutch, MD</td>
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<td>George Mutter, MD</td>
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<td>Sang Young Ryu, MD</td>
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<td>Nick Spirtos, MD</td>
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<td>Frederick Stehman, MD</td>
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<tr>
<td>Matthew Powell, MD</td>
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</tbody>
</table>

For questions or comments about this CME activity, please contact Zelika W. Compaore, Manager, Education Programs and CME Compliance of The Gynecologic Oncology Group at: zcompaore@gog.org.
GOG Mission

The Gynecologic Oncology Group (GOG) is a non-profit organization (national) with the purpose of promoting excellence in the quality and integrity of clinical and basic scientific research in the field of Gynecologic malignancies. The Group (gynecologic oncologists, medical oncologists, pathologists, radiation oncologists, nurses, statisticians, basic scientists, quality of life experts, data managers and administrative personnel) is committed to maintaining the highest standards in clinical trials development, execution, analysis and distribution of results. Continuous evaluation of our processes is utilized in order to constantly improve the quality of patient care.

GOG CME Mission

The purpose of the GOG CME program is to provide and promote an infrastructure dedicated to enhancing the knowledge base of GOG meeting participants and guests centered on the development, execution, analysis and application of GOG-supported clinical trials. To that end, the CME Program engages in these discussions member researchers and invited clinicians committed to reducing the risk and improving outcomes for women at risk for or afflicted with a gynecologic malignancy.
Faculty Listing

Carol Aghajanian, MD
Chief of the Gynecologic Medical Oncology Service
Memorial Sloan-Kettering Cancer Center
Associate Professor of Medicine
Joan and Sanford I. Weill Medical College at Cornell University
New York, NY

Mark H. Einstein, MD, MS
Associate Professor of Obstetrics & Gynecology
and Women’s Health
Director of Clinical Research
for Women’s Health and Gynecologic Oncology
Albert Einstein College of Medicine
and Albert Einstein Cancer Center
Montefiore Medical Center-Weiler Division
Bronx, NY

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Associate Professor of Medicine
Associate Attending Physician
Memorial Sloan-Kettering Cancer Center
Department of Medical Oncology
New York, NY

Matthew A. Powell, MD
Assistant Professor
Director, Gynecologic Oncology Fellowship
Washington University School of Medicine
Department of OB/GYN
St. Louis, MO

D. Scott McMeekin, MD, FACOG, FACS
Virginia Kerley Cade Chair in Cancer Developmental Therapeutics
Section Chief and Fellowship Director Gynecologic Oncology
University of Oklahoma Health and Science Center
Department of Gynecologic Oncology
Oklahoma City, OK

David Scott Miller, MD, FACOG, FACS
Director & Dallas Foundation Chair in Gynecologic Oncology
Professor of Obstetrics & Gynecology
University of Texas Southwestern Medical Center
Division of Gynecologic Oncology
Dallas, TX

Kathleen N. Moore, MD
Assistant Professor, Division of Gynecologic Oncology
Mai Eager Anderson Chair in Clinical Trials
Oklahoma University Health Science Center
Department of Obstetrics and Gynecology
Oklahoma City, OK

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Division of Gynecologic Oncology
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Creighton University School of Medicine
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Washington University School of Medicine
St. Louis, MO

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Associate Professor of Pathology
Harvard Medical School
Department of Pathology
Brigham and Women’s Hospital
Boston, MA

Sang Young Ryu, MD, PhD
Head Chief, Department of Obstetrics and Gynecology
Korea Cancer Center Hospital
Korea Institute of Radiological & Medical Science
Korea

Nick M. Spirto, MD
Professor and Director
Division of Gynecologic Oncology
University of Nevada School of Medicine
and the Women’s Cancer Center of Nevada
Las Vegas, NV

GOG COMMITTEE ON EDUCATIONAL ACTIVITIES

Ronald Alvarez, MD – Committee Chair
University of Alabama
School of Medicine
Birmingham, AL

Frederick Stehman, MD – Co-Chair
Indiana University School of Medicine
Indianapolis, IN

Neil Horowitz, MD
Dana Farber Partners Cancer Care
Massachusetts General Hospital
Boston, MA

John Farley, MD
Walter Reed Army Hospital
Washington, DC
GOG 2010 SUMMER SYMPOSIUM
“New Frontiers in Cervical and Corpus Cancers”
Thursday, July 15, 2010
8:00 am - 3:15 pm

PROGRAM DESCRIPTION
The July 2010 Gynecologic Oncology Group educational symposium is entitled “New Frontiers in Cervical and Corpus Cancers”, with noted oncologists and scientists serving as speakers and moderators. The targeted audiences are members and non-members of the GOG research teams to include: Gynecologic Oncologists, Medical Oncologists and other MDs engaged in gynecologic oncology research and/or clinical practice; Oncology Nurses, Nurse-practitioners, and other interested Allied Health professionals. The speakers will focus their presentations on intermediate risk as well as advanced stage and recurrent cervical and corpus cancers. The faculty will also explore new approaches in the management of corpus sarcomas and a question and answer period will conclude the symposium with audience participation.

LEARNING OBJECTIVES

- Become familiar with new FIGO staging criteria and develop new management strategies for intermediate risk cervical and corpus cancers.
- Identify ways to optimize chemo radiation and systemic therapies for cervical and corpus cancers. Review translational research opportunities in these cancers.
- Develop optimal surgical management strategies for corpus sarcomas. Determine role of chemotherapy and targeted agents in sarcomas

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the American College of Surgeons and the Gynecologic Oncology Group. The American College of Surgeons is accredited by the ACCME to provide continuing medical education for physicians.

AMA PRA Category 1 Credits™
The American College of Surgeons designates this educational activity for a maximum of 6.25 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.
<table>
<thead>
<tr>
<th>TIME</th>
<th>TOPIC</th>
<th>Speaker/Moderator</th>
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<tbody>
<tr>
<td>7:00 am</td>
<td>REGISTRATION</td>
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<tr>
<td>8:00 am</td>
<td>WELCOME</td>
<td>Welcome: Program Chairs</td>
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<tr>
<td>8:05-9:50 am</td>
<td>SESSION I: “Revisiting intermediate risk in cervical and corpus cancers”</td>
<td>Moderator: Bradley J. Monk, M.D.</td>
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<tr>
<td>8:05-8:35 am</td>
<td>Rationale for Modifying FIGO staging system in cervical and corpus cancer</td>
<td>David Mutch, M.D. Washington University School of Medicine</td>
</tr>
<tr>
<td>8:40-9:10 am</td>
<td>Expanding the role of systemic chemotherapy in surgically managed intermediate and high-risk stage cervical cancer</td>
<td>Sang Young Ryu, M.D., PhD Korea Cancer Center Hospital</td>
</tr>
<tr>
<td>9:15 -9:45 am</td>
<td>Rationale for new approaches in the management of intermediate risk epithelial corpus cancers</td>
<td>D. Scott McMeekin, M.D. University of Oklahoma</td>
</tr>
<tr>
<td>9:50 – 10:05 am</td>
<td>BREAK</td>
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</tr>
<tr>
<td>10:10 am – 12:30 pm</td>
<td>SESSION II: “Moving forward in advanced stage and recurrent cervical and corpus cancers”</td>
<td>Moderator: Bradley J. Monk, M.D.</td>
</tr>
<tr>
<td>10:10-10:40 am</td>
<td>Optimizing combination chemotherapy and radiation in treating locally advanced cervical cancer</td>
<td>Kathleen N. Moore, M.D. Oklahoma University Health Science Center</td>
</tr>
<tr>
<td>10:45 - 11:15 am</td>
<td>New systemic approaches to management of corpus cancer</td>
<td>Carol Aghajanian, M.D. Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>11:20 - 11:50 am</td>
<td>Optimizing translational research opportunities in corpus cancers</td>
<td>George L. Mutter, M.D. Harvard Medical School</td>
</tr>
<tr>
<td>11:55am – 12:25 pm</td>
<td>Optimizing translational research opportunities in cervical cancers</td>
<td>Mark H. Einstein, M.D. Montefiore Medical Center</td>
</tr>
<tr>
<td>12:30-1:15 pm</td>
<td>BREAK (LUNCH)</td>
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<tr>
<td>1:20 – 3:00 pm</td>
<td>SESSION III: “New approaches in the management of corpus sarcomas”</td>
<td>Moderator – David Scott Miller, M.D.</td>
</tr>
<tr>
<td>1:20 - 1:50 pm</td>
<td>What are the optimal surgical approaches to corpus sarcomas?</td>
<td>Nick M. Spirtos, M.D. Women’s Cancer Center</td>
</tr>
<tr>
<td>1:55 - 2:25 pm</td>
<td>New systemic strategies for the management of carcinomas of the uterus</td>
<td>Matthew A. Powell, M.D. Washington University School of Medicine</td>
</tr>
<tr>
<td>2:30 - 3:00 pm</td>
<td>Role of anti-angiogenesis and other targeted agents in corpus leiomyosarcomas</td>
<td>Martee L. Hensley, M.D. Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>3:00 - 3:15 pm</td>
<td>QUESTIONS AND ANSWERS</td>
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</tbody>
</table>

**Program Chairs:**

David Scott Miller, MD  
Univ. of Texas Southwestern Medical Center  
Dallas, TX

Bradley J. Monk, MD  
Creighton University School of Medicine at St. Joseph’s Hospital and Medical Center  
Phoenix, Arizona
Bradley J. Monk, MD
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
Comprehensive Cancer Center
Creighton University School of Medicine
at St. Joseph’s Hospital and Medical Center
a member of Catholic Healthcare West
Phoenix, AZ

Education/History
Bradley J. Monk, MD, graduated at the top of his class from the University of Arizona College of Medicine in 1988, and completed a residency in obstetrics and gynecology at the University of California, Los Angeles, in 1992. He is the recipient of three fellowships: in medical genetics from the National Institutes of Health, Bethesda, Maryland (1988); in gynecologic oncology as a Felix Rutledge Fellow from the M.D. Anderson Cancer Center, Houston, Texas (1990); and in gynecologic oncology from the University of California, Irvine (UCI) (1992-1995). In 1995, Dr. Monk was appointed director of gynecologic oncology at Texas Tech University Health Services Center, and, in addition, in 1996, he became associate medical director of the Southwest Cancer Center, both in Lubbock, Texas. Since 1998, Dr. Monk has been at the University of California, Irvine where he became tenured associate professor of obstetrics and gynecology in the department of OB/GYN in 2004. He is board certified by the American Board of Obstetricians and Gynecologists, with subspecialty certification in Gynecologic Oncology.

Professional Society Affiliations
Dr. Monk is a fellow of the American College of Surgeons, the American College of Obstetricians and Gynecologists, and the American Society for Colposcopy and Cervical Pathology. He is also a full active member of the Society of Gynecologic Oncologists, the American Society of Clinical Oncology, and the American Association for Cancer Research, among numerous other professional organizations.

Publications/Editorial Experience
Dr. Monk serves as a reviewer for several peer-reviewed journals, including Clinical Cancer Research, Obstetrics and Gynecology, Cancer, and The Journal of Clinical Oncology. He currently sits on the editorial boards of Community Oncology, American Journal of Hematology/Oncology, Gynecologic Oncology, and Clinical Ovarian Cancer. He has authored or co-authored numerous textbook chapters and more than 120 articles in peer-reviewed journals dealing predominantly with the prevention and chemotherapy of gynecologic malignancies, and with quality-of-life (QOL) aspects of cancer care.

Research Interests
Dr. Monk’s research focuses on areas that include chemotherapeutic agents used to treat ovarian and cervical carcinoma; etiology, clinical significance, and prevention of postoperative adhesions following radical pelvic surgery; biomarkers in gynecologic cancers; human papillomavirus (HPV) infection in women; and QOL issues in advanced ovarian cancer patients. Dr. Monk has been an investigator for the Gynecologic Oncology Group (GOG) since 1995. There, he serves as the Group’s Cervical and Vulvar Committee Chair and also as a member of the Tissue Utilization, Publications, and Protocol Development committees. He is principal investigator for GOG at UCI and study chair for both group-wide phase III trials in cervical cancer. He also serves as study chair or co-chair for four other trials investigating novel therapeutic modalities in cervical and ovarian carcinoma. Dr. Monk has also received career-development funding from the National Cancer Institute to investigate strategies against HPV-related genital diseases in women.

Current Position
After 12 years as a tenured faculty member and Director of Research in the Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, at the Chao Family Comprehensive Cancer Center, UCI Medical Center, Dr. Monk relocated to Creighton University School of Medicine at St. Joseph’s Hospital and Medical Center, a member of Catholic Healthcare West.
Rationale for Modifying FIGO staging system in cervical and corpus cancers

David G. Mutch, MD, FACOG
Judith and Ira Gall Professor of Obstetrics and Gynecology
Director, Division of Gynecologic Oncology
Washington University School of Medicine
St. Louis, Missouri

David G. Mutch, MD, is the Judith and Ira Gall Professor of Obstetrics and Gynecology and the Director of Gynecologic Oncology at the Washington University School of Medicine in St. Louis, Missouri. He is a member of the Division of Gynecologic Oncology of the American Board of Obstetrics and Gynecology and serves as a reviewer for multiple medical journals related to women’s health and cancers of the female reproductive tract.

Dr. Mutch has been the recipient of multiple research grants for studies from the American Cancer Society and the National Institutes of Health, among others. He is the Principal Investigator for the Gynecologic Oncology Group at Washington University and served as the Program Chair of the 2004 meeting of the Society of Gynecologic Oncologists. Dr. Mutch is the immediate past president of the Society of Gynecologic Oncologists (SGO). He has authored or co-authored over 200 peer-reviewed publications as well as numerous book chapters on the treatment of cancers of the female reproductive tract. He is currently the co-PI on an NIH grant looking at defective DNA mismatch repair in endometrial cancers as well as a co-PI on a recently awarded endometrial SPORE (Special Project of Research Excellence) grant.

Dr. Mutch attended the Washington University School of Medicine, and did his residency training there as well. He underwent fellowship training at Duke University Medical Center before returning to Washington University in 1988. He is the recent recipient of the Washington University School of Medicine Distinguished Alumni Award and is a member of AOA.
Revised FIGO and GOG Trials
July 2010

David G. Mutch, MD
Judith and Ira Gall Professor
Director Division of Gynecologic Oncology
Washington University School of Medicine

Disclosure

• I have no disclosures relevant to this talk

FIGO

• FIGO proposed the first rules for classification in 1958
• International Union Against Cancer (UICC) in 1966
• American Joint Commission on Cancer 1976
• These three organizations have tried to coordinate their efforts.
FIGO Revisions

- First time in more than a decade that the staging system has been revised
- Began the process in 2006 approved in 2006
- Changes were vetted by:
  - IGCS
  - SGO
  - GCIG
  - AJCC
  - ISGyP

FIGO Purpose

- Allow comparison of patients between centers
- Divide patients and their tumors into prognostic groups.

Cervical Cancer

- Oldest staging system in the literature
- Surgical vs Clinical
  - Correlation of FIGO and TNM is poor
  - Especially in IB2 and II
- 90% of cervical cancer is diagnosed in countries where surgical staging and imaging cannot be readily obtained
Approved Changes to the FIGO Staging System

- Deletion of Stage 0
- Stage IIA1: tumor size of less than or equal to 4 cm with involvement of less than the upper two-thirds of the vagina
- Stage IIA2: tumor size of more than 4 cm with involvement of less than the upper two-thirds of the vagina.

Affect on GOG Trials

- There is no affect of eligibility of patients for GOG clinical trials with these changes

Endometrial Cancer

- Current surgical staging system adopted in 1989
- Represented a huge change to the previous staging system that was a clinical system
Uterine Cancer: Surgical Staging

- Clinical Stage I will be upstaged 30% of the time at laparotomy
  - 5% for positive adnexa (Surgical Stage IIIa)
  - 6% for positive para-aortic lymph nodes (Surgical Stage IIIc)
  - 9% for positive pelvic nodes (Surgical Stage IIIc)
  - 12% for positive cytology on pelvic washings (Surgical Stage IIIa)
  - 6% other (eg. cervical (St II) or abdominal disease (St IV))
- Clinical Stage II or III will be upstaged 60% of the time at laparotomy

What did we learn?

- Morbidity of node dissection was low
- Most patients did not need radiation therapy
- Which patients were most likely to recur
- We were very bad at predicting which patients needed post op therapy without staging
- Other prognostic features
  - LVSI
  - Depth of invasion
  - Aggressive histologic types

Endometrial Cancer Prognosis:

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<th>Uterine Stage</th>
<th>% 5yr survival</th>
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<td>IA</td>
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<td>IB</td>
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<td>IC</td>
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<td>32</td>
</tr>
<tr>
<td>IVA</td>
<td>20</td>
</tr>
<tr>
<td>IVB</td>
<td>5</td>
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</table>

- Overall 5Yr Survival 84%
- Stage and Grade are the most important prognostic factors
- Altered oncogene/tumor suppressor gene expression is now being evaluated (molecular staging concept)
Heterogeneity of IIIA Disease

- Positive cytology only in stage I and II – 73%
- Positive cytology extra uterine disease – 13%
- Kadar et. al. Gyn Oncol 1992

Heterogeneity of IIIA Disease

- 49 Patients fully staged 1989-2002
- Within this group survival varied between 13 and 79%
- Endometrioid positive cytology 79%
- Endometrioid serosa/adnexa 65%
- Non endometrioid pos cytology 64%
- Non endometrioid serosa/adnexa 13%

Microscopic IIIC

- Survival benefit if nodes are removed
- Kilgore
- Cragan
IIIC Macroscopic

- Corn
  - Resection gross paraaortic nodes vs no resection
  - Followed by the same RT
  - 39% vs 13% PA failure rate
- Mariani
  - 51 patients with positive nodes
  - 77% 5-year survival if PA node dissection
  - 42% 5-year survival if no PA node dissection

Heterogeneity of Stage IIIC Disease

- 46 of 374 had stage IIIC disease and endometrioid histology
- 22 node only
  - 32% recurred
- 24 other features-cytology, adnexal, serosal or vaginal involvement
  - 67% recurred

FIGO Endometrium

- Stage IA and IB are combined
- Endocervical involvement only does not change stage
- Positive cytology is no longer a criteria by itself for upstaging a patient
- Lymph nodes are IIIC and divided into positive pelvic nodes C1 and positive para aortic nodes C2
Endometrial Cancer

• Stage I: tumor confined to the corpus uteri.
  • IA: no or less than half myometrial invasion.
  • IB: invasion equal to or more than half of the myometrium.
• Stage II: tumor invades cervical stroma, but does not extend beyond the uterus.

Endometrial Cancer

• Stage III: local and/or regional spread of the tumor.
  • IIIA: tumor invades the serosa of the corpus uteri and/or adnexae.
  • IIIB: vaginal and/or parametrial involvement.
  • IIIC: metastases to pelvic and/or para-aortic lymph nodes.
    • IIIC1: positive pelvic nodes.
    • IIIC2: positive paraaortic lymph nodes with or without positive pelvic lymph nodes.

Endometrial Cancer

• Stage IV: tumor invades bladder and/or bowel mucosa, and/or distant metastases.
  • IVA: tumor invasion of bladder and/or bowel mucosa.
  • IVB: distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes.
Objectives

• To describe the overall survival (OS) of women with stage I endometrial cancer to see if there is a difference between these groups.

• To examine how the estimated stage-specific OS is altered in the 2009 system as compared to the 1988 system.

FIGO Sarcomas

• Sarcomas previously staged as endometrial cancer

• No FIGO data on any other staging system

• Arbitrary decision to use other soft tissue sarcomas as a model.

• Data will be collected over the coming years and the system revised.

Results

• 1658 women with endometrial endometrioid cancer were analyzed.

• Based on the 1988 system 1307 stage I patients:
  – IA (570)
  – IB (593)
  – IC (144)

• Comprehensive surgical staging with lymph node dissection was performed in 791 (61%) stage I cases with a median of 19 nodes (range 1-92).
1988 FIGO Stage IA, IB, IC

Revised 2009 System

- Patients were restaged using the 2009 system, a total of 1411 stage I patients identified including:
  - 1249 revised stage IA
  - 162 revised stage IB
Concordance Probabilities

- Concordance probabilities for the FIGO 1988 stage I group and 2009 stage I group were 0.612 ± 0.0014 and 0.536 ± 0.0111 respectively.
- The 2009 system appears inferior to the 1988 system.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Events</th>
<th>CPE</th>
<th>Bootstrap Corrected CPE</th>
<th>Concordance Probability</th>
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<tr>
<td>1988 IA</td>
<td>1307</td>
<td>91</td>
<td>0.0014</td>
<td>0.612</td>
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<tr>
<td>2009 IA</td>
<td>1411</td>
<td>100</td>
<td>0.0111</td>
<td>0.536</td>
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</tbody>
</table>

Sarcoma Staging

- IA: less than 5 cm.
- IB: greater than 5 cm
- II: tumor extends to the pelvis
- IIA: adnexal involvement.
- IIB: tumor extends to extrauterine pelvic tissue.
Sarcoma Staging

- Stage III: tumor invades abdominal tissues (not just protruding into the abdomen).
  - IIIA: one site.
  - IIIB: more than one site.
  - IIIC: metastasis to pelvic and/or para-aortic lymph nodes.
- Stage IV: tumor invades bladder and/or rectum and/or distant metastasis.
  - IVA: tumor invades bladder and/or rectum.
  - IVB: distant metastasis.

Adenosarcoma

- Adenosarcomas
  - IA: tumor limited to endometrium/endocervix (without myometrial invasion).
  - IB: tumor invades up to less than half of myometrium.
  - IC: tumor invades to more than one half of myometrium [4].
- Stage II: tumor extends to the pelvis.
  - IIA: adnexal involvement.
  - IIB: tumor extends to extrauterine pelvic tissue.

Adenosarcomas

- Stage III: tumor invades abdominal tissues (not just protruding into the abdomen).
  - IIIA: one site.
  - IIIB: more than one site.
  - IIIC: metastasis to pelvic and/or para-aortic lymph nodes.
- Stage IV: tumor invades bladder and/or rectum and/or distant metastasis.
  - IVA: tumor invades bladder and/or rectum.
  - IVB: distant metastasis.
- Two different substagings for LMS/ESS and adenosarcomas.
Expanding the role of systemic chemotherapy in surgically managed intermediate and high-risk stage cervical cancer

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Department of Obstetrics and Gynecology
Korea Cancer Center Hospital
Korea Institute of Radiological & Medical Science
Korea

Dr. Ryu was born in Korea and graduated with his medical degree from Seoul National University in Seoul, Korea. After completing his residency and fellowship at Seoul National University, he worked as a Gynecologist at the Korea Cancer Center Hospital (KCCCH) where he also served as Director of Obstetrics & Gynecology, and is currently the Head Chief of Dept of Obstetrics & Gynecology.

Dr. Ryu had never been to the United States prior to his 30th birthday, and his first visit to the US occurred during his honeymoon trip to Hawaii. His only opportunity to learn English presented itself during his research work in the Department of Immunology at UC San Diego from 2003-2005. Despite the language barrier, his proposal of KGOG 1008 was accepted by the Cervical Cancer committee in 2008 at the GOG’s semi-annual meeting, and the protocol was successfully developed and is now opened as GOG 263.

Dr. Ryu’s work focuses on clinical trials and immunotherapy in gynecologic cancers especially in cervical cancer. GOG 263 is also investigating the role of chemoradiation in cervical cancer with intermediate risk factors after surgery.

As an active member of the KGOG, Dr. Ryu continuously tries to expand his clinical trial network internationally.
Expanding the role of systemic chemotherapy in surgically managed intermediate and high-risk cervical cancer

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Korea Cancer Center Hospital
Seoul, Korea

Financial Disclosure

I have no financial disclosure relevant to this activity
Disclosure

✓ No conflict of interest
✓ But... a conflict of English
  • If I don’t understand your question, you can try again with slow and clear English.
  • If the situation is not improved, you can ask Dr. Monk to translate your English clearer and simpler.

KGOG 1008/GOG 263; Randomized Phase III Clinical Trial of Adjuvant Radiation vs Chemoradiation In Intermediate Risk, Stage IIIA Cervical Cancer Treated With Initial Radical Hysterectomy and Pelvic Lymphadenectomy

"That’s just one of many protocols for GOG, one giant leap for KGOG."

KGOG

GO K
"Holding Tightly Fast-Running Mommy's Back" Strategy

KGOG1008/GOG263

- A prototype of international collaboration
  - Simple and precise
- Obstacles
  - Communication difficulty
    - Handicapped in English
  - Cultural differences
    - 'Bomb shot'

"Conspiracy Theory"
The Dr. DiSaia's desire is to make GOG as a 24 hour working system

KGOG Sleep  GOG Work  KGOG Work  GOG Sleep
Expanding the role of systemic chemotherapy in surgically managed intermediate and high-risk cervical cancer

1. What is the essential one in systemic chemotherapy in cervical cancer?

2. What is the difference between advanced and intermediate or high-risk cervical cancer?

Systemic chemotherapy in cervical cancer

- Chemoradiation
- Consolidation chemotherapy
- Neoadjuvant chemotherapy
- Palliative chemotherapy

Expanding the role of systemic chemotherapy in surgically managed intermediate and high-risk cervical cancer

Risk factor grouping

(GOG 49, Delgado et al., 1989, 1990)
High Risk Cervical Cancer

- **High risk factors**
  - After radical hysterectomy
  - Factors increase recurrence up to 25-30%
  - High risk factors
    - Positive lymph node
    - Parametrial involvement
    - Positive resection margin

Intermediate risk factor

- Do not decrease recurrence or survival significantly as a single factor
- Combination of factors increase recurrence up to 25-30%

GOG criteria of Intermediate risk factor

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHM and Tumor size</td>
</tr>
<tr>
<td>Positive</td>
<td>Deep 1/3</td>
</tr>
<tr>
<td>Positive</td>
<td>Middle 1/3</td>
</tr>
<tr>
<td>Positive</td>
<td>Superficial 1/3</td>
</tr>
<tr>
<td>Negative</td>
<td>Deep or middle 1/3</td>
</tr>
</tbody>
</table>

* Capillary lymphatic space tumor involvement.

Delgado et al., 1989
Sedlis et al., 1999
### Classic vs GOG criteria

<table>
<thead>
<tr>
<th></th>
<th>Classic criteria</th>
<th>GOG criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSI</td>
<td>CLS(+) Deep 1/3, Any size</td>
<td>CLS(+) Deep 1/3, Any size</td>
</tr>
<tr>
<td>Stromal invasion &gt; 1/3</td>
<td>CLS(+), Middle 1/3, Tumor &gt; 2 cm</td>
<td>CLS(+), Superficial 1/3, Tumor ≤ 5 cm</td>
</tr>
<tr>
<td>Tumor size ≥ 2 cm</td>
<td>CLS(-), Superficial 1/3, Tumor &gt; 4 cm</td>
<td>CLS(-), Deep or middle 1/3, Tumor &gt; 4 cm</td>
</tr>
</tbody>
</table>

### Table 1. Recurrence according to the number of risk factors

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of patient</th>
<th>No. of recurrence</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic Criteria</td>
<td>137</td>
<td>12</td>
<td>8.8</td>
</tr>
<tr>
<td>GOG Criteria</td>
<td>70</td>
<td>6</td>
<td>8.6</td>
</tr>
<tr>
<td>Category 1</td>
<td>38</td>
<td>3</td>
<td>7.9</td>
</tr>
<tr>
<td>Category 2</td>
<td>8</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>Category 3</td>
<td>23</td>
<td>2</td>
<td>8.7</td>
</tr>
<tr>
<td>Category 4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Ryu et al., UROB 2010
Intermediate Risk Factor

- Spectrum of relative risk for recurrence
  - No definite cut-off value
- Take the certain point of risk for a specific purpose of the study

Recurrence rate

I. Chemoradiation

NCI Clinical Alert

- National Cancer Institute, 1999

*Strong consideration should be given to the incorporation of concurrent Cisplatin-based chemotherapy with radiation therapy*
Chemoradiation

- 5 RCTs; 30-50% improvement of survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Cisplatin</th>
<th>5-FU</th>
<th>No. of cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 85</td>
<td>50 mg/m²/3wk</td>
<td>4 g/m²/96hr/3wk</td>
<td>2</td>
</tr>
<tr>
<td>GOG120</td>
<td>40 mg/m²/week</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>GOG 123</td>
<td>50 mg/m²/4wk</td>
<td>4 g/m²/96hr/4wk</td>
<td>3</td>
</tr>
<tr>
<td>SWOG 8797/GOG139</td>
<td>70 mg/m²/2wk</td>
<td>1 g/m²/96hr/2wk</td>
<td>4</td>
</tr>
<tr>
<td>RTOG 88-01</td>
<td>75 mg/m²/2wk</td>
<td>4 g/m²/96hr/2wk</td>
<td>3</td>
</tr>
</tbody>
</table>

Meta-analysis, Systemic review

- Systemic Review (Green et al., 2001), Cochrane review (Green et al, 2005)
  - Improvement in both PFS and overall survival
    - A greater effect in stage I or II disease
- MAC 2008
  - The benefit of chemoradiation
    - Both platinum and non-platinum chemotherapy
    - No treatment type, dose, or schedule
    - Advantage in additional chemotherapy
      - Improvement of 5YSS; 19%

NCI Canada trial

In 2002, NCI Canada: sixth prospective randomized trial

- 259 patients
  - Stage IB to IVA
  - Squamous cell
  - > Sum, or pelvic lymph node (+)

Arm 1: RT plus weekly Cisplatin 40 mg/m²
Arm 2: RT only

No significant difference in PFS and 5YSS
69% v 66% and 62% v 58%, respectively; P = .42
NCIC trial

✓ The authors' explanation
  - Short radiation therapy ('optimal' vs 'protracted' RT?)
  - Detrimental effect of hydroxyurea
  - Within statistical error (Rose and Bundy 2002)
✓ Other explanation
  - Small sample size (n=253)
  - No surgical staging
  - No treatment of severe anemia
  - Weekly cisplatin 40mg/m² may not an optimal dose schedule

Cisplatin+5-FU

• 5-FU+Cisplatin, most popular regimen
  - This dose schedule hypothesizes
    • Not only increase the synergy of chemoradiation (?)
    • But also eradicate the possible micrometastasis (?)
  - Showed the survival benefit in all the trials
  - But, higher toxicity, low compliance

Victory of Weekly Cisplatin 40mg/m²

• Weekly cisplatin 40mg/m²
  - Favored because more convenient, equally efficacious and less toxic
• GOG 120
  - 3 arms;
    • Control arm; HU
    • Arm 1; Weekly cisplatin 40mg/3
    • Arm 2; Tri-weekly 50mg/m² + 5-FU 4 g/m²/96hr/4wk x 2
  - Comparable outcome in Arm 1 and Arm 2
Genesis of weekly cisplatin

In the beginning, was the cisplatin.
Among the many sons, tri-weekly cisplatin combined with 5-FU was the most popular.
However, because of the toxic twin brother of 5-FU, the weekly cisplatin 40mg/m² took the only heir of chemoradiation in cervical cancer treatment.

Chapter 1 closed.

GOG 165

- The 5-FU did not showed an active radiosensitizer.
  - GOG 165 (Lanciano et al., 2005)
    - To investigate the role of 5-FU as a radiosensitizer
      - Arm 1: Weekly Cisplatin 40mg/m²
      - Arm 2: PVI 5-FU 225mg/m²/d for 5days/wik
    - Closed prematurely
      - Interim analysis: not likely to achieve a better outcome
      - 4YSDR: 64% vs 55%

Cisplatin dose schedule

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>5-FU</th>
<th>No. of cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 85</td>
<td>50mg/m²/3wk</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>GOG120</td>
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<td>6</td>
<td></td>
</tr>
<tr>
<td>GOG 123</td>
<td>50mg/m²/4wk</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>SWOG 8797</td>
<td>40mg/m²/week</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>RTDG 16-01</td>
<td>70mg/m²/3wk</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

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Cisplatin dose schedule

1. Weekly cisplatin 40-50mg/m²

2. Tri-weekly cisplatin 70-75mg/m²

-> But, no randomized trial in GOG

Challenging Trial to Weekly Cisplatin

Weekly Cisplatin vs Tri-Weekly Cisplatin ; KCCH clinical trial

- 2002-2004
- 105 patients
  - Stage IIIIB-IVA
    - Arm 1: Weekly cisplatin 40mg/m²
    - Arm 2: Tri-weekly cisplatin 75mg/m²
- Primary end point: compliance
  - Percentage of completed cycle
  - Treatment delay
### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Weekly (n=52)</th>
<th>Tri-weekly (n=53)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years)</td>
<td>54.6 (IQR 51-57)</td>
<td>54.4 (IQR 51-57)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial Hb (mean mg/dL)</td>
<td>11.35 (SD 0.16)</td>
<td>11.44 (SD 0.17)</td>
<td>NS†</td>
</tr>
<tr>
<td>Tumor size (mean cm)</td>
<td>4.63 (SD 0.16)</td>
<td>4.79 (SD 0.25)</td>
<td>NS†</td>
</tr>
<tr>
<td>Stage (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>28 (53.8%)</td>
<td>34 (64.2%)</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>19 (36.5%)</td>
<td>16 (30.2%)</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>5 (9.6%)</td>
<td>3 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Histology (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>47 (90.4%)</td>
<td>47 (88.7%)</td>
<td></td>
</tr>
<tr>
<td>Non-SCC</td>
<td>5 (9.6%)</td>
<td>6 (11.3%)</td>
<td></td>
</tr>
<tr>
<td>Pelvic Lymph node (%)</td>
<td>30 (57.7%)</td>
<td>27 (50.9%)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>22 (42.3%)</td>
<td>23 (43.4%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24 (46.2%)</td>
<td>25 (47.2%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (11.5%)</td>
<td>5 (9.4%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Compliance

<table>
<thead>
<tr>
<th></th>
<th>Weekly (%)</th>
<th>Tri-weekly (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed cycle</td>
<td>44 (84.6%)</td>
<td>49 (92.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Incomplete cycle</td>
<td>8 (15.4%)</td>
<td>4 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>3 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (1.9%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5 (9.6%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2 (3.8%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed cycle</td>
<td>49 (94.2%)</td>
<td>52 (98.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Delayed cycle</td>
<td>3 (5.8%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>1-2 weeks</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;2 weeks</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

### Table 3. Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Weekly (%)</th>
<th>Tri-weekly (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>20 (38.5%)</td>
<td>21 (40.4%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>21 (41.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 5-6</td>
<td>1 (1.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophilopenia</td>
<td>13 (25.0%)</td>
<td>5 (9.6%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13 (25.0%)</td>
<td>5 (9.6%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (7.7%)</td>
<td>3 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (25.0%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>8 (15.4%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (9.6%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>13 (25.0%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>P-value (A-E)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>20 (38.5%)</td>
<td>21 (40.4%)</td>
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</tr>
<tr>
<td>Grade 3-4</td>
<td>21 (41.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 5-6</td>
<td>1 (1.9%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Long term outcome of Weekly vs Tri-weekly Cisplatin based chemoradiation in locally advanced cervical cancer

- 5YSR (n=105)
  - 88% (Tri-weekly)
  - 66% (Weekly)
  - HR 0.375
  - 95% CI (0.154-0.914)
p=0.03

• GOG 43: dose density trial (Bonomi et al., 1985)
  - 3 Arms (497 pts)
    - Cisplatin 50mg/m²/3wk
    - Cisplatin 100mg/m²/3wk
    - Cisplatin 20mg/m² for 5days/3wk
  - Conclusion
    - No differences in CR or survival and toxicity
    - 100mg/m², significant higher RR (31.4%) vs (20.7%, 25%)
    - Cisplatin dose-response curve not so steep
    - In other cancer: higher cisplatin dose, higher response
    - Not chemoradiation study (90% already received RT)

Is weekly cisplatin 40mg/m² a golden standard?

- Phase I (Wadanabe et al, 2006)
  - Previous trial, wide range of compliance 49.4-81%
  - MTD:
    - 40mg/m² for the weekly schedule
    - 80mg/m² for the monthly schedule
  - Recommendation
    - Cisplatin 20mg/m² for the weekly
    - Cisplatin 75mg/m² for the monthly
  - To increase the compliance up to 70% by this dose modification
Is weekly cisplatin 40mg/m² a golden standard?

- Synergy of chemoradiation
  - Increasing the exposure time of chemotherapy
    - Continuous infusion of cisplatin
    - Daily injection of cisplatin (Nagy et al., 2007; Mitsuhashi et al., 2005)
    - Weekly cisplatin 30mg/m²
    - Weekly cisplatin 40mg/m²
  - Increasing the peak concentration of chemotherapy
    - Tri-weekly 50mg/m² (GOG129)
    - Tri-weekly 75mg/m²
    - Tri-weekly 100mg/m²
  - Chemoradiation during brachytherapy
    - Tri-weekly cisplatin

Weekly vs Tri-weekly Cisplatin

- Hypothesis for Tri-weekly Cisplatin
  - Peak concentration of cisplatin may be more important.
  - To induce synergy of chemoradiation
  - To eliminate the micrometastasis
  - The role of cisplatin during brachytherapy may be important.
    - The third cycle of cisplatin was administered around brachytherapy.
- Tri-weekly cisplatin
  - Lower compliance in I-IIA cervical cancer (n=40) (Chumworathayi et al., 2005)
- Re-explanation of NCIC results
If we include Tri-weekly cisplatin in GOG protocol,

- Weekly Cisplatin 40mg/m² x6
- Tri-weekly Cisplatin 75mg/m² x3
- Weekly Cisplatin 40mg/m² x6 + Paclitaxel-Carbo x2
- Tri-weekly Cisplatin 75mg/m² x3 + Paclitaxel-Carbo x2

Expanding the role of systemic chemotherapy in surgically managed intermediate and high-risk cervical cancer

Chemoradiation in intermediate-high risk cervical cancer

High Risk Cervical Cancer

- SWOG 8797 (Peters III et al. 2000)
  - Eligibility: postoperative stage IA2, IB, IA with high-risk factors
    - Positive pelvic nodes, Parametrial involvement, Positive surgical margins
    - Arm 1: RT
    - Arm 2: RT + Cisplatin 75mg/m² + 5-FU 1g/m²/96hr; every 3 weeks, 4 cycles
  - Improve PFS, OS
    - 4 year OS: 71% vs 61%
  - Toxicity: more frequent in the CRT group
    - Compliance (3 cycles or more): reached up to 71%
GOG 92
Adjuvant radiation in Intermediate risk factor

Cervical cancer
Stage IB
Radical hysterectomy+BPLND
2 of intermediate risk factors
LVSI
Stromal invasion
Tumor size

Control Arm; Observation

Randomization

RT Arm

GOG 92
Adjuvant radiation in Intermediate risk factor

GOG 92 (Sadle, 1999):
Rec Rate: 28 vs 15%
2Y-DFS: 88 vs 79%, RR 0.53

Chemoradiation in Intermediate risk Cervical Cancer
A retrospective study

Ryu et al., JROB 2010
Adjuvant Chemoradiation in Intermediate risk factor
KGOG 1008/GOG 263

Cervical cancer
Stage I-IIA
Radical hysterectomy+ BPLND
≥2 of intermediate risk factors

Control Arm: Radiation therapy

CRT Arm: Weekly CDDP
40mg/m² concurrent to radiation

II. Consolidation chemotherapy

Consolidation
Additional chemotherapy, so called ‘consolidation chemotherapy’
-Eradicate the possible micrometastasis?
Consolidation chemotherapy

- MAC 2008
  - Additional chemotherapy; absolute improvement of 19% at 5YSR
  - Not conclusive
    - Based on two relatively small trials
      » SWOG9747: cisplatin+FP, Kantardzic et al. 2004: cisplatin+BLM
  - Nevertheless, the results are promising and may warrant a direct comparison with chemoradiotherapy alone.

Consolidation chemotherapy

- Single agent
  - GOG 40: Cisplatin (50mg, 100mg/m²/day); 30-40% RR (Borani et al., 1986)
  - Paclitaxel (170mg/m²/day); 17-25% RR (McGuire et al., 1996)
  - GOG 119, 650: Ifosfamide (16% RR), Topotecan (14-19% RR), Irinotecan (11% RR)

- Combination chemotherapy
  - Paclitaxel+Cisplatin; 46% RR (Rose et al., 1999)
  - GOG 119: Paclitaxel+Cisplatin vs cisplatin; Improved RR, but not OS (Moore et al., 2004)
  - GOG 179: Topotecan+Cisplatin; Improved OS (Lung et al., 2005)

- GOG 204: topotecan, gemcitabine, vinorelbine, paclitaxel
  - Interim analysis; no significant benefit

- Consequently, the consensus regimen: cisplatin-paclitaxel
  - Improved response rate and PFS (Moore et al., 2005)

Consolidation chemotherapy

- Paclitaxel-Carboplatin
  - Carboplatin; less neurotoxicity
    - Objective responses; 29% in PT versus 53% in CT
    - In previously treated with cisplatin; 15.7% vs 51% (Moore et al., 2007)

- Radiosensitization
  - Carboplatin in patients previously treated with cisplatin
    - An effective and less toxic regimen
    - Easy administration as an outpatient
Expanding the role of systemic chemotherapy in surgically managed intermediate and high-risk cervical cancer

Consolidation chemotherapy in intermediate-high risk cervical cancer

Consolidation chemotherapy in high risk cervical cancer

- SWOG 8797 (Peter et al., 1999, Monk et al., 2005)
  - High risk cervical cancer Better outcome in additional chemotherapy
    - Recurrence rate
      - ≤ 2 courses: 31%
      - 3, 4 courses: 13%
    - Subset analysis
      - When only one node was positive
      - When the tumor size was < 2 cm

Consolidation chemotherapy in high risk cervical cancer

- RTOG/GOG 0724: Consolidation in High risk cervical cancer
  - Addition of 2 cycles of paclitaxel + carboplatin
  - Point of interest
    - Can consolidation chemotherapy improve PFS or Survival?
    - Any difference of outcome in subset
      - < 1 LN, < 2cm vs > 1 LN, > 2cm
Consolidation chemotherapy in intermediate risk cervical cancer?

**RTOG/GOG 0724**
- High risk Cxca.
  - Weekly Cisplatin 40mg/m² x6
  - Weekly Cisplatin 40mg/m² x6 + Paclitaxel-Carbo x2
  - Tri-weekly Cisplatin 75mg/m² x3

If we include Tri-weekly cisplatin in GOG protocol,

**RTOG/GOG 0724**
- High risk Cxca.
  - Weekly Cisplatin 40mg/m² x6
  - Tri-weekly Cisplatin 75mg/m² x3

**KGOG1008/GOG263**
- Intermediate risk Cxca.
  - RT only
  - Weekly Cisplatin 40mg/m² x6
  - Tri-weekly Cisplatin 75mg/m² x3

**Conclusion**

- Cisplatin-based chemoradiation
  - Also benefit in intermediate-high risk cervical cancer
    - KGOG1008/GOG 263
    - Optimal dose and dosing schedule of Cisplatin
      - Next GOG trial
  - Consolidation chemotherapy
    - May be effective in high risk cervical cancer
      - RTOG/GOG0724
        - Additional 2 cycles of Paclitaxel-Carbo
    - Intermediate risk cervical cancer
      - May be an overtreatment
It is time to act for GOG. “See something, do something”

- To define optimal cisplatin dose and dosing schedule
  - The lesson from NCIC study should not be ignored.
- New proposal
  - Arm 1: Weekly cisplatin 40mg/m²
  - Arm 2: Tri-weekly cisplatin 75mg/m² 3cycles

Thank you for your attention.

KGOG1008/GOG263


Dr. DiSaia, Dr. Trimble, Dr. Kang
GOG members
KGOG members
Rationale for new approaches in the management of intermediate risk epithelial corpus cancers

D. Scott McMeekin, MD, FACOG, FACS
Virginia Kerley Cade Chair in Cancer Developmental Therapeutics
Section Chief and Fellowship Director Gynecologic Oncology
University of Oklahoma Health and Science Center
Department of Gynecologic Oncology
Oklahoma City, OK

Dr. McMeekin is the Virginia Kerley Cade Chair in Cancer Developmental Therapeutics, and Deputy Director for Clinical Research at the University of Oklahoma Cancer Institute. He serves as a Presbyterian Foundation Presidential Professor at the University of Oklahoma in the Section of Gynecologic Oncology. He received his MD from the Loyola University, Stritch School of Medicine in 1990. He completed his residency in Obstetrics and Gynecology at UC Irvine in 1994, and continued at UCI to complete a fellowship in Gynecologic Oncology in 1998. Since 1998, Dr. McMeekin has been on the Obstetrics and Gynecology faculty at the University of Oklahoma. He was named Fellowship Director in 2003, and Section Chief in 2006. He has served the GOG on the Gynecologic Oncology, Uterine Corpus, and Developmental Therapeutics committees. He currently sits on the GOG Board of Directors and serves as Secretary of the Board.
Rationale for New Approaches in the Management of Intermediate Risk Epithelial Corpus Cancers

D. Scott McMeekin, MD
University of Oklahoma

Financial Disclosure

- Bristol-Myers Squibb (BMS)
  - One time Ad Board

Presentation Goals

- What is risk in early stage endometrial cancer
- Patterns of failure inform treatment decisions
- Treatment options
- Clinical trials
What are our options...

- **New**
  - “The Laser”
  - “The Robot”
  - “The Biologic”

- **Old (School..)**
  - Surgery alone
  - Pelvic radiation
  - Vaginal Cuff Brachytherapy (VCB)
  - Chemotherapy
  - Radiation + Chemotherapy

The Challenge

“Intermediate Risk”

Less @ Risk
No or “less therapy”

Enriched for Risk
Clearly defined therapy
Clearly defined benefit

What makes EndoCA @ Risk...

EndoCA IR based on clincio-path variables

Nodal Disease (+)

1*, but unrecognized

Recurrence

Vag Cuff
Pelvic
Any Distant

Death- due to Disease
Death- not disease
Fundamental Truth: Risk

• One of 2 things happens after surgery (Hyst)
  • All of the disease is removed or it is not
  • Risk is related to the probability that extrauterine disease exists- whether it is recognized or not,
  • Lymph node dissection alters risk by more accurately classifying risk/spread,
  • What makes “high-risk”, high-risk
  • Greater probability of spreadÆ ie that it is really stage III or IV
  • Therapy that works for stage III/IV disease should also work for high-risk disease
  • Given smaller tumor burdensÆ it may work much better!

Conclusions

• Today–
  – Surgical staging remains best tool for distinguishing risk
  – Uterine characteristics must be factored-independent of nodal information
  – Risk models best tools to classify
• Tomorrow–
  – Molecular markers for prediction and prognosis- identified and validated

Risk Assessment

• 1970’s Assumption
  – All patients are at risk for extrauterine disease Æ all require XRT
• 1980’s Assumption
  – GOG 33- association of depth of invasion + grade with nodal metastases
  – “any myometrial invasion” associated with 20-25 % risk of recurrence Æ premise of GOG 99
• 1990’s Assumption
  – Lymph node dissection fine tunes risk assessment – (-) nodes = Very low risk, (+) nodes = High Risk
• 2000’s
  – Selection, selection, selection
### Adjuvant Radiation Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Compared</th>
<th>SS</th>
<th>Local Failure</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aalders</td>
<td>VCB +/- WP</td>
<td>No</td>
<td>2% VCB + WP vs 7% VCB</td>
<td>(p&lt;) 89% WP vs 91% obs</td>
</tr>
<tr>
<td>1980</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PORTEC 2000</td>
<td>Observe vs WP</td>
<td>No</td>
<td>4% WP vs 14% obs</td>
<td>(p&lt;) 81% WP vs 85% obs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 99</td>
<td>Observe vs WP</td>
<td>Yes</td>
<td>2% WP vs 9% obs</td>
<td>(p&lt;) 92% WP vs 86% obs</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTEC/NCIC 2007</td>
<td>+/- VCB vs WP</td>
<td>Yes</td>
<td>3% WP vs 6% obs</td>
<td>(p&lt;) 84% for both</td>
</tr>
</tbody>
</table>

VCB: vaginal Cuff brachytherapy, WP: whole pelvic radiation

### “Intermediate Risk”

Less @ Risk No or “less therapy”

Surgical Staging

### Routine staging: Node (-) pts are at very low risk

<table>
<thead>
<tr>
<th>IB-2</th>
<th>IB-C</th>
<th>IB-3</th>
<th>IB-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local-3%</td>
<td>Local-2%</td>
<td>Local-2%</td>
<td>Local-2%</td>
</tr>
<tr>
<td>Dist-2%</td>
<td>Dist-0.6%</td>
<td>Dist-0.6%</td>
<td>Dist-0.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IB-C*</th>
<th>IB-C</th>
<th>IB-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local-14%</td>
<td>Local-14%</td>
<td>Local-6%</td>
</tr>
<tr>
<td>Dist-7%</td>
<td>Dist-31%</td>
<td>Dist-5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>IB-C</th>
<th>IB-C</th>
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</thead>
<tbody>
<tr>
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<td>Local-6%</td>
<td>Local-6%</td>
</tr>
<tr>
<td>Dist-7%</td>
<td>Dist-5%</td>
<td>Dist-5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IB-C*</th>
<th>IB-C</th>
<th>IB-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local-6%</td>
<td>Local-6%</td>
<td>Local-6%</td>
</tr>
<tr>
<td>Dist-7%</td>
<td>Dist-5%</td>
<td>Dist-5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IB-C*</th>
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<th>IB-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local-6%</td>
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<td>Local-6%</td>
</tr>
<tr>
<td>Dist-7%</td>
<td>Dist-5%</td>
<td>Dist-5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IB-C*</th>
<th>IB-C</th>
<th>IB-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local-6%</td>
<td>Local-6%</td>
<td>Local-6%</td>
</tr>
<tr>
<td>Dist-7%</td>
<td>Dist-5%</td>
<td>Dist-5%</td>
</tr>
</tbody>
</table>

Received XRT
Example: IC, Grade 3

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>SS</th>
<th>Rx</th>
<th>Recurrence</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PORTEC</td>
<td>99</td>
<td>N</td>
<td>Pelvic</td>
<td>14% Local</td>
<td>5 yr OS = 58%</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td>31% Distant</td>
<td></td>
</tr>
<tr>
<td>Rasool</td>
<td>54</td>
<td>Y</td>
<td>18% Obs</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td>23% VCB</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>44% Pelvic</td>
<td>17% Total</td>
<td></td>
</tr>
<tr>
<td>Creasman</td>
<td>120</td>
<td>Y</td>
<td>---</td>
<td>---</td>
<td>5yr OS = 66%</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Straughn</td>
<td>47</td>
<td>Y</td>
<td>53% XRT</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td>47% Obs</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

Modern Math: Unstaged IC, Gr 3 = Stage IIIC,
Staged IC, Gr 3 = Unstaged Stage IB, Gr1-2

GOG 33

Aalders Study: Vaginal Cuff Brachytherapy +/- Whole Pelvic XRT

<table>
<thead>
<tr>
<th>DFN</th>
<th>N</th>
<th>SS</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr 3 + DOI&gt;50%</td>
<td>95/540 (18%)</td>
<td>No</td>
<td>Pel/Vag failure: 20% V vs 5% V+P</td>
<td>Death from cancer: 28% V vs 18% V +P</td>
</tr>
</tbody>
</table>
PORTEC

- \( N = 714, \text{No SS} \)

<table>
<thead>
<tr>
<th></th>
<th>Gr 1</th>
<th>Gr 2</th>
<th>Gr 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>221 (31%)</td>
<td>73 (10%)</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>142 (20%)</td>
<td>277 (39%)</td>
<td></td>
</tr>
</tbody>
</table>

Randomize

Pelvic XRT \( N = 354 \)
Observation \( N = 360 \)

Creutzberg. Lancet 2000;355:1404-1411

PORTEC

<table>
<thead>
<tr>
<th></th>
<th>Pelvic XRT ( N = 354 )</th>
<th>Observation ( N = 360 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Vault</td>
<td>5 (1.6%)</td>
<td>19 (6.4%)</td>
</tr>
<tr>
<td>Pelvic</td>
<td>4 (2%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Distant</td>
<td>24 (8%)</td>
<td>20 (7%)</td>
</tr>
<tr>
<td>5 yr local-reg PFS</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>5 yr OS</td>
<td>81%</td>
<td>85%</td>
</tr>
</tbody>
</table>

PORTEC: H-IR model

<table>
<thead>
<tr>
<th></th>
<th>DFN</th>
<th>N</th>
<th>SS</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gr 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>@ 10 yr locoreg:</td>
</tr>
<tr>
<td>• Age ≥ 60</td>
<td>10%</td>
<td></td>
<td>72%</td>
<td></td>
<td>23% (obs) vs. 4.6% (XRT)</td>
</tr>
<tr>
<td>• 50% DOI</td>
<td></td>
<td></td>
<td>59%</td>
<td></td>
<td>@ 5 yr dist failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5% (obs) vs 6% (XRT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Endoca deaths: 8% (obs) vs 11% (XRT)</td>
</tr>
</tbody>
</table>

GOG 99

- **N=392, (+) SS, “any degree of myometrial invasion”, IB, IC, occult IIA-B**

<table>
<thead>
<tr>
<th>Gr 1</th>
<th>Gr 2</th>
<th>Gr 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>229 (58%)</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>126 (32%)</td>
<td></td>
</tr>
<tr>
<td>166 (42%)</td>
<td>154 (39%)</td>
<td>72 (18%)</td>
</tr>
</tbody>
</table>

[Randomize Pelvic XRT \( N=190 \) Observation \( N=202 \)]

GOG 99

<table>
<thead>
<tr>
<th>Pelvic XRT ( N=190 )</th>
<th>Observation ( N=202 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrences</td>
<td></td>
</tr>
<tr>
<td>Vaginal Vault</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Pelvic</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Distant</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>2 yr PFS</td>
<td>3%</td>
</tr>
<tr>
<td>4 yr OS</td>
<td>92%</td>
</tr>
</tbody>
</table>

GOG 99: H-IR model

<table>
<thead>
<tr>
<th>DFN</th>
<th>N</th>
<th>SS</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSI, Gr 2-3, outer 1/3 DOI</td>
<td>132/392 (33%)</td>
<td>Yes</td>
<td>28/44 (64%) recs @ 48mo- 27% (obs) vs. 13% XRT</td>
<td>22/32 (68%) endoca deaths</td>
</tr>
</tbody>
</table>

[Keys, Gynecol Oncol 2004; 92: 744-751]
“Subset Analysis”

- Low Risk - without H-IR features
  - Age, LVSI (+), DOI (outer 1/3), Grade (Gr 2-3)
  - any age +3, >50 +2, >70 +1

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Pelvic XRT</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=48 mo</td>
<td>n=126</td>
<td>n=122</td>
</tr>
<tr>
<td>Isolated local failure</td>
<td>0%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Distant failure</td>
<td>1.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Recurrence or death</td>
<td>2.1%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

Keys. Gynecol Oncol 2004;92:744-751

Pattern of Failure GOG 99 H-IR

<table>
<thead>
<tr>
<th></th>
<th>Obs @48 mo</th>
<th>XRT @48 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrence</td>
<td>27%</td>
<td>13%</td>
</tr>
<tr>
<td>Local</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Distant</td>
<td>19%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Do Serous Tumors belong in IR?

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>S8</th>
<th>Rx</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tchabo 2009</td>
<td>23</td>
<td>+</td>
<td>13% - Obs 65% - C or C + XRT</td>
<td>13% rec</td>
</tr>
<tr>
<td>Thomas 2007</td>
<td>42</td>
<td>81</td>
<td>40% - Obs 43% - XRT 17% - C or C + XRT</td>
<td>5 yr PF3 =78%</td>
</tr>
<tr>
<td>Havrilesky 2007</td>
<td>83</td>
<td>+</td>
<td>59% - Obs 20% - XRT 20% - C or C + XRT</td>
<td>22% rec 3 yr PF3 = 68%</td>
</tr>
<tr>
<td>Dullesder 2004</td>
<td>24</td>
<td>+</td>
<td>100% VCB</td>
<td>13% rec</td>
</tr>
<tr>
<td>Huh 2003</td>
<td>60</td>
<td>+</td>
<td>95% - Obs 14% - C</td>
<td>15% rec 3yr DFS =78-88%</td>
</tr>
</tbody>
</table>

Obs = observation, XRT = radiation therapy, C = chem, VCB = vaginal cuff brachytherapy
Is risk independent of nodal status?

- Yes...
  - GOG 99 H-IR model- is for node (-) pts
  - PORTEC- “presumed node (-)”
  - Grade 3, DOI > 50%, cervical stromal dz more significant determinant of survival than nodal status*

- But...
  - Most/many recurrences in (-) node pts are at cuff
  - For now, ? We are treating node (+) patients differently than node (-)


Are factors associated with nodal disease the same as with recurrence?

<table>
<thead>
<tr>
<th>Nodal Disease</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>LND...</td>
<td>Nodal status...</td>
</tr>
<tr>
<td>DOI</td>
<td>DOI</td>
</tr>
<tr>
<td>Cervix (+)</td>
<td>Grade</td>
</tr>
<tr>
<td>Grade</td>
<td>LVSI</td>
</tr>
<tr>
<td>Histology</td>
<td>Pt age</td>
</tr>
<tr>
<td>Histology</td>
<td>Histology</td>
</tr>
</tbody>
</table>

Target Based Adjuvant Therapy

- Mayo experience of 915 pts, 190 (21%) recurred
  - Rec @ 5 yr: Direct extension (5% vaginal), hematogenous (9%), lymphatic (6%), intraperitoneal (6%)
  - Different patterns of spread predicted by path:
    - Hematogenous: DOI > 50%, >66% (with (-) nodes)
    - Nodal-LVSI, (+) nodes
    - Peritoneal- Stage IV, LVSI/wash (+), (+) nodes, type 2 dz (2 or more factors)
  - Apply risk factors: 35% of all pts considered for risk, identified 141/158 pts (89%) who recurred (Heme, Node, Peritoneal sites)
  - Different adjuvant therapy
    - Eg. 48% of all recurrences had a hematogenous component (21% isolated heme)
    - Tailored multimodality therapy

Mariani. Gynecol Oncol 95:120-126.2004
**Post-op Adjuvant Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Pelvic XRT</th>
<th>Vaginal Cuff Brachytherapy</th>
<th>Chemotherapy</th>
<th>Chemo + Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic XRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo + Radiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**VCB Only**

**PORTEC-2**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Vaginal</th>
<th>Pelvic</th>
<th>Distant</th>
<th>3 yr PFS/OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBXRT</td>
<td>214</td>
<td>2%</td>
<td>0.7%</td>
<td>5.7%</td>
<td>89%—91%</td>
</tr>
<tr>
<td>VCB</td>
<td>213</td>
<td>0.9%</td>
<td>3.5%</td>
<td>6.3%</td>
<td>89%—90%</td>
</tr>
</tbody>
</table>

Recurrence % @ 3 yrs

H-IR pts: > 60 yrs + I/CGr1-2, IB/Gr3, any age + IIA/Gr1-2, IBGr3
EBXRT: 46 Gy/23 fractions, VCB: 21 Gy HDR/3 fractions or 30 Gy LDR
Increased bowel sx, diarrhea with EBXRT, better QoL with VCB
### Distant Failure Rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Aalders</th>
<th>PORTEC</th>
<th>GOG 99</th>
<th>ASTEC/EN.5</th>
<th>PORTEC 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>540</td>
<td>714</td>
<td>392</td>
<td>905</td>
<td>427</td>
</tr>
<tr>
<td>Staged</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>30%</td>
<td>No</td>
</tr>
<tr>
<td>Observation</td>
<td>5%*</td>
<td>7%</td>
<td>8%</td>
<td>8%**</td>
<td>6.3%*</td>
</tr>
<tr>
<td>Pelvic XRT</td>
<td>9.8%</td>
<td>8%</td>
<td>5%</td>
<td>9%</td>
<td>5.7%</td>
</tr>
<tr>
<td>@ 5yr</td>
<td>@ 5yr</td>
<td>@ 4yr</td>
<td>@ 5yr</td>
<td>@ 3yr</td>
<td></td>
</tr>
</tbody>
</table>

* = all received vaginal cuff brachytherapy, **=51% received vaginal cuff brachytherapy

---

### Distant Failure Rates

<table>
<thead>
<tr>
<th>Study</th>
<th>ASTEC</th>
<th>CONSORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1408</td>
<td>514</td>
</tr>
<tr>
<td>No LND</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>LND</td>
<td>8%</td>
<td>8%</td>
</tr>
</tbody>
</table>

---

### Distant Sites of Failure

<table>
<thead>
<tr>
<th>PORTEC</th>
<th>GOG 99</th>
</tr>
</thead>
<tbody>
<tr>
<td>All XRT</td>
<td>Obs</td>
</tr>
<tr>
<td>IC, Gr 1-6%</td>
<td>All-8%</td>
</tr>
<tr>
<td>IB, Gr 2-3%</td>
<td>H-IR-19%</td>
</tr>
<tr>
<td>IC, Gr 2-8%</td>
<td>Low-R-3%</td>
</tr>
<tr>
<td>IB Gr 3-20%</td>
<td>H-IR-10%</td>
</tr>
<tr>
<td>IC, Gr 3-31%</td>
<td>Low-R-2%</td>
</tr>
</tbody>
</table>
### Chemo + Reduction(?) of Distant Failures

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>% Distant Failure</th>
<th>Stage</th>
<th>Chemo Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>JGOG XRT</td>
<td>193</td>
<td>13.5%</td>
<td>58% IC 25% IIIA,C</td>
<td>CAP</td>
</tr>
<tr>
<td>Chemo</td>
<td>192</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maggi XRT</td>
<td>166</td>
<td>26.5%</td>
<td>26% IC 62% IIIA,C</td>
<td>CAP</td>
</tr>
<tr>
<td>Chemo</td>
<td>174</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 122 XRT</td>
<td>202</td>
<td>38.6%</td>
<td>71% IIIA,C 29% IV</td>
<td>AC</td>
</tr>
<tr>
<td>Chemo</td>
<td>194</td>
<td>31%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAP = cyclophosphamide, doxorubicin, cisplatin. AC = doxorubicin, cisplatin.

### XRT vs XRT + Chemo

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>% Distant Failures</th>
<th>Stage</th>
<th>Chemo Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 34 XRT</td>
<td>89</td>
<td>23%</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>XRT - A</td>
<td>92</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 184 XRT-AC</td>
<td>261</td>
<td>26% for both</td>
<td>88% III (13% serous)</td>
<td></td>
</tr>
<tr>
<td>XRT-TAP</td>
<td>278</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSGO/EORTC XRT</td>
<td>196</td>
<td>16.8%</td>
<td>49% IC (26% serous)</td>
<td></td>
</tr>
<tr>
<td>Chemo-XRT</td>
<td>186</td>
<td>10.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A= doxorubicin, AC= doxorubicin + cisplatin, TAP= paclitaxel, doxorubicin, cisplatin.

### GOG 249- Study Design

Eligible: (FIGO 2009) Stage I endometrial carcinoma, with H-IR features,
Stage II (occult) endometrial carcinoma (any histology), with or without risk factors, and
Stage I-II (occult) serous or clear cell endometrial carcinoma, with or without other risk features

**TREATMENT RANDOMIZATION**

Regimen I: Pelvic Radiation Therapy (4500/25 fractions-5040 cGy/28 fractions) over 5-6 weeks
Optional Vaginal Cuff Boost ONLY for Stage II patients and Stage I S/C patients

OR

Regimen II: Vaginal Cuff Brachytherapy + 3 cycles of chemotherapy
Paclitaxel 175 mg/m² (3hr) + Carboplatin AUC 6 q 21 days
Outcomes

- **Outcome measures:**
  - Primary: Duration of recurrence-free survival;
  - Secondary: Duration of overall survival, cumulative incidence of pelvic/vaginal recurrence, cumulative incidence of extra-pelvic recurrence, contributing cause of death.
- Randomization will be stratified by
  - 1) Lymph node dissection
  - 2) Use of VCB in arm I

Is 249 Obsolete?

- Risk groups in PORTEC 2 not same
  - No serous, no stage II, ? Lower risk
- Pelvic failures high with VCB alone
- Role of chemotherapy???
  - Will it reduce distant failures
  - Will it provide pelvic control
- No staging + VCB for all → best patient care or cheap/ "universal" patient care plan?

Where are we today?

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 249</td>
<td>H-III stage I-II, PS/CC I-II</td>
<td>WP vs VCB + TC X 3</td>
</tr>
<tr>
<td>PORTEC 3</td>
<td>IB Gr3 + LVSI, IC Gr 3, IIIA-C, IB-III PS/CC</td>
<td>Pelvic XRT vs Pelvic XRT + CDDP (X2) → T/C X 4</td>
</tr>
<tr>
<td>RT0G 0921</td>
<td>IC-RA Gr 3, IIB Gr 2-3, III-IVA</td>
<td>IMRT + CDDP + bev → T/C X 4</td>
</tr>
<tr>
<td>GOG 238</td>
<td>Locally recurrent dz</td>
<td>Pelvic XRT +/- weekly CDDP</td>
</tr>
</tbody>
</table>
What would be better: **Early stage disease**

- Can molecular/genetic features define those who are @ risk from those not
  - Challenge: not to reinvent wheel (Grade, DOI, histology, etc)
  - Pre-test probability in node (-) pt for recurrence is low—enrich risk by something
- Ferguson- evaluated global gene expression profiling to distinguish risk
  - 75 IR pts – 13 recurred vs. 62 NED
  - Gene expression profiling could stratify pts into low and high risk groups
  - No single gene significantly correlated with recurrence
  - Clinicopath features were similar between low and high risk groups except for SS (35% low risk vs 69% high risk not SS)
- Supports proof of principle


---

**“Intermediate Risk”**

Better/validated clinical path models- GOG 249
Predictive + Prognostic Molecular markers- GOG 210, 249
Targeted therapy program- GOG 229, 86P

Enriched for Risk
Clearly defined therapy
Clearly defined benefit

---

What is needed to for continued evolution:

- Define the role of LND- which populations, optimal procedure, what outcome
- Prognostic nomograms → Individualized risk assessment
- Biomarkers to predict risk of nodal disease, risk of recurrence, predictors of response (or not) to chemo, xrt, biologics
- Understand how to use chemotherapy in endometrial cancer
- New opportunities with targeted agents
Optimizing combination chemotherapy and radiation in treating locally advanced cervical cancer

Kathleen N. Moore, MD
Assistant Professor
Division of Gynecologic Oncology
Mai Eager Anderson Chair in Clinical Trials
University of Oklahoma
Oklahoma City, OK

Dr. Moore is currently an Assistant Professor in the Division of Gynecologic Oncology at the University of Oklahoma.

She received her MD from the University of Washington School of Medicine in 2000. She completed her residency in Obstetrics and Gynecology at Magee Womens Hospital, Pittsburgh, PA in 2004 and went on to complete her fellowship in Gynecologic Oncology at the University of Oklahoma in 2007.

She has been on faculty at the University of Oklahoma since 2007. She serves the GOG as a member of the Gynecologic Oncology, Ovarian, Developmental Therapeutics and Phase I committees and was recently appointed to the working group for development of clinical trials in our elderly patients.
Optimizing Combination Chemotherapy and Radiation in Treating Locally Advanced Cervical Cancer

Kathleen N. Moore, MD
Assistant Professor, Division of Gynecologic Oncology
University of Oklahoma

Disclosures:

• I have no disclosures to make

Objectives:

• Review the current standard therapy for locally advanced cervix cancer
• Discuss strategies for improvement of outcomes
  – Improved local control
  – Reduced distant failures
  – Development of predictive biomarkers
  – Improved QOL/reduction in treatment toxicities
• Review current and under development clinical trials in locally advanced cervical cancer
Epidemiology

- In the 50 years following the introduction of cervical cytology, US cancer rates decreased by 75% and mortality by 74%
- The introduction in unscreened populations reduced cervical cancer rates by 60-90% within 3 years of implementation
- Current 2009 estimates for US women are that 11,270 new cases of cervix cancer will be diagnosed with 4,070 deaths*

* ACS: Facts and Figures 2009

Epidemiology

GOG 85
NCI Alert: Current SOC

- The findings of these 5 trials demonstrated
  - an absolute improvement in survival of 8-18%
  - 40% reduction in the risk of death
- Weekly cisplatin at 40mg/m2 became the most widely used regimen due to convenience and acceptable toxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Arms</th>
<th>Local Rec</th>
<th>Distant Rec</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 85</td>
<td>IIB-IVA</td>
<td>Hu PF</td>
<td>53% 43%</td>
<td>30% 25%</td>
<td>21% 17.5%</td>
<td>57% 67%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 120</td>
<td>IIB-IVA</td>
<td>P PFHu Hu</td>
<td>34% 34% 55%</td>
<td>19% 20% 30%</td>
<td>15% 14% 25%</td>
<td>58% 57% 35%</td>
</tr>
<tr>
<td>Rose et al 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 90-01</td>
<td>IIB-IVA</td>
<td>PF EFRT</td>
<td>19% 35%</td>
<td>14% 33%</td>
<td>67% 40%</td>
<td>73% 58%</td>
</tr>
</tbody>
</table>

Hu = Hydroxyurea
P= Cisplatin
PF= Cisplatin & 5-Fluorouracil
EFRT= extended field radiation
Distant Recurrence

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Arms</th>
<th>Rec</th>
<th>Local Rec</th>
<th>Distant Rec</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 85</td>
<td>IIB-IVA</td>
<td>Hu</td>
<td>53%</td>
<td>36%</td>
<td>21%</td>
<td>57%</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PF</td>
<td>43%</td>
<td>25%</td>
<td>17.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 120</td>
<td>IIB-IVA</td>
<td>P</td>
<td>34%</td>
<td>19%</td>
<td>5%</td>
<td>58%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PFHu</td>
<td>34%</td>
<td>20%</td>
<td>14%</td>
<td>57%</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hu</td>
<td>55%</td>
<td>30%</td>
<td>25%</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>RTOG 90-01</td>
<td>IIB-IVA</td>
<td>PF</td>
<td>19%</td>
<td>35%</td>
<td>14%</td>
<td>67%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EFRT</td>
<td></td>
<td></td>
<td></td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

Hu = Hydroxyurea  
P= Cisplatin  
PF= Cisplatin & 5-Fluorouracil  
EFRT= extended field radiation

Treatment Failures

- Even with the addition of platinum based chemotherapy, local recurrences still occur in 20-25% of patients and distant recurrences still occur in ~15%
- Can we impact the rate of local/distant failures?
  - Neo-adjuvant chemotherapy
  - Additional cytotoxic/biologics during RT
  - Consolidation chemotherapy after chemo/RT
- Can we predict failures and adjust therapy? “individualized treatment”

Can we Add Chemotherapy Before Radiation and Make a Difference?
Neo-Adjuvant Chemotherapy (NACT)

- Possible Advantages
  - Tumor size reduction facilitates local tx
  - NACT may increase radiosensitivity & decrease hypoxic cell fx
  - NACT may tx micrometastases
- Cited Disadvantages
  - Non-response to NACT = treatment delay
  - Potential cross resistance b/t certain chemo * radiation
  - Added toxicity

NACT: The Evidence

- Cochrane Review Updated 2009
- Compilation of data from 1975 to 2006; attempted to do 2 comparisons
  - NACT followed by local tx vs. local tx alone
  - NACT followed by surgery +/- RT vs. RT alone

NACT Cochrane Comparison 1: NACT Followed by Local Tx vs. Local Tx Alone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trials</th>
<th>HR (95% CI)</th>
<th>p value</th>
<th>Heterogeneity</th>
<th>5-year OS p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of chemotherapy</td>
<td>≥14 days</td>
<td>11</td>
<td>1.35 (1.07-1.66)</td>
<td>0.005</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>≤14 days</td>
<td>6</td>
<td>0.76 (0.46-1.26)</td>
<td>0.005</td>
<td>0.19</td>
</tr>
<tr>
<td>Cyclophosphamide dose intensity</td>
<td>≥25 mg/m²</td>
<td>7</td>
<td>1.35 (1.11-1.64)</td>
<td>0.002</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>≥25 mg/m²</td>
<td>11</td>
<td>0.91 (0.67-1.25)</td>
<td>0.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>
NACT Cochrane Comparison 1: NACT Followed by Local Tx vs. Local Tx Alone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trials</th>
<th>HR (95% CI)</th>
<th>p value</th>
<th>Heterogeneity</th>
<th>5-year OS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of chemotherapy</td>
<td>&gt;14 days</td>
<td>1.23 (1.17-1.30)</td>
<td>0.001</td>
<td>0.23</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤14 days</td>
<td>0.76 (0.67-0.86)</td>
<td>0.001</td>
<td>0.19</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Cisplatin dose intensity</td>
<td>≤25 mg/m²</td>
<td>1.35 (1.11-1.64)</td>
<td>0.002</td>
<td>0.74</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;25 mg/m²</td>
<td>0.91 (0.78-1.05)</td>
<td>0.20</td>
<td>0.001</td>
<td>71%</td>
<td></td>
</tr>
</tbody>
</table>

NACT Cochrane Comparison 2: NACT Followed by Surgery +/-RT vs. RT Alone

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. events/patients</th>
<th>HR 95% CI, p</th>
<th>Heterogeneity γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>30/1872</td>
<td>0.60 (0.35-1.05, 0.086)</td>
<td>0.06</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>4/1872</td>
<td>0.68 (0.34-1.39, 0.29)</td>
<td>0.06</td>
</tr>
<tr>
<td>Two-regional disease-free survival</td>
<td>4/1872</td>
<td>0.68 (0.34-1.39, 0.29)</td>
<td>0.065</td>
</tr>
<tr>
<td>All cause death survival</td>
<td>1/1872</td>
<td>0.60 (0.32-1.14, 0.086)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

NACT chemotherapy for locally advanced cervix cancer (Review) The Cochrane Collaboration. 2009 Issue 4
NACT Cochrane Comparison 2: NACT Followed by Surgery +/-RT vs. RT Alone

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. events/patients</th>
<th>HR (95% CI), p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>540/172</td>
<td>0.83 (0.71-0.98)</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>440/172</td>
<td>0.84 (0.64-1.10)</td>
</tr>
<tr>
<td>Two-regional disease-free survival</td>
<td>482/172</td>
<td>0.68 (0.53-0.89)</td>
</tr>
<tr>
<td>All cause death</td>
<td>281/172</td>
<td>0.63 (0.45-0.87)</td>
</tr>
</tbody>
</table>

*Neoadjuvant chemotherapy for locally advanced cervix cancer (Review) The Cochrane Collaboration. 2009 Issue 4

NACT

- and yet we are unmoved.....Why?
  - Many confounding factors in the meta-analysis comparison 2
  - Out of date neoadjuvant regimens
  - Sub-standard (by current standards) RT in the comparison arms
  - GOG 141

NACT: GOG 141

- IB2 randomized to RHPPLN vs. NACT + RHPPLN
- NACT was cisplatin 50mg/m2 and vincristine 1mg/m2 q 10 days for 3 cycles
- Closed at 70% accrual (288 pts) due to
  - Slow accrual
  - Off protocol RT use

Kathy G et al. Gyn Onc 2007;103:236-8
Is NACT a Done Concept?

• not quite.....
• EORTC 55994
  – Randomized Phase III trial activated in 2002
  – Stage IB2-IIIB
  – Arm 1: Patients are given q21 day platinum
    based chemotherapy followed by class III-IV
    RH +/- RT based on LN/parametria or borders
  – Arm 2: standard cis/RT

Is NACT a Done Concept?

• not quite.....
• NCT00600210
  – Phase II Trial
  – Stage IB2-IIIB
  – Neoadjuvant Bevacizumab + Carboplatin
    followed by concurrent bevacizumab,
    carboplatin and RT

How about combining agents
with cisplatin and radiation?
Cisplatin + Cytotoxic + RT

- Cisplatin + Paclitaxel
  - GOG 9803/9804
- Cisplatin + Topotecan
  - GOG 9913
- Cisplatin + Gemcitabine
  - GOG 9912
  - Dueñas-Gonzales ASCO
- Carboplatin + Paclitaxel

GOG 9803/9804: A Phase I/II Trial of Paclitaxel & Cisplatin during RT for Stage IB2-IVa (PALN -/+)

- Paclitaxel is a known radiation sensitizer
- 9803 (PALN-)
  - MTD 40mg/m2 paclitaxel and 40mg/m2 Cisplatin
  - Median time to complete RT 59 days
  - Complete response rate = 89%
- 9804 (PALN+)
  - Same MTD
  - Median time to complete RT 56 days
  - 3 and 4 year survival estimates are 66% and 54%
- Although promising and feasible, little support in the international community for further development due to toxicity concerns

Cisplatin + Gemcitabine + RT?: GOG 9912 and Dueñas-Gonzales

- GOG 9912
- Phase I study of gemcitabine followed by cisplatin during chemo/RT
  - MTD was 50mg/m2 gem and 40mg/m2 cisplatin
  - 13 pts enrolled with significant hematologic and non-hematologic toxicity
  - Further expansion of this protocol was held
- Dueñas-Gonzales (ASCO 2009)
  - RCT/Phase III trial
    - Cisplatin RT vs. Cisplatin 40mg/m2, Gemcitabine 125mg/m2 RT
    - Followed by nothing vs. 2 cycles cis/gem
    - Median duration tx = 49 d
    - 3 yr PFS 74% vs. 65%
    - 3 yr OS 78% vs. 69%
    - Distant Failure 8% vs. 16%
    - Local Failure 11% vs. 16%
Cisplatin + Gemcitabine + RT in Perspective:

<table>
<thead>
<tr>
<th>Study</th>
<th>Arms</th>
<th>Local Rec</th>
<th>Distant Rec</th>
<th>3 year PFS</th>
<th>3 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 85 Whitney et al. 1999</td>
<td>HU CDDP/5-FU x 2</td>
<td>30%</td>
<td>21%</td>
<td>50%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>CDDP/5-FU</td>
<td>25%</td>
<td>17.5%</td>
<td>60%</td>
<td>67%</td>
</tr>
<tr>
<td>GOG 120 Rose et al. NEJM 1999</td>
<td>HU CDDP wkly CDDP/5-FU</td>
<td>30%</td>
<td>25%</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>CDDP/5-FU</td>
<td>19%</td>
<td>15%</td>
<td>62%</td>
<td>68%</td>
</tr>
<tr>
<td>RTOG 9001 Morris et al. NEJM 1999</td>
<td>EFRT CDDP/5-FU</td>
<td>35%</td>
<td>33%</td>
<td>50%</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>CDDP/5-FU</td>
<td>19%</td>
<td>14%</td>
<td>70%</td>
<td>76%</td>
</tr>
<tr>
<td>More chemo with RT? Not yet..</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 3 year OS for RTOG 9001 and Duenas-Gonzales are remarkably similar
- Both studies used chemo following completion of RT
- The recurrence rates may reflect shorter f/u as compared to > 5 year f/u for GOG 85, 120 and RTOG 9001
- Issues with hematologic toxicities, “perfect radiation” make interpretation of this study difficult
- At present, a second cytotoxic used during chemo/RT should be used only on protocol

Cisplatin + Targeted Therapy + RT

- Cisplatin + Bevacizumab
- Cisplatin + Cetuximab
- Cisplatin + Tirapazamine
- Cisplatin + Celecoxib + 5-FU
- Cisplatin + Sorafenib
- Cisplatin + Erlotinib
Cisplatin + Cetuximab: 9918

- Cetuximab: chimerized monoclonal antibody targeted the epidermal growth factor receptor
- Binding to EGFR leads to cell cycle arrest, apoptosis and inhibition of angiogenesis
- Cetuximab displays supra-additive in growth inhibition of tumor cells when given with chemotherapy
- GOG 9918 is evaluating cisplatin + cetuximab in LN+ and – cohorts

Cisplatin + Tirpazamine: GOG 219

- Tirpazamine (TPZ) is a bioreductively activated, hypoxia selective antitumor agent
- The reduced product causes single and double strand DNA breaks and accentuates DNA repair
- TPZ is synergistic with cisplatin
- Phase III trial of cisplatin/RT vs. cisplatin/TPZ/RT accrued 402 patients and was stopped early due to loss of TPZ supply

Cisplatin + Tirpazamine: GOG 219

- Completion of > 5 cycles of chemotherapy
  - Cisplatin/RT – 90.2%
  - Cisplatin/TPZ/RT – 79.2%
- Completion of Radiation ≤52 days
  - Cisplatin/RT – 71%
  - Cisplatin/TPZ/RT – 70.6%
- Toxicity
  - Grade 3/4 toxicities Cisplatin vs. TPZ
    - Diarrhea 11 vs. 20%
    - Pain 2 vs. 28%
    - Rash 0 vs. 15%
    - Metabolic derangements 24% vs. 36%
Cisplatin + Bevacizumab: RTOG 0417

- Bevacizumab is a humanized IgG1 monoclonal antibody that binds VEGF-A
  - VEGF binding inhibits proliferation of endothelial cells and decreases microvessel density
  - Elevated VEGF is a least a marker of poor prognosis – Its predictive value remains to be seen
- RTOG 0417
  - Phase II trial of Bevacizumab 10mg/kg q 2 weeks with weekly cisplatin 40mg/m²
  - This study is closed to accrual and results are pending

Cisplatin + Other Biologics

- RTOG C-0128: Cisplatin + 5 FU + Celecoxib (Phase I/II)
  - No survival benefit
- Cisplatin + Triapine (Phase I)
  - 3 x weekly small molecule inhibitor of RNR
  - Feasible with weekly cisplatin
- Cisplatin + Erlotinib (Phase I)
  - Oral tyrosine kinase inhibitor of EGFR
  - Feasible at dose of 150mg with weekly cisplatin
- Cisplatin + Sorafenib (Phase I)
- Cisplatin + Sunitinib (Phase I)
- Cisplatin + Velcade (Phase I)

Studies currently ongoing

What if we consolidate our chemoradiation with more chemotherapy?

Consolidation Chemotherapy

- Consolidation Chemotherapy proof of concept
  - RTOG 90-01
    • Used 1 additional cycle of cisplatin/5FU following EBRT
  - Dueñas-Gonzales
    • Used 2 additional cycles of cisplatin/gemcitabine following EBRT
  - GOG 109
    • Used 2 additional cycles of cisplatin/5FU following EBRT for high risk patients after radical hysterectomy
  - RTOG 0724
    • Ongoing Phase III RCT in high risk early stage cervix cancer
    • Cisplatin/RT +/- adjuvant chemotherapy

ANZGOG Trial

- International, multi-institutional, Phase III RCT Trial
- Local-regional advanced cervix cancer
- Randomized b/t standard cisplatin/RT vs. cisplatin/RT + 4 cycles Paclitaxel & Carboplatin

Can Radiation Efficacy be Improved and Toxicity Reduced?
Optimization of Radiation

Biomarker Development: Can we Predict Treatment Failure?

- Imaging biomarkers
  - Dynamic contrast enhanced MRI (DC-MRI)
  - Diffusion Weighted MRI (DW-MRI)
  - Magnetic Resonance Spectroscopy (MRS)
  - Positron emission tomography (FDG-PET)
- Molecular biomarkers
  - VEGF 0417
  - mi RNA
  - DNA methylation

Global Strategy

- New treatments and technologies will likely impact on outcomes for patients with local regionally advanced cervix cancer
  - Primarily in resource rich settings
- The larger mission is to improve outcomes for patients in resource poor settings where cervix cancer is most prevalent and lethal
  - Prevention is key
  - Widespread availability of vaccines
  - Widespread access to screening
Thank You
New systemic approaches to management of corpus cancer

Carol Aghajanian, MD
Chief of the Gynecologic Medical Oncology Service
Memorial Sloan-Kettering Cancer Center
Associate Professor of Medicine
Joan and Sanford I. Weill Medical College at Cornell University.
New York, NY

Carol Aghajanian, MD, a medical oncologist and authority on gynecologic cancers, is the Chief of the Gynecologic Medical Oncology Service at MSKCC. She is also an Associate Professor of Medicine in the Joan and Sanford I. Weill Medical College at Cornell University. Dr. Aghajanian is the Chair of the Developmental Therapeutics Committee of the Gynecologic Oncology Group (GOG). In this capacity, Dr. Aghajanian is responsible for the peer reviewed grant, strategic plan, and conduct of all phase I and II clinical trials and vaccine programs directed by the GOG. Dr. Aghajanian represents the GOG on the Investigational Drug Steering Committee, NCI. Dr. Aghajanian has served as the Study Chair/Principal Investigator of 25 phase I and II clinical trials. Dr. Aghajanian’s main research interest is in the biology of ovarian and endometrial cancers and molecular targeted therapeutics. She is an active member of the International Society for the Study of Trophoblastic Diseases and directs the gestational trophoblastic disease program at MSKCC. In 2003, Dr. Aghajanian was awarded the MSKCC Louise and Allston Boyer Award for Distinguished Achievement in Biomedical Research, in acknowledgment of this translational research.
New Systemic Approaches to Management of Corpus Cancer

Carol Aghajanian, MD
Chief, Gynecologic Medical Oncology Service
Memorial Sloan-Kettering Cancer Center

Speaker Disclosure

- Watermark Research Partners, Inc
  - DSMB
- IMER
  - One time speaker (January 2010)
- Sanofi/BiPar
  - One time Ad board (January 2010)

Risk Factors

- Unopposed estrogen
- Obesity
- Nulliparity
- Menopause after the age of 52
- HTN
- DM
- Complex atypical hyperplasia
- Use of tamoxifen

Type I Vs. Type II Endometrial Carcinoma

- **Type I: Endometrioid**
  - Unopposed estrogen (hyperplasia)
  - Low to moderate grade, minimal myometrial invasion
  - Good prognosis

- **Type II: Serous**
  - Lack of unopposed estrogen (atrophy)
  - High grade, often with metastases
  - Poor prognosis (cause a disproportionate number of deaths)


Endometrial Tumorigenesis

- Normal epithelium
- Simple hyperplasia
- Complex hyperplasia
- Atrophy
- Endometrial intraepithelial carcinoma
- Serous cancer
- Type I: Endometrioid
- Type II: Serous


Hormonal Therapy

- Advanced/Recurrent Endometrial Cancer
- No Prior Chemotherapy
Hormonal Treatment of Advanced/Recurrent Endometrial Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>RR (%)</th>
<th>PFS (mos)</th>
<th>OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 153</td>
<td>56</td>
<td>MA 80 mg bid x 3 weeks alternating with T 20 mg bid x 3 weeks</td>
<td>27</td>
<td>2.7</td>
<td>14</td>
</tr>
<tr>
<td>GOG 121</td>
<td>58</td>
<td>MA 800 mg daily</td>
<td>24</td>
<td>2.5</td>
<td>7.6</td>
</tr>
<tr>
<td>GOG 81</td>
<td>154</td>
<td>MPA 1,000 mg daily vs. MPA 200 mg daily</td>
<td>14</td>
<td>2.5</td>
<td>7</td>
</tr>
<tr>
<td>GOG 119</td>
<td>58</td>
<td>T 20 mg bid plus MPA 100 mg bid every other week</td>
<td>33</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>GOG 81-F</td>
<td>68</td>
<td>T 20 mg bid</td>
<td>10</td>
<td>1.9</td>
<td>8.8</td>
</tr>
</tbody>
</table>

MA (megestrol acetate, Megace®); MPA (medroxyprogesterone acetate, Provera®); T (tamoxifen)

FDA Approved Treatment: Megestrol Acetate

- Approved in 1971 for the palliative treatment of advanced carcinoma of the breast and endometrium (i.e., recurrent, inoperable, metastatic disease)
- RR: 10%–33%
- PFS: 1.9–3.2 months

GOG 189

- Endometrial cancer
- Recurrent, persistent
- Primary stage IV
- Measurable disease

Randomize

- Doxorubicin 45 mg/m² Day 1
- Cisplatin 50 mg/m² Day 1
- Paclitaxel 160 mg/m² over 3 hours Day 2 G-CSF

Megestrol acetate 80 mg bid x 3 weeks alternating with Tamoxifen 20 mg bid x 3 weeks

- Open: 5/7/01
- Closed: 8/12/02
- Accrual: 42 patients

Closed due to lack of accrual
Chemotherapy

Advanced/Recurrent Endometrial Cancer

Endometrial Cancer: Single Agents With No Prior Chemotherapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>RR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>37</td>
<td>Thigpen et al, 1979</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>20</td>
<td>Thigpen et al, 1989</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>28</td>
<td>Long et al, 1988</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>Green et al, 1990</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>36</td>
<td>Ball et al, 1996</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>24</td>
<td>Sutton et al, 1996</td>
</tr>
<tr>
<td>Topotecan</td>
<td>20</td>
<td>Wadler et al, 2003</td>
</tr>
</tbody>
</table>

Phase II Studies 129 Series (1 prior)

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>N</th>
<th>RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>129-C</td>
<td>Paclitaxel</td>
<td>44</td>
<td>27.3a</td>
</tr>
<tr>
<td>129-H</td>
<td>Liposomal doxorubicin</td>
<td>42</td>
<td>9.5</td>
</tr>
<tr>
<td>129-J</td>
<td>Topotecan</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>129-K</td>
<td>Oxaliplatin</td>
<td>52</td>
<td>13.5</td>
</tr>
<tr>
<td>129-N</td>
<td>Docetaxel (weekly)</td>
<td>26</td>
<td>7.7b</td>
</tr>
<tr>
<td>129-P</td>
<td>Irinotecan</td>
<td>50</td>
<td>12c</td>
</tr>
<tr>
<td>129-O</td>
<td>Pemetrexed</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>129-Q</td>
<td>Gemcitabine</td>
<td>23</td>
<td>4</td>
</tr>
</tbody>
</table>

Thresholds: 10%, 25%  
*aNo prior taxane allowed  
b77% (20/26) prior paclitaxel  
c94% (47/50) prior paclitaxel

Liposomal Doxorubicin

- GOG 86-M – 1st line
  - Doxil 40 mg/m² IV q 4 weeks
  - RR - 11.5% (6/52)
    - Homesley, Gyn Onc 98: 2005
- GOG 129H – 2nd line
  - Doxil 50 mg/m² IV q 4 weeks
  - 32/42 received prior doxorubicin
  - RR – 9.5% (4/42)
    - Muggia, JCO 20: 2002

Randomized Phase III: IXAMPLE2

- Advanced Endometrial cancer
- Measurable or Non-Measurable
- 1 prior chemotherapy

Primary endpoint: PFS
Estimated Enrollment: 370

Randomized Phase III Studies

Advanced/Recurrent Endometrial Cancer

No Prior Chemotherapy
GOG 107

- Endometrial cancer
- Recurrent/persistent
- Primary stage IV
- Measurable disease
- No prior chemotherapy

RANDOMIZE

Doxorubicin 60 mg/m² (n = 150)

Doxorubicin 60 mg/m²
Cisplatin 50 mg/m² (n = 131)

Open: 12/1/88
Closed: 12/1/92
Accrual: 281 patients

RR: 42% vs. 25% (p = .004)

PFS: 5.7 vs. 3.8 months (p = .014)

OS: 9 vs. 9.2 months

Thigpen et al. JCO 22(19):3902-8, 2004

GOG 163

- Endometrial cancer
- Recurrent/persistent
- Primary stage IV
- Measurable disease
- No prior chemotherapy

RANDOMIZE

Doxorubicin 60 mg/m²
Cisplatin 50 mg/m²

Doxorubicin 50 mg/m²
Paclitaxel 150 mg/m² over 24 hours

Open: 8/12/96
Closed: 11/30/98
Accrual: 328 patients

RR: No differences in RR, PFS, or survival

PFS: 8.3 vs. 5.3 months (p < .01)

OS: 15.3 vs. 12.3 months (p = .037)


Standard Initial Chemotherapy (GOG 177)

- Endometrial cancer
- Recurrent/persistent
- Primary stage IV
- Measurable disease
- No prior chemotherapy

RANDOMIZE

Doxorubicin 60 mg/m²
Cisplatin 50 mg/m²

Doxorubicin 45 mg/m² Day 1
Cisplatin 50 mg/m² Day 1
Paclitaxel 160 mg/m² over 3 hours Day 2
G-CSF

Open: 12/28/98
Closed: 8/14/00
Accrual: 273 patients

RR: 57% vs. 34% (p < .01)

PFS: 8.3 vs. 5.3 months (p < .01)

OS: 15.3 vs. 12.3 months (p = .037)

Fleming et al. JCO 22(11):2159-2166, 2004
Standard Initial Chemotherapy (GOG 209)

- Endometrial cancer
- Stage III, IV, or recurrent
- Measurable and non-measurable
- No prior chemotherapy

Randomize

- Doxorubicin 45 mg/m² Day 1
- Cisplatin 50 mg/m² Day 1
- Paclitaxel 160 mg/m² over 3 hours Day 2
- G-CSF

- Paclitaxel 175 mg/m² over 3 hours
- Carboplatin AUC 6

Primary objective: Determine if paclitaxel/carboplatin is therapeutically equivalent to TAP with regards to OS

Open: 8/25/03
Closed: 4/20/09
Accrual: 1,381 patients

Adjuvant Therapy

Stage III Disease

Endometrial Cancer: GOG 122

Stage III, IV
No single site of residual disease >2 cm

Randomize

- Doxorubicin 60 mg/m²
- Cisplatin 50 mg/m²
  - q 3 weeks
  - x 8 cycles

WART (AP/PA)

- 30 Gy x 20 = 150 Gy
- 15 Gy boost pelvic +/- PA

Primary end point: PFS
Second end point: OS
Median F/U: 60 months
- 73% stage III

Open: 5/4/92
Closed: 2/28/00
Accrual: 396

Endometrial Cancer: GOG 122 (cont.)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AP</th>
<th>WART</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>194</td>
<td>202</td>
</tr>
<tr>
<td>Completed (%)</td>
<td>63.4</td>
<td>84.2</td>
</tr>
<tr>
<td>Toxicity (grade 3/4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (%)</td>
<td>62</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac (%)</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>GI (%)</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Treatment-related death</td>
<td>N = 8 (4%)</td>
<td>N = 5 (2%)</td>
</tr>
<tr>
<td>PFS HR 0.71 (0.55–0.91; p &lt; .01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS HR 0.68 (0.52–0.89; p &lt; .01)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


GOG 122
PFS


GOG 122
Survival

GOG 184

Register

- Endometrial cancer
- Stage III
- ± TAH/BSO
- Optional LN sampling
- < 2 cm residual

Tumor Directed RT

AP

TAP

Open: 7/3/00
Closed: 9/13/04
Registered: 616 patients
Randomized: 552 patients

*All stage IV patients randomized; June, 2003 closed to stage IV

Randomized: 552 patients

- RT within 8 weeks after surgery;
- chemotherapy within 8 weeks after RT

Optional LN sampling

< 2 cm residual


RFS By Randomized Treatment

Proportion Surviving

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

Months from Randomization 0 1 2 3 4 5 6 7 8 9 10

Treatment Alive, Failed Total

CD 159 111 270
CDP 175 107 282

3-year RFS

62%
64%


Outcomes in Adjuvant Stage III/IV EmCa Studies

Study N Stage III (%) Stage IV (%) PFS (%) OS (%)
GOG 122 396 73 27 Dox-Cis 50 WAI 38
GOG 184 616 (but 552 made it to chemotherapy) 88 12 Dox-Cis 62 Dox-Cis-Pac 64 Not mature


- Both arms of GOG 184 appear to be doing very well, but…
GOG 184 and GOG 122

- GOG 184 has fewer stage IV patients than GOG 122 so as a group they should do better
- GOG 184 RFS is being reported at 3 years, not 5 years
- GOG 184 outcomes reflect only those patients who do not progress or have an AE during RT and the survival clock starts up to 14 weeks later
- PFS at 3 years for stage III patients on GOG 122 was approximately 60%

RFS By Regimen and Residual Tumor Status

<table>
<thead>
<tr>
<th>Regimen</th>
<th>GRD + CD</th>
<th>GRD + CDP</th>
<th>No GRD + CD</th>
<th>No GRD + CDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx/GRD Alive</td>
<td>155</td>
<td>90</td>
<td>245</td>
<td>163</td>
</tr>
<tr>
<td>CD/No GRD Alive</td>
<td>4</td>
<td>21</td>
<td>25</td>
<td>12</td>
</tr>
</tbody>
</table>

RFS Treatment HRs by Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No/GRD</th>
<th>95% CI (logrank)</th>
<th>95% CI (Wald)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV</td>
<td>0.843</td>
<td>0.592-1.191</td>
<td>0.634-1.297</td>
<td>1.000</td>
</tr>
<tr>
<td>Age &gt; 70</td>
<td>0.811</td>
<td>0.582-1.134</td>
<td>0.607-1.348</td>
<td>1.000</td>
</tr>
<tr>
<td>Residual Disease</td>
<td>0.499</td>
<td>0.392-0.635</td>
<td>0.324-0.713</td>
<td>0.000</td>
</tr>
<tr>
<td>Ext Field RT</td>
<td>1.054</td>
<td>0.882-1.264</td>
<td>0.791-1.411</td>
<td>0.000</td>
</tr>
<tr>
<td>Ext Field RT Present/Residual</td>
<td>1.237</td>
<td>0.958-1.600</td>
<td>0.721-2.110</td>
<td>0.000</td>
</tr>
<tr>
<td>Tumor Site</td>
<td>0.933</td>
<td>0.794-1.103</td>
<td>0.699-1.380</td>
<td>1.000</td>
</tr>
<tr>
<td>Tumor Cell Type &amp; Grade</td>
<td>0.967</td>
<td>0.745-1.254</td>
<td>0.606-1.471</td>
<td>1.000</td>
</tr>
</tbody>
</table>

**RTOG 9708**

s/p TAH/BSO; grade 2/3; > 50% MI, SI cervix, or pelvic confined extrauterine disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPRT/IVRT</td>
<td>4,500 cGy + cisplatin 50 mg/m² Days 1, 2</td>
</tr>
<tr>
<td>Then</td>
<td>Paclitaxel 175 mg/m² + cisplatin 50 mg/m² q 4 weeks x 4</td>
</tr>
</tbody>
</table>

42 patients 98% completed therapy

At 24 months

- DFS: 83%
- OS: 90%
- Pelvic recurrence: 2%
- Distant recurrence: 17%


---

**GOG 258**

Endometrial cancer Stage III/IVA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPRT</td>
<td>Carboplatin AUC 6 q 21 days x 6 cycles</td>
</tr>
<tr>
<td>Followed</td>
<td>Paclitaxel 175 mg/m² over 3 hours</td>
</tr>
<tr>
<td>by</td>
<td>Carboplatin AUC 5 q 21 days x 4 cycles</td>
</tr>
</tbody>
</table>

Open: 6/29/09

---

**Developmental Therapeutics**
Endometrial Cancer: Novel Therapy Trials in Progress – mTOR Inhibitors (Rapalogues)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temsirolimus</td>
<td>NCIC-Clinical Trials Group</td>
</tr>
<tr>
<td>(CCI779)</td>
<td>(CTEP phase II contract)</td>
</tr>
<tr>
<td></td>
<td>Presented at ASCO 2006, 2008</td>
</tr>
<tr>
<td>Everolimus</td>
<td>The University of Texas M. D. Anderson Cancer Center</td>
</tr>
<tr>
<td>(RAD001)</td>
<td>Presented at ASCO 2008</td>
</tr>
<tr>
<td>Ridaforolimus</td>
<td>Multi-center/ARIAD pharmaceuticals</td>
</tr>
<tr>
<td>(Deforolimus, AP23573, MK-8669)</td>
<td>Presented at ASCO 2007</td>
</tr>
</tbody>
</table>

Temsirolimus (CCI779)

- Two single-agent phase II trials (NCIC)
  - 25 mg IV weekly (1 cycle = 4 weeks)
  - Chemo-naïve: RR 7/28 (25%)
    - 3 PR: Serous cancers
  - One prior chemotherapy – RR 2/27 (7%)
- Phase I study
  - Paclitaxel, carboplatin, temsirolimus


Temsirolimus (CCI779)

- GOG 248
  - Randomized phase II study of temsirolimus vs. temsirolimus/hormones (alternating megestrol acetate and tamoxifen)
  - Prior adjuvant chemotherapy allowed
  - Primary end point: RR
    - Two parallel phase II studies – 2 stage design
    - > 5/24 responses in first stage to go to second stage
    - > 13/45 responses – worthy of further study
    - 20% / 40%
**Everolimus**  
(RAD001)

- 1–2 prior chemotherapy regimens
- Restricted to endometrioid histology
- Clinical benefit rate (SD > 8 weeks)  
  - 44% (11/25)

Slomovitz BM, et al. ASCO 2008, Abstract # 5502

---

**Ridaforolimus**  
(Deforolimus, AP23573, MK-8669)

- 12.5 mg (fixed dose) IV over 30 min daily x 5 every 2 weeks  
  - (28 days = 1 cycle)
- Oral formulation now available
- Phase II trial  
  - Measurable disease
  - Endometrial cancers and carcinosarcomas of the uterus
  - 0–2 prior cytotoxic regimens
  - 45 patients – 4 PR (9%)
    - 2 endometrioid
    - 1 PS
    - 1 clear cell

N. Colombo et al. ASCO 2007 (Abstract #5516)

---

**Ridaforolimus**  
(Deforolimus, AP23573, MK-8669)

- Ongoing studies
  1) Phase II study of oral ridaforolimus
     - Chemo-naïve (adjuvant therapy allowed)
  2) Randomized phase II study of oral ridaforolimus vs. progestins or chemotherapy*  
    (NCT00739830)
     - 1-2 prior lines of chemotherapy
     - Primary end point: PFS
     - 150 patients planned

*Chemotherapy - carboplatin, paclitaxel, doxorubicin, pegylated liposomal doxorubicin or topotecan administered as a single agent or as a doublet, and will be administered at doses and schedules chosen by the investigator
Rapalogues
- Rapalogues are active in endometrial cancer
- Responses seen in PTEN positive and negative patients (by IHC)
- Responses seen in both endometrioid (type I) and serous (type II) cancers
- Question: Is rapa sensitivity related to PI3K pathway alteration?
  - Initial correlative studies are inadequate to answer the question
  - Needs a comprehensive PI3K pathway analysis

GOG 86-P
- Randomized phase IIA (285 patients)
  - Paclitaxel/carboplatin/bevacizumab
  - Paclitaxel/carboplatin/tempo-rolimus
  - Ixabepilone/carboplatin/bevacizumab
- No prior chemotherapy
- Advanced/recurrent disease
  - PI, Carol Aghajanian, MD & Doug Levine, MD
  - ARRA/SU2C funded

GOG 86-P (cont.)
- Prospective patient samples (330)
  - Central pathology review
  - Clinical data (primary end point: PFS)
- FFPE archived tissue on all patients
  - Mutational profiling: Sequenom
  - Targeted sequencing of candidate genes
  - Copy number: Agilent IM Chip
  - IHC for PTEN, class III β-tubulin
  - MSI analysis
**Endometrial Cancer – 229 Series**

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>N</th>
<th>RR (%)</th>
<th>PFS at 6 Months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>229-C</td>
<td>Gefitinib</td>
<td>26</td>
<td>3.8</td>
<td>15.4</td>
</tr>
<tr>
<td>229-D</td>
<td>Lapatinib</td>
<td>30</td>
<td>3.3</td>
<td>10.0</td>
</tr>
<tr>
<td>229-E</td>
<td>Bevacizumab</td>
<td>52</td>
<td>13.5</td>
<td>40.4</td>
</tr>
<tr>
<td>229-F</td>
<td>VEGF-TRAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>229-G</td>
<td>Bevacizumab-Temsirolimus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>229-H</td>
<td>AZD6244 (MEKi)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>229-I</td>
<td>Brivanib (FGFR2i)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>229-J</td>
<td>Cediranib</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- RR: 10%, 30%
- PFS: 15%, 35%

Both stages of accrual completed

**Endometrial Cancer – Non-GOG Studies**

- Phase II trial of XL147 (PI3K) – Exelixis
- Phase II trial of Sunitinib – NCI
- Phase II trial E7080 (VEGFR 3/2) - Eisai

**Summary**

- Endometrial cancer is the new disease of chemotherapy
  - Adjuvant therapy
  - Therapy for advanced/recurrent disease
- Options are limited after primary chemotherapy (Paclitaxel/carboplatin or TAP)
- Anti vascular agents and agents affecting the PI3K/AKT/mTor (PAM) pathway are of promise
Dr. Mutter is a gynecologic pathologist and molecular biologist who after graduating from Harvard Medical School in 1982 completed his pathology residency at Columbia Presbyterian Medical Center, New York, New York. This was followed by a postdoctoral fellowship in the Department of Genetics at Columbia University, also performed at Columbia Presbyterian Medical Center. He has been a Pathologist in the Women’s and Perinatal Division of the Department of Pathology at Brigham and Women’s Hospital since 1988, and is currently an Associate Professor of Pathology at Harvard Medical School, Boston, MA. He has an active basic and translational research program in the area of endometrial carcinogenesis and gynecologic cancer biology, and is a practicing subspecialty gynecologic pathologist. Dr. Mutter is known within the pathology community for translational integration of molecular tools and data into improved patient diagnosis and management strategies.
Optimizing Translational Research opportunities in Corpus Cancers

George L. Mutter, MD
Harvard Medical School and
Brigham and Women’s Hospital
Boston, MA

Disclosures

I have no financial disclosures relevant to this topic

GOG Tx Research

**Strengths**
- Clinical Outcomes
- Volume
- Funding carveouts
- Multidisciplinary and Peer Input
- Infrastructure
- Impact

**Weaknesses**
- Admin Lag time
- Culture: Group vs investigator controlled model
- Funding coordination
How to Maximize GOG Tx Research

• Scientific Priorities
  Endometrial Cancer
  Leiomyosarcoma
• Infrastructure and Technical
• Oversight + funding (PI, GOG, NIH)

Broad Translational Targets

• Minimal Residual Disease Endpoints
• Molecular Classification (GOG210)
  – For diagnosis, early detection
  – For triaging into Rx
• Personalized Medicine
  – How to fit into study design
  – Dynamic changes of Rx based upon measured response
• Pathogenesis
  – Genetic and non-genetic
  – Therapeutic Targets
  – Prevention

Endometrial Adenocarcinoma

Scientific Opportunities
Differences in Type I/II Endometrial Carcinomas

<table>
<thead>
<tr>
<th>Feature</th>
<th>Endometrioid</th>
<th>Non-Endometrioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 mutation</td>
<td>5-10%</td>
<td>80-90%</td>
</tr>
<tr>
<td>PTEN inactivation</td>
<td>55%</td>
<td>11%</td>
</tr>
<tr>
<td>Histotype</td>
<td>endometrioid, mucinous, secretory, squamous</td>
<td>papillary serous, clear cell, carcinosarcoma</td>
</tr>
<tr>
<td>Grades</td>
<td>I-III</td>
<td>not applicable</td>
</tr>
<tr>
<td>Behavior</td>
<td>Indolent</td>
<td>Aggressive</td>
</tr>
<tr>
<td>Risk factors</td>
<td>hormonal</td>
<td>not significant</td>
</tr>
</tbody>
</table>

PTEN loss: Type I Pathway
PTEN mutation: Type II Pathway

EM Cancer Types Idealized

Type I
Endometrioid

Type II
Non-Endometrioid
EM Cancer Types: The Reality

Questions:
- Biology of Overlap
- Group Assignment of Subtypes (Clear Cell, Carcinosarcoma)
- Mechanism of gene inactivation
- Clinical integration of markers

Effective Treatment for Serous Cancers

- Badly needed:
  - 10% of incident disease, >80% of deaths
- Molecular Target: p53 pathway
  - Big target, no bullets!
- Prevention strategies not defined
  - Equivocal precursor (serous EIC)

Serous Endometrial Intraepithelial Carcinoma
Serous EIC
Usually has frank Carcinoma Elsewhere

Endometrioid Carcinoma

• Pathobiology of carcinogenesis defined
  – Epi risk factors (estrogen, progesterone)
  – Precursor lesion (EIN)
  – Genetic changes beginning in normal tissues
  – Prevention Target
• Still cannot predict myoinvasion from examination of surface tumor

Sampling Limitations

• Pipelle/EMC CA Dx sensitivity 97-99%
• Problem: Myoinvasive component
  – Inaccessible from lumen
  – May differ from surface
Lineage Relationships in areas of Endometrial Adenocarcinoma

Markers and Preclinical Disease

Precancer (EIN)

Normal

PTEN monoclonal 6h2.1
PTEN, a Tumor Suppressor
Inactivated During Endometrial Carcinogenesis

43% Proliferative
“Normal”
EIN
Premalignant
Adenocarcinoma
Malignant

Case 05-176: Conservation of PTEN Clone with additional mutation

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Secretary</th>
<th>Secretary</th>
<th>Polyp</th>
<th>EII in Polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time(Yrs)</td>
<td>0</td>
<td>0</td>
<td>8.4</td>
<td>8.4</td>
</tr>
<tr>
<td>PTEN/n</td>
<td>normal, present</td>
<td>null, absent</td>
<td>normal, present</td>
<td>null, absent</td>
</tr>
<tr>
<td>Mutation</td>
<td>wild type</td>
<td>956 del ACTT</td>
<td>wild type</td>
<td>956 del ACTT; 925 G=A; IVS 3+188T&gt;A</td>
</tr>
</tbody>
</table>
Inert IUD decline in Latent Precancers Parallels CA rate

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer HR</td>
<td>1.00</td>
<td>0.5</td>
</tr>
<tr>
<td>Latent Precancer</td>
<td>33%</td>
<td>15%</td>
</tr>
</tbody>
</table>

p=0.007

Mutter, Lin, & Viswanathan, 2006

Inert IUD decline in Latent Precancers Parallels CA rate

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p=0.007

Mutter, Lin, & Viswanathan, 2006

Hit 1 Initiation
Hit 2+ Histologic Emergence
Hit 3+ Malignant Transformation

Polyclonal (Normal)
Latent Precancer(s) (Normal)
Monoclonal Precancer (EIN)
Monoclonal Cancer (Adenocarcinoma)

Preclinical / Clinical
New Markers for Endometrial Neoplasia

Uterine Leiomyosarcoma

Scientific Opportunities

Uterine Leiomyosarcoma

- Rx imported from other sites
  - Not as effective as needed
- No good specific molecular targets
  - complex genomic changes
- Uncertain Pathogenesis (? Precursor)
- Innaccurate Diagnosis of Threshold lesions
  - STUMP, "uncertain malignant potential"
Leiomyosarcoma Threshold

Atypical Leiomyoma ?? Leiomysarcoma

- Atypia
- +/− mitoses
- Pushing Border
- Mitoses
- + Atypia
- Coagulative Necrosis
- Invasion

Atypical Leiomyoma → Smooth Muscle Tumor of Uncertain Malignant Potential (STUMP) → Leiomysarcoma

STUMP Outcomes, Persistence

- MD Anderson 7% (Malpica, 2009)
- Brigham & Women’s 25% (Quade, 2010)

Technical Issues

- Biorepository Format
  - Frozen, paraffin, serum
- Sample Stabilization and (Age weeks to years)
- Sampling Errors
George L. Mutter, MD

Paraffin Section
Ag Loss with Accelerated Storage*

Stabilization of Paraffin Tissue Sections

• Storage in Nitrogen
  – Works well
• Encapsulation with O2 and humidity control
  – Works well
• Dip in soluble sealant (?paraffin)
  – Anecdotal
• Cold Storage
  – Anecdotal

103
Slide Encapsulation

- Impermeable envelope (foil-plastic laminate)
- Vacuum
- Heat Seal
- Oxygen Scavenger packets
- Humidity control
Ag Preservation by Encapsulation*  

Sealed

Exposed

Time 0

Week 2

Week 4

Week 8

Week 12

37°C, 70-80% humidity, ER (ERIDS), EMCA

Mutter, 2004 (unpublished)

Efficient Examination of Many Specimens

• Tissue Arrays

• Available through GOG Repository

• Must be written into protocol

Array of Tissue Cores

H&E

Keratin
**Oversight and Funding**

- Specific to each Tx project
- Best if Tx projects are in GOG protocol at start (addenda OK)
- Requires GOG approval of Tx proposal, LOS available
- Funding (NIH PA-08-134, PA-08-133, or other)
- GOG cores and stat support available
Mark H. Einstein, MD, MS, Associate Professor of Obstetrics & Gynecology and Women’s Health and Director of Clinical Research for Women’s Health and Gynecologic Oncology at the Albert Einstein College of Medicine and Montefiore Medical Center. Dr. Einstein received his Bachelors in Science and Medical Degree at the University of Miami in their combined BS/MD program. After completing his residency in Obstetrics and Gynecology in New Jersey he then had subspecialty training in Gynecologic Oncology at the Albert Einstein College of Medicine/Montefiore Medical Center. He joined the Einstein faculty after fellowship. Dr. Einstein’s primary research interests focus on the pathogenesis, therapy, and prevention of cervical cancer. His translational work in cervical cancer is multi-faceted; investigating the host and virally-induced epigenetic, genetic and immune profiles along the malignant transformation path to provide insight into the process of cervical carcinogenesis. Dr. Einstein has developed and has been leading numerous multi-institutional clinical trials in targeting HPV and cervical cancer as well as cervical cancer prevention. He is active in clinical trial cooperative groups as Co-Chair of the Gynecologic Oncology Group Vaccine Committee and sits on the GOG Cervix Committee. He is on the HPV working group of the NCI Aids Malignancy Consortium. He is also an active member and a program leader of the Gynecology Division of the New York Cancer Consortium- a Montefiore-based P01 Phase II clinical trial consortium and is the PI of many of its gynecologic cancer therapeutics trials accruing patients throughout New York hospitals. He is active in policy-making regarding cervical cancer prevention participating in the development of the American Cancer Society recommendations for HPV vaccines and is on the working group for the 2011 ACS cervical cancer screening update. He also was part of the working group for the Society of Gynecologic Oncology’s (SGO) HPV vaccine recommendations as well. He also is Chair of the Gynecologic Oncology Foundation’s (GCF) National Cervical Cancer Public Education Campaign and sits on their Board of Directors. He is also a Board member of the American Society for Colposcopy and Cervical Pathology. Dr. Einstein is also a consultant to the World Health Organization (WHO), developing their modules on the immunologic basis of HPV vaccines. He has received funding for cervical cancer-related translational research by the NIH, GCF, ACOG and the Berlex Foundation. He has been funded by and named an American Cancer Society Research Scholar. Dr. Einstein is a Fellow of the American Board of Obstetrics and Gynecology and a Fellow of the American College of Surgeons.
Optimizing translational research opportunities in cervical cancers

Mark H. Einstein, MD, MS, FACOG, FACS
Associate Professor of Obstetrics & Gynecology and Women’s Health,
Director of Clinical Research for Women’s Health and Gynecologic Oncology
Department of Obstetrics & Gynecology and Women’s Health
Albert Einstein College of Medicine
Albert Einstein Cancer Center
Montefiore Medical Center

Disclosures

- Advised or participated in educational speaking activities, but do not receive an honorarium, from any companies. In specific cases, my hospital, Montefiore Medical Center has received payment for my time spent for these activities from Merck, GSK, Roche, Hologic, Advaxis, PDS Biotechnologies, Aura Biosciences
- Montefiore has received grant funding for research-related costs of clinical trials that I have been the Montefiore PI from Merck, GSK, Roche, and Hologic

Objectives

- Develop a basic knowledge of some of the immune, genetic, and cellular mechanisms of HPV infection and its progression to cervical cancer
- Understand some of the translational testing currently being explored as biomarkers for efficacy and targets for therapies
- Discuss some of the current novel targeted therapies in clinical development for cervical cancer
Pathway to Cervical Cancer

Exposure → HPV infection → Persistent infection → CIN I/II → High Grade CIN → CANCER

Adapted from Einstein and Burk, Papillomavirus Report, 2001

Natural History of HPV Infection

Exposure to HPV → Active infection with viral replication → Persistent infection → Integration and expression for HPV genome → E6 and E7 inactivate p53 and pRB, respectively → Cancer

Organization of HPV Genome

- Upstream regulatory region (URR)
  - Regulates viral proteins
- Early region
  - 6 open reading frames (ORF's)
  - E6 and E7 inactivate p53 and pRB, respectively
- Late region
  - L1 encodes for major capsid proteins
  - L2 encodes for minor capsid proteins

Courtesy of RD Burk

Screening and Vaccines in Europe and US

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Western Europe</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nationalized Screening Programs</td>
<td>Yes</td>
<td>No (financially incentivized): still about 70% follow guidelines</td>
</tr>
<tr>
<td>National payment by government</td>
<td>Many only for one age group, such as age 12</td>
<td>Vaccines for Children program pays up to age 19 for low income adolescents (males also)</td>
</tr>
<tr>
<td>School-based vaccination programs</td>
<td>Most</td>
<td>As of Jan, 2010: 41 States have legislation Virginia and DC with school mandates with wide opt-out</td>
</tr>
<tr>
<td>Coverage</td>
<td>UK/Australia &gt;90% Belgium, Netherlands, Scandinavia &gt;85% France, Italy, less</td>
<td>9/2009 from CDC-40% of 13-18 year olds have had at least 1 dose (&gt;10% completed series) &gt;19 yo: 10% *ethnic minority outreach appears higher than expected</td>
</tr>
</tbody>
</table>

Decreasing Trends of Cervical Cancer Incidence in the U.S.

With the advent of the Pap smear, the incidence of cervical cancer has dramatically declined.

The curve has been stable for the past decade because we are not reaching the unscreened population.

Reprinted by permission of the American Cancer Society, Inc.
Regions in US with High Cervical Cancer Incidence
Cancer Mortality Rates by County (Age-adjusted 1970 U.S. Population)
Cervix Uteri: All Races, Females, 1970-1989

- Hispanics living along US-Mexico border
- African American women in the Mississippi Delta
- White, Non-Hispanic women in Appalachia, rural New York State and Northern New England
- American Indian women
- Vietnamese-American women
- Areas with limited resources and limited healthcare access

NIH publication 05-5282, 2005
**Biology of HPV Infections**

<table>
<thead>
<tr>
<th>Normal Cervix</th>
<th>HPV Infection (CIN* 2)</th>
<th>Cervical Cancer (Invasive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious Viral Particles</td>
<td>Perinuclear Clearing (Koilocytosis)</td>
<td></td>
</tr>
</tbody>
</table>

*CIN = cervical intraepithelial neoplasia; ICC = invasive cervical cancer.

Immunity to HPV infection - HPV Evades Host Immune Responses

- Replicates without inducing cell death and resulting proinflammatory mechanisms
  - Low levels of viral protein
  - HPV replication occurs in an immunologically isolated site
  - HPV 16 negatively impacts appropriate cell mediated immune responses
  - HPV 16 downregulates TLR3 expression
  - Polymorphisms in cytokine genes and the transporter associated with antigen presenting (TAP) potentially can increase or protect the host

1 Stanley M, multiple papers
2 al-Saleh W, J Pathol. 1998
3 Hasan UA, J Immunol. 2007
4 Einstein MH, Clin Cancer Res. 2009

Host Immune Response to HPV infection

Innate immune responses limit viral load and play a role in HPV clearance. Little activation of adaptive immunity


With persistent HPV infection, the host immune response is unable to control infection. Qualitative nature of innate and adaptive immune response differs than with what happens with clearance

Vaccine-Induced Protective Responses to HPV infection

In vaccinated women, the immune response is dominated and sustained by a rapid elevation in serum antibody. The high serum levels correlate with high levels of antibody at the cervix.


Difficulties in Assessing the Serologic Immune Responses

- What is the test measuring?
  - total IgG, functional IgG, IgA
- Performance characteristics of the assay
  - Sensitivity, Specificity, ROC curves
  - Avidity of antibody and degradation
- Need for standardized, validated assays
  - normalized curves need to be explored

Background: Study NCT00423046

- The immunogenicity and safety of these vaccines in healthy women aged 18–45 years has been demonstrated in a Phase IIIb trial (Study HPV-010; NCT00423046)
  - At Month 7, the bivalent vaccine demonstrated significantly higher immune responses when compared with the quadrivalent vaccine1
- Observer-blinded study conducted across 40 US sites
- Women (n=1,106) were stratified by age (18–26, 27–35 and 36–45 years) and randomized (1:1) to receive the bivalent or quadrivalent vaccine

Objectives: Study NCT00423046

- Primary objective was to compare serum neutralizing antibody responses to HPV-16 and -18 at each 6 month time point after vaccination with either vaccine in women aged 18–26 years in the according-to-protocol (ATP) cohort for immunogenicity
  - ATP cohort is women on study who were HPV DNA-negative and HPV seronegative at baseline
- Secondary objectives were to assess:
  - neutralizing responses stratified by age groups and HPV types
  - antibody responses by ELISA
  - cell mediated (T-cell and B-cell) immune responses
  - antibody responses in CVS
  - safety and compliance of both vaccines

Serum antibody response: age 18–26 (ATP cohort)

Pathway to Cervical Cancer

Adapted from Einstein and Buk, Papillomavirus Report, 2001
Mark H. Einstein, MD, MS, FACOG, FACS

Pathway to Cervical Cancer

Exposure → HPV Infection → Persistent Infection → CIN I/II → High Grade CIN → CANCER

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Pathway to Cervical Cancer

Exposure → HPV Infection → Persistent Infection → CIN I/II → High Grade CIN → CANCER

Therapies Effective

Adopted from Einstein and Burk, Papillomavirus Report, 2001
Mark H. Einstein, MD, MS, FACOG, FACS

Pathway to Cervical Cancer

Exposure

Latency

Persistent infection

HPV infection

CIN I / II

CIN II

CIN I / II

CIN III ~ Carcinoma

CANCER

Adopted from Einstein and Burk, Papillomavirus Report, 2001

HumanMethylation27 Content Summary

Inactivation of tumor suppressor genes such as p16

Inactivation of DNA repair genes

CpG hypermethylation

CpG loci within classically defined CpG island (20,007 loci)

CpG loci outside of classically defined CpG island (7,572 loci)

<table>
<thead>
<tr>
<th>MARKER</th>
<th>DESCRIPTION</th>
<th>AVG COVERAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>H471</td>
<td>Total Bf/Bc, Genes</td>
<td>1.9 sites</td>
</tr>
<tr>
<td>42,833</td>
<td>Well-annotated genes described in the NCBI</td>
<td>1.9 sites</td>
</tr>
<tr>
<td>913</td>
<td>Tumor suppressor genes</td>
<td>5.6 sites</td>
</tr>
<tr>
<td>619</td>
<td>Cancer-related targets</td>
<td>1.9 sites</td>
</tr>
<tr>
<td>112</td>
<td>mRNA promoters</td>
<td>2.2 sites</td>
</tr>
</tbody>
</table>

Illumina, Inc. San Diego, CA 6/1/2010

Differential DNA methylation in OPSCC

○ CpG loci within classically defined CpG island (20,007 loci)

○ CpG loci outside of classically defined CpG island (7,572 loci)
Differential DNA methylation in OPSCC

<table>
<thead>
<tr>
<th>Patient Set 1 (N=24)</th>
<th>Patient Set 2 (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male 19 (79%)</td>
<td>16 (76%)</td>
</tr>
<tr>
<td>Female 5 (21%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>Median Age (Range)</td>
<td></td>
</tr>
<tr>
<td>62 (40-79)</td>
<td>61 (46-84)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White 16 (67%)</td>
<td>11 (52%)</td>
</tr>
<tr>
<td>Black or African</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>American 10 (48%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Unknown 3 (12%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino 6 (25%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>Non-Hispanic/Latino 16 (67%)</td>
<td>16 (76%)</td>
</tr>
<tr>
<td>Unknown 2 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tumor Stage</td>
<td></td>
</tr>
<tr>
<td>I 1 (4%)</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>II 2 (8%)</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>III 3 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IV 18 (75%)</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Node Status</td>
<td></td>
</tr>
<tr>
<td>97% CGI</td>
<td>96% non-CGI</td>
</tr>
<tr>
<td>Hypermethylated (N=630)</td>
<td>23% CGI</td>
</tr>
<tr>
<td>Hypomethylated (N=328)</td>
<td>77% non-CGI</td>
</tr>
</tbody>
</table>

Can methylation be pharmacologically re-expressed in a model system for ex vivo testing?

- manipulate expression and study phenotype
- study mechanism in a model system
- Inhibitors of DNA methylation
- HDAC inhibitors

The Cancer Genome Atlas (TGCA) Project

- Comprehensive and coordinated effort to accelerate the molecular basis of cancer through the application of genome analysis technologies
- In the second phase, adding 20 additional cancers including cervical cancer (RFA-NCI-1008-AS)
- Comprehensively abalyze DNA copy number changes
  - Large and small rearrangements
  - Transcription profiles
  - Epigenetic modifications
  - Sequence variations
- Case-matched controls
- For cervix, will need to also analyze by effects of oncogenic HPV infection
Relationship between acquired immune responses to HPV and the development of cervical cancer

- Cervical Cells with Oncogenic HPV Infection
- B- and T-cell Activation
- No Immune Response
- Inadequate Immune Response
- Adequate Immune Response
- Persistent Infection
- Latent or Subclinical Infection
- High-Grade CIN
- HPV Clearance
- Less likely to be influenced by natural immunity: continued clonal proliferation, HPV integration, random mutations leading to the malignant phenotype

Difficulties in Assessing the Human Cell-Mediated Immune Responses

- Poor reproducibility in ex-vivo assays
  - Often do not correlate with clinical responses in humans
- Oncogenic HPV can skew T-cell responses to favor survival
- Differences in systemic vs. local T-cell responses
- Biologic plausibility established in immunosuppressed patients with HPV

Einstein, MH Cancer Immunology, Immunotherapy. 2008.
Why immunotherapy?

- Virally-mediated disease process
- Current treatment strategies target ablation of the lesion, but are not specific for eradicating HPV from the genital tract.
- Most early CIN lesions will regress to normal without treatment. This regression is modulated by cellular and humoral immune responses.

Rationale for HPV Therapeutic Vaccines

REGRESSION
HPV-, CIN-

HYPOTHESIS
IMMUNOTHERAPY

PERSISTENCE
HPV+, CIN+

PROGRESSION TO CANCER

LEEP and Risk of PTL/pPROM/PTB

Einstein and Kadish, Curr Opin Oncol 2004
Therapeutic Vaccine Platforms

- Protein or Peptide Vaccines
  - Fusion proteins such as heat shock proteins
  - Simple peptides
- Local immunomodulators
- Recombinant Vaccine Vectors
  - Vaccinia
  - Listeria
  - Semlicki forest virus-DNA based vector
- Bacterial Recombinants
  - Listeria, Lactobacillus

Kadish and Einstein, Curr Opin Oncol 2005

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Kadish and Einstein, Curr Opin Oncol 2005

SGN-00101 (HspE7)* Vaccine

<table>
<thead>
<tr>
<th>Heat Shock Protein (Hsp65)</th>
<th>HPV 16 E7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Stimulation</td>
<td>HPV Antigen</td>
</tr>
</tbody>
</table>

- Effective induction of tumor regression in murine HPV tumor system
- Activity in HPV 16 associated
  - Anal intraepithelial neoplasia
  - Recurrent Respiratory Papillomatosis (RRP)
  - Carcinoma in Situ of the Cervix

*Nventa Biopharmaceuticals (San Diego, CA- formerly Stressgen Biotechnologies); 1 Palefsky et al., 2002 International HPV Conference 2 Derkay et al., 2005 Ann Otol Rhinol Laryngol 3 Einstein et al., 2007 Gynecol Oncol
Schema Cohort 2

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<th>Visit 1</th>
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<th>Month 0</th>
<th>M1</th>
<th>V2</th>
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<th>V7</th>
<th>M7</th>
<th>V8</th>
<th>M8</th>
<th>LEEP</th>
</tr>
</thead>
</table>

- Vaccination with SGN-00101
- Blood draw for Immunologic Testing
- HPV Typing

---

Response Criteria

- Complete Pathologic Response (pCR)
  - No CIN
  - CIN I
- Partial Response (PR)
  - >50% colposcopic reduction in size of lesion
- Stable Disease (SD)
  - <50% colposcopic reduction in size of lesion
- Progressive Disease
  - Any colposcopic increase in lesion size
  - Any invasive cancer

---

Results

- A clinical response was observed in 45/58 patients (78%, 95% CI = 67-89%)
- 13 (22.5%) had a complete pathologic response-absence of CIN (n=8) or CIN I (n=5) on final pathology
  - 32 (55%) had a partial response
  - 11 (19%) had stable disease
  - 2 (3.5%) had progressive disease (microinvasive SCC)
- No significant demographic, behavioral, or clinical risk factors associated with regression
- HspE7 was well tolerated in this patient population

---

Einstein et al., 2007 Gynecol Oncol
Inflammation in LEEP specimens (100X Mag)

Complete Response
Partial Response
Stable Disease
Progressive Disease

Association Between Inflammation and Response

Grade of Inflammation

Response

p=0.04 using Mann-Whitney

E7 Antibody Serologic Responses

Van Doorslaer et al. Gynecol Oncol 2010
Results

- Women who had a previous LEEP or ablation for CIN \((n=11)\) were 2.7 times more likely to have a pCR compared to women without prior treatment (pCR rates 5/11=46% for previous LEEP vs. 8/47 = 17% for no LEEP; 95% CI for rate ratio: 0.95-6.19, \(p=0.10\)).
- No difference in responses in women infected with HPV 16 compared to women without HPV 16 (22/25 or 88% vs. 23/33 or 70%, \(p=0.12\)).

Risk of Cervical Precancer and Cancer in Women with HPV 16 or 18

Dilemma of LGSIL/CIN I/ and Persistent HPV Infection

- About 2-4% of the population
- Have no correlative markers of progression
- Typing may have utility
- Current management is close observation
- CIN I-specific issues:
  - Misclassification
  - What to do about patients with poor follow-up
  - Potential for overtreatment of CIN I
- Need for a well-tolerated therapeutic
E2 Peptides Vaccine for CIN

Immunogenicity of E2 Peptides

Fig. 2A. HLA-A2 transgenic mice were immunized with E2 peptides as indicated. Two weeks after immunization, colcemid treated and DEP cells were collected and DEP cells were enriched using Dynal beads. Cells were restimulated with E2 peptides in culture. The number of IFN-gamma positive cells were determined by ELISPOT assay. NP = no peptide, P = peptide used in immunization. IP = irrelevant peptide.

Fig. 2B. Mice were immunized with pooled E2 peptides and stimulated with individual peptides, as indicated in the legend. The number of IFN-gamma positive cells were determined by ELISPOT assay.

E2 Peptides Vaccine for CIN

Efficacy of E2 vaccine

Fig. 5. HLA-A2 transgenic mice were immunized with HPV 16 E2 peptides. Two weeks after immunization, B16 AAD E2 was injected at 1.5 X 10^6 s.c. Fig. 6A shows the size of the tumor on day 22. Fig. 6B shows the progression of tumor growth for 26 days. Naïve mice and mice given GM+aCD40 (adjuvant alone) were used as controls. Experimental mice received GM+aCD40 and E2 peptides.

E2 Peptides Vaccine for CIN

ASCUS/HPV+ or LSIL

Screening/HPV/HLA testing

E2 peptides + GM-CSF + Montanide ISA

OR

Normal Saline + GM-CSF + Montanide ISA

•Dosing weeks 2,6,10,14,18, and 22

•HPV typing and Pap at week 38, month 12

•Immunologic Assessment at weeks 22 and 38
Therapeutic Vaccine Platforms

- Protein or Peptide Vaccines
  - Fusion proteins such as heat shock proteins
  - Simple peptides
- Local immunomodulators
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  - Vaccinia
  - Listeria
  - Semlicki forest virus-DNA based vector
- Bacterial Recombinants
  - Listeria, Lactobacillus

Listeria Vaccine in Cervical Cancer

- Genes for attenuation and LLO-fusion protein are encoded in a plasmid
- Plasmid is transferred to Listeria
- Tumor Antigen fused to LLO is released into APC cytosol
- APC matures & is stimulated to activate T cells, secrete cytokines, etc.

Therapeutic Vaccine Platforms

- Adoptive Immunotherapy
  - HPV E7-specific T cell clones using Dendritic Cells loaded with peptide antigens
  - Often use adjuvants to improve responses
- Gene Transfer
  - Carry transgenic E7-specific T cell receptor
  - DNA vaccines
    - RNA replicon vectors or suicidal DNA vectors
    - Can have an MHC class I and II response
- Chimera
  - Therapeutic and prophylactic potential

Kadish and Einstein, Curr Opin Oncol 2005
Therapeutic Vaccine Platforms

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Kadish and Einstein, Curr Opin Oncol 2005

Johns Hopkins DNA Vaccine - Cervical SPORE

SPR0702/GOG Cervical Cancer (PI C. Trimble)
SPR0703/GOG CIN 3/3 (PI C. Trimble)

PowderMed Core Capability
Particle Mediated Epidermal Delivery (PMED)

- The epidermis cannot be accessed with needle and syringe
- PowderMed device is designed to deliver to the epidermis

SPR0702/GOG Cervical Cancer (PI C. Trimble)
SPR0703/GOG CIN 3/3 (PI C. Trimble)
Future Vaccines: Immunotherapy for HPV

- Why are we operating on a virally-mediated disease?
- Rapidly advancing vaccine technologies giving us access to many vaccine platforms
- Immune correlates of response need further development
- Optimal dosing schedules and use of adjuvants still in its infancy
- Potentially a major decrease health burden if it is effective

Optimizing Translational Research In Cervical Cancer

- Essential to think of the translational aspects of cervical cancer and CIN in concept designs
  - Paraffin-embedded tissue
  - Sera/PBMCs
  - Cervicovaginal lavage/brushes for HPV testing
- Consider new molecular technologies
  - FISH, gene markers, epigenetic markers

M. Einstein Acknowledgements

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  - Gloria Ho, PhD
  - Laura Reimers, MPH
  - Montefiore Medical Center
    - Gary L. Goldberg, MD
    - Gloria S. Huang, MD
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  - Mimi Kim, MD
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  - Gynecologic Cancer Foundation
  - NIH/NCRR (K12 RR017672)
  - NIH/NCI (N01-CM17103-74)
Session III: New Approaches in the management of corpus sarcomas

Moderator

David Scott Miller, MD, FACOG, FACS
Director & Dallas Foundation Chair in Gynecologic Oncology
Professor of Obstetrics & Gynecology
University of Texas Southwestern Medical Center
Division of Gynecologic Oncology
Dallas, TX

Dr. Miller is Director of and Dallas Foundation Chair in Gynecologic Oncology and Professor of Obstetrics & Gynecology at the University of Texas Southwestern Medical Center at Dallas. He serves as Medical Director of Gynecologic Oncology and Chair of the Cancer Committee for the Parkland Health and Hospital System. Among his numerous professional affiliations, Dr. Miller is a fellow of the American College of Obstetricians & Gynecologists and the American College of Surgeons, a member of the American Society of Clinical Oncology and the Society of Gynecologic Oncologists, and was President of the Western Association of Gynecologic Oncologists. He is certified by and is an examiner for the American Board of Obstetrics & Gynecology and its Division of Gynecologic Oncology. Long active in the development of clinical trials for the treatment of gynecologic cancers, he is Study Chair for multiple national trials of the Gynecologic Oncology Group, served on the Board of Directors, and is Chair of its Uterine Corpus Committee. The National Cancer Institute’s Cancer Therapy Evaluation Program appointed him to the Gynecologic Cancer Steering Committee. He is also Chair of the Endometrial Committee for the Gynecologic Cancer InterGroup. He has sought to add to the body of knowledge in gynecologic oncology having authored over 100 articles and book chapters and given over 400 invited lectures.
What are the optimal surgical approaches to corpus sarcomas?

Nick M. Spirtos, MD  
Professor and Director  
Division of Gynecologic Oncology  
University of Nevada School of Medicine  
and the Women’s Cancer Center of Nevada  
Las Vegas, NV

Nick M. Spirtos, M.D. was born in South Dakota and is one of 18 MDs in his family.

Dr. Spirtos attended the University of Chicago as an undergraduate and Northwestern University School of Medicine. He was a resident at USC/LA County and a fellow at Stanford University Medical Center. Following fellowship he remained on the full-time faculty until he founded the Women’s Cancer Center. Currently he is Professor and Vice-Chairman in the Department of Obstetrics and Gynecology at the University Of Nevada School Of Medicine and remains the Medical Director of the Women’s Cancer Center of Nevada. Dr. Spirtos has been a Principal Investigator of the GOG for over 15 years and was instrumental in the integration of minimally-invasive surgery into the treatment paradigm of gynecologic malignancies.
What are the optimal surgical approaches to corpus sarcomas

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Disclosures

I have no financial disclosure relevant to this topic

Definition of Sarcomas

- Carcinosarcoma
- Leiomyosarcoma
- Poorly Differentiated Endometrial Stromal Sarcoma
- Adenosarcoma
Carcinosarcoma should be staged as carcinoma of the endometrium
- Leiomyosarcoma
- Endometrial Sarcoma (ESS) and adenosarcoma

### Staging Carcinosarcoma: 2008

- **Stage I** - Less than or no myoinvasion
- **Stage II** - Equal or greater than ½ myoinvasion
- **Stage II** - Invades the cervical stromal

### Staging Carcinosarcoma: Stage III

- **Stage III** - Local and/or regional spread of tumor
- **Stage IIIA** - Tumor invades the serosa of the corpus and/or adnexae
- **Stage IIIB** - Vaginal or parametrial involvement
- **Stage IIIC1** - (+) pelvic LN
- **Stage IIIC2** - (+) Aortic LN +/- pelvic LN
Carcinosarcoma Staging: Stage IV

- Stage IV A – Bowel or bladder mucosa
- Stage IV B – Distant Metastases including intra-abdominal metastases and/or inguinal lymph nodes

Leiomyosarcoma – Stage I & II

- Stage IA - <5 cm
- Stage IB - >5 cm
- Stage II A - Adnexal Involvement
- Stage II B - Tumor extends to extrauterine pelvic tissue

Leiomyosarcoma Stage III and IV

- III A - Tumor invading abdominal tissues: one site
- III B - Greater than one site
- III C - Metastases to pelvic and/or aortic lymph nodes
- IVA - Invades Bladder/Rectum
- IVB - Distant Metastases
Endometrial Stromal Sarcoma and Adenosarcoma: Stages I and II

- Tumor limited to uterus
- IA - Limited to endometrium/endocervix
- IB - Less than or equal ½ myoinvasion
- IC - More than ½ myoinvasion

ESS and Adenosarcoma: Stage II - IV

- Stage IIA - Adnexal involvement
- Stage IIB - Extraperitoneal pelvic tissue
- Stage III - Invades abdominal tissue
- Stage IIIA, IIIB - One or more sites
- Stage IIIC - Pelvic and/or Aortic LN
- Stage IV A & B - Bladder/Rectum/Distant disease

What are the optimal surgical approaches to corpus sarcomas: Objectives

- Determine the extent of surgical staging necessary during initial procedures
- Determine what uterine sarcomas warrant surgery to complete staging and/or cytoreduction
- Determine in what setting is secondary cytoreduction beneficial
Problems in Determining the Optimal Surgical Approaches to Corpus Sarcomas

- Only 1 Prospective Study on Staging Uterine Sarcomas (GOG)
- Diagnosis of Uterine Sarcoma is often made post-operatively
- The Prognosis for Early-Stage disease is poor enough that all patients need at least adjuvant treatment
- The Prognosis & Natural History of Advanced-Stage Uterine Sarcoma is so dismal as to not warrant surgery beyond removal of the primary site of disease
- The literature is contradictory

Only 1 Prospective Study on Staging Uterine Sarcomas (GOG)

GOG: Clinico-Pathologic Studies

- Majors FJ
- Kaku T
- Silverberg
Prognostic Factors in Early-Stage Uterine Sarcoma: Majors et al (GOG): Cancer 1993

- 453 Uterine Sarcomas
- C/S - 301
- LMS - 59
- ESS/AS - 93

Prognostic Factors in Early-Stage Uterine Sarcoma: Majors et al (GOG): Cancer 1993

- LMS: 8/59 (13.5%) Upstaged
- C/S: 61/301 (20.2%) Upstaged

Prognostic Factors in Early-Stage Uterine Sarcoma: Majors et al (GOG): Cancer 1993

- Prognostic Factors Based on Multivariate Analysis (C/S)
- LN Metastases (not related to sarcoma grade)
- Adnexal Metastases
- Histology (HO vs HE)
- Sarcoma Grade (2-3)
Prognostic Factors in Early-Stage Uterine Sarcoma: Majors et al (GOG): Cancer: 1993

- C/S
  - 42/51 (83%) of Lymph Node (+) patients recurred
  - 31/34 (91%) of patients with (+)adnexae recurred

Prognostic Factors Based on Multivariate Analysis (LMS)

- Prognostic Factors Based on Multivariate Analysis (LMS)
- Mitotic Index

<table>
<thead>
<tr>
<th></th>
<th>C/S</th>
<th>LMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph Nodes - Positive</td>
<td>16.9%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Cytology - Positive</td>
<td>24% (44% in LN+)</td>
<td>5.3%</td>
</tr>
</tbody>
</table>
Endometrial Stromal Sarcoma: Kaku et al (GOG):
46 cases

- High grade or undifferentiated - 26
- Low grade - 20

GOG: Conclusions
- Staging and Lymph Node Dissection reasonable in Carcinosarcoma (MMMT)
- Staging Unnecessary in Leiomyosarcoma and Endometrial Stromal Sarcoma
- Post-Operative Treatment not standardized

Diagnosis of Uterine Sarcoma is often made post-operatively
Inaccurate Pre-operative Diagnosis

- Need to address need to complete staging
- What procedures need to be undertaken?
- How can we use the information from the initial procedure?

C5: Diagnostic Accuracy of D&C

- Ho and Ho: Singapore Med J 2002
  - 15/26 (58%) Diagnosed on D&C
  - 6/10 cases (60%) diagnosed on D&C
- Abnormal pap smear in 47%

Accuracy of Pre-operative biopsy: LMS

- Vardi and Tovell: 1980; 5/24 (21%)
- Berchuck et al.: 1988; 8/14 (57%)
- Goff et al: 1993; 3/21 (13%)
- Gard et al: 1999; 12/49 (24%)
Cytology: Obtained at primary Surgery

- Callister et al: 2004: 199/300 (66%) had cytology with 26% positive (C/S)
- Hussein et al: 2002: 24/59 (41%) had cytology with 29% positive (C/S/LMS/ESS)
- Kanbour et al: 1989: 19/28 (68%) positive with 9/10 with ascites positive (C/S)

Issues: Complete Staging

- BSO in Leiomyosarcoma: Does it need to be undertaken?
- What is necessary in patients in whom the cytology was obtained and is positive?
- Is Lymphadenectomy necessary?
- Is Cytoreductive surgery necessary?

Authors demonstrating no difference in survival with ovarian preservation: does ER matter?

- Berchuck 1988 - 46 patients (8 with ovarian preservation)
- Gadducci 1996 - Relapse in 33% with BSO vs 24% in those with at least one ovary
- Larson 1990 - 50 patients (31 with ovarian preservation)
Need for BSO

- Mayo 2002 - 25/25 case-matched control (stage: age: grade)
- Equivalent disease-specific survival & risk of recurrence

LMS: Australian Experience

- Ovarian Conservation
- 2/35 (6%) had ovarian metastases, both with other sites of disease
- Consistent with GOG data (3.5%) in early stage disease

Conclusion: Re: Need for BSO

- The preponderance of the evidence suggests there is no benefit to performing a BSO except in cases with macroscopic metastases

- 19/28 (68%) patients positive
- 9/10 ascites; 10/18 washings
- Median survival 8 vs 42 months (positive vs negative cytology)
- Stage I and II = 21 patients
- Stage III and IV = 7 patients

Cytology: MMT (C/S): Callister et al: J Rad Oncol: 2004

- 199/300 (66%) had cytology obtained
- Positive in 92/199 (26%) - 10% 5 yr survival
- Negative in 147/199 (78%) - 44% 5 yr survival


- 59 patients
- 7/24 (+) - all DOD
- 17/24 (-) - 54% OS at 5 years
- Only 7 patients had LNDx - No Information
Conclusion: Re: Positive Cytology and or Ascites and its impact on Restaging

- Given the poor survival documented associated with positive cytology there is no indication to re-explore any patient with positive cytology.

Carcinosarcoma and LMS: The Prognosis for Early-Stage disease is poor enough that all patients need at least adjuvant treatment.

Early-Stage C/S and LMS: Problems

- LMS: No effective adjuvant treatment and low incidence of isolated nodal disease.
- C/S: Even with treatment 40-50% of early stage disease die.
C/S: Completely Resected Stage I and II
GOG: Sutton 2005

C/S: Significance of LN Count

- 45 patients – Stage I & II
- Significant Difference in PFI if > 11 LN removed
- Number of positive nodes not mentioned
- Median survival 12 vs. 24 months

The Prognosis & Natural History of Advanced-Stage Uterine Sarcoma is so dismal as to not warrant surgery beyond removal of the primary site of disease and visible metastases.
Carcinosarcoma

Norris et al: CS

- Ob Gyn 1966
- 14/31 patients had extrauterine disease including 3 with positive lymph nodes
- All pts with extrauterine disease expired

Carcinosarcoma: Survival with Extra-Uterine Disease

- DiSaia et al: 1973
- 0/25 Patients alive at 2 years if disease was found outside the pelvis
- 3/35 (8.5%) NED at 2 years with extrauterine disease limited to the pelvis
Carcinosarcoma

- Shaw et al: British Jo Ob Gyn 1983
- 28 patients
- 5 Ln Dx
- 1/2 Positive had extra-uterine disease; both DOD

CS and ESS: University of Michigan

- 59 pts with clinical stage I/II disease underwent staging
- 8/59 (13.6%) with positive nodes
- 4/13 (31%) with positive nodes after the "1970s"
- No "long-term survivors" in this group

LMS: Treatment
Berchuck et al
Ob Gyn: 1988

- 46 patients: 34 stage I/II and 12 stage III/IV
- 8/14 (57%) diagnosed on D & C
- 12/12 stage III/IV recurred and or died within 18 months of surgery
- 10/14 PFI (29%) with a median f/u 7.5 yrs with 7/10 having disease confined to a polyp or myoma
Pre-operative Dx and Treatment: Japanese Experience: Sagae et al. Oncology 2004

- Pre-operative diagnosis in 25-35% of LMS and ESS
- Pre-operative diagnosis in 94% of patients with CS
- Using combination of cytology, U/S, MRI or CT

Chen SS GynOnc 1989

- Leiomyosarcoma: 3/4 positive lymph nodes (A/P = 2: P=1)
- Stromal Sarcoma: 1/2 positive lymph nodes (A/P = 1)
- Carcinosarcoma: 5/14 positive lymph nodes (A/P = 3: P=2)

Survival: Chen - 1989

- Within 2 years all 9 patients with positive nodes were Dead

- 24/38 (63%) patients underwent Pelvic and or PALNDs
- 5/24 (21%) had positive LN and 4/5 also had extra-uterine disease present

C5: Lymph Node Dissection

- Ho and Ho: Singapore Med J. 2002
  - 4/16 (25%) had positive lymph nodes
  - 14/26 (54%) had intraperitoneal disease
  - All Stage III and IV patients were DOD within 2 years

Leiomyosarcoma
Nodal Disease LMS

- Risk Factors
- Deep Myoinvasion
- Age > 65
- Only present when other extrauterine disease is present

LMS: Incidence of Positive LN

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>No. of (+) LN</th>
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<tr>
<td>Aaro et al</td>
<td>AnJObGyn 1966</td>
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<td>Baret et al</td>
<td>Gyn Onc 1985</td>
<td>0/7</td>
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<tr>
<td>Chen</td>
<td>Gyn Onc 1985</td>
<td>3/4</td>
</tr>
<tr>
<td>Goff et al</td>
<td>Gyn Onc 1992</td>
<td>4/15</td>
</tr>
<tr>
<td>Major et al</td>
<td>Cancer 1993</td>
<td>2/57</td>
</tr>
<tr>
<td>Gard et al</td>
<td>AustNZObGyn 1999</td>
<td>2/11</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>11/99 (11%)</td>
</tr>
</tbody>
</table>

Goff et al: 1993

- 12 years (1981-1991) 31 patients
- 21 patients with LMS: 15 LNDx; 87% EMB negative
- 10 patients with ESS: 7 LNDx
Goff et al: 1993

- LMS: 4/15 (27%) with positive LN but all with intra-abdominal disease. 3 of 4 DOD within 48 months. 1 AWD at 27 months.
- ESS: 0/7 with positive LN.

LMS: Gadducci et al: Gyn Onc 1996

- 126 patients
- Lymph Node Dissection in 7 patients
- 0/4 in apparent stage I disease
- 2/3 in Stage III and IV patients...virtually no survival.

LMS: Australian Experience

- 49 patients
- 2/11 (18%) had positive Lymph nodes
- Both with other sites of extraterine disease.
LMS: Nodes positive only if Extra-uterine disease present

- Goff et al - 1993
- Major et al - 1993
- Morice et al - 2003
- Guintoli et al - 2004
- Menczer et al - 2005

Lecimyosarcoma: Guintoli et al: Gyn Onc: 2002(Mayo Clinic)

- 36/208 (16%) underwent LN DX
- A/P = 19; P alone = 15; A alone = 2
- 4/36 (11%) Positive LN with 3/4 having extrauterine disease
- No survival difference +/- LN Dx

Survival Locally Advanced Sarcoma: MD Anderson 1983: Hannigan et al

- 39 patients with advanced disease
- 17 LMS
- 19 MMT
- 3 "pleiomorphic sarcoma"
- All dead within 32 months: Median survival 7.2 months
Conclusions: Re: LMS

- Few patients have positive LN and most have other sites of disease
- Patients with extra-uterine invariably are DOD within a short period of time
- On this basis there is little benefit to be derived from restaging
- There remains a small benefit from resecting all visible disease at primary surgery

So, on one hand we have data suggesting the presence of extra-uterine disease is deadly and on the other...

CS Mayo Experience: Nelson et al Gyn Onc 1989

- 52/60 (87%) patients had all macroscopic disease resected. 18/26 (69%) with intra-abdominal metastases were completely resected
- PFI for Stage II at 2 and 5 yrs (59% and 42%)
- PFI for Stage III/IV at 2 and 5 yrs (21% and 14%)
CS: Mayo Experience: Nelson et al
Gyn Onc 1989

- 18/26 (69%) stage III and IV patients
  DOD under 24 months
- 22/26 (85%) DOD under 36 months
- Of the 4 remaining alive at 4, 5, 8, and 16 years all had complete cytoreduction

CS: NYC: Incidence and Trends in Survival

- Survival and Cytoreductive Surgery
- 35 patients with gross residual 77%
  DOD within 24 months
- 46 patients NED only 39% DOD

LMS & CS: Extrauterine Disease Treated with XRT
U of Minn Dusenbery et al
Gyn Onc: 2004

- 19 patients: 13 CS and 6 LMS
- CS: 10/13 DOD within 4 years with 8/13 DOD within 1 yr. 3 long-term survivors
- LMS: 3/6 DOD within 2 years: 1 AWD at 6 yrs: 1 DNED at 2 yrs: 1 ANED at 14 yrs.
**LMS: Benefit of Cytoreduction**
Mass General
Dinh et al: Gyn Onc: 2004
- 27 patients: 8/8 LNDX were (+)
- Bowel resection in 7/27 (26%)
- 16/27 (59%) - Stage IV
- 16/27 (59%) - optimal cytoreduction: median survival not reached at 90 months (p<.0003)
- 2 long-term survivors - > 6 years with stage IV disease

---

**LMS: Resection of Pulmonary and Extrapulmonary Recurrences**
Leitao et al: Gyn Onc: 2002
- 41 pts with 1st recurrence (Median 15 months)
- No differences in survival assoc. with site of recurrence or post-op treatment
- Recurrence after 12 months assoc with improved median survival (1.5 vs 5.1 yrs)
- Median Survival Optimal vs suboptimal resection (3.9 vs 0.7 yrs)

---

**LMS: Secondary Cytoreduction**
Giuntoli et al. Gyn Onc: 2007
- 60/128 (47.5%) underwent secondary cytoreduction
- Time to first recurrence of > 6 months associated with improved survival
- Median survival associated with surgery, chemotherapy and XRT (2.0, 1.5, 1.3)
- Surgery and time to first recurrence associated with improved survival (Hazard ratio of 0.26 and 0.58 (p<0.001 and p=0.03)
Royal Marsden: Survival, Patterns of spread and Prognostic Factors in Uterine Sarcoma
Moskovic et al. British Jo Radiology 1995

- Impact of Residual Disease
  - 54 patients presenting after 1980
  - 17/19 (89%) with residual disease DOD
  - 22/35 (62%) of those NED after surgery DOD. RR = 0.39, 95% CI (0.20, 0.74) with p = 0.005

CS: Australian Experience
Inthasorn et al. Intl Jo Gyn Onc: 2002

- 37 patients
- 20/37 (54%) underwent LNDx
- 7/20 (35%) were positive
- Node status did not affect OS
- Residual Disease significant finding
Conclusions: Re: Primary and Secondary Cytoreductive Surgery

- Complete cytoreductive surgery benefits appropriate surgical candidates with both C/S and LMS.
- The benefits of secondary cytoreductive surgery may seem inconsistent with our primary knowledge but it is clear a defined population does indeed benefit from additional surgery.

ESS and Adenosarcoma

- Much less known about these conditions

Endometrial Stromal Sarcoma: Kaku et al. GOG

- 50% Low grade - upstaged vs 33% (high-grade) and 20% (undifferentiated)
- Lymph node Metastases equivalent 14% - 20%
- Low-grade - 0 deaths vs 45-60% for high-grade
- Recurrence- 10% (low-grade) vs. 50-60% (high-grade or undifferentiated)
Adenosarcoma: GOG

- Positive Pelvic Lymph Nodes 2/31 (6.5%)
- No positive Aortic LN identified
- ASO with rhabdosarcomatous element and extrapelvic disease - 5/5 DOD with 13 months

Adenosarcoma with Sarcomatous Overgrowth
Krivak et al.
Gyn Onc; 2001

- 11 Adenosarcomas with sarcomatous overgrowth
- 9/11 DOD within 39 months; only 2 Stage I pts alive at 18, 19 months
- 5/11 DOD within 8 months
- 3/11 (27%) Positive LNDx; 2/3 had other disease...only 1/11 (9%) upstaged with LNDx

Conclusions: Re: ESS and Adenosarcoma

- Since pre-operative and or intra-operative diagnosis unlikely patient will best served by resecting all visible disease and probably removing pelvic and aortic lymph nodes
- If pre-op dx known- LNDx not indicated with ASO or ESS
Overall Conclusions: Optimal Surgery for Uterine Sarcoma

- TAH-BSO (can spare Ovaries in LMS)
- Resect all visible disease
- Lymph Node dissection under limited, individualized circumstances.
New systemic strategies for the management of carcinosarcomas of the uterus

Matthew A. Powell, MD
Assistant Professor
Director, Gynecologic Oncology Fellowship
Washington University School of Medicine
Department of OB/GYN
St. Louis, MO

Dr. Powell is currently an Assistant Professor in the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology at Washington University School of Medicine. He received his B.S. in Biochemistry/Biophysics from Washington State University in 1990, and was a funded research fellow at the University of Washington from 1987 to 1989. He received his medical degree from Michigan State University in 1995. Dr. Powell continued his medical training at Ohio State University, completing his four-year residency in Obstetrics and Gynecology in 1999. He did his subspecialty training in Gynecologic Oncology at Washington University, completing the three-year program in 2002. He is currently the Director of the Gynecologic Oncology fellowship at Washington University. He has served the Program Chair for the SGO winter meeting Fellow’s Forum in 2007 & 2008.

He is author or co-author on over 90 peer-reviewed articles involving ovarian, uterine and cervical cancer. He is a member of the Alvin J. Siteman Cancer Center’s Protocol Review and Monitoring Committee for the Washington University Human Studies Committee.

Dr. Powell is also the principal investigator for multiple industry-sponsored investigator-initiated clinical trials at Washington University dealing with uterine, cervical and ovarian cancer. He is an active member of the NCI-funded Gynecologic Oncology Group at Washington University, and has been a voting member of the GOG Uterine Corpus, Rare tumor, and developmental therapeutics Committees. Currently he is the national study chair for Three GOG trials: GOG 232B, GOG 261, and GOG 229I involving the management of women with uterine cancer.
New systemic strategies for the management of carcinosarcomas of the uterus

Matthew A. Powell, MD
Asst. Professor
Washington University, St. Louis

Disclosures

Speaker/Consultant: Sanofi-Aventis, OrthoBiotech, Merck, Covidian, Intuitive Surgical, Ethicon Endosurgery

Introduction

• Uterine carcinosarcoma (malignant mixed mullerian tumor) < 5% uterine neoplasms
• Annual incidence < 2 per 100,000
• Very aggressive with poor survival often presenting with extra-uterine disease
• Possible role for Radiation?
• Chemotherapy:
  – Single agents
  – Combination
  – Winner: Carboplatin/paclitaxel
• 41% of patients on trial with CS
• No difference in either overall or disease-free survival
• Increased local control for CS patients

<table>
<thead>
<tr>
<th>U2, n = 95</th>
<th>Radiotherapy (n = 46)</th>
<th>Observation (n = 49)</th>
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<tr>
<td>Distant metastases</td>
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<td>Distant alone</td>
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<tr>
<td>Any distant metastases</td>
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Do we want to give Ifos / Taxane or Gem / Taxane after RT??

Single-agent chemotherapy response rates:

- Ifosfamide (29–36%) [Sutton, ’92, ’94]
- Cisplatin (28–42%) [Thigpen, ’86; Gershenson, ’87]
- Doxorubicin (10–25%) [Muss, ’85; Omura, ’85]
- Etoposide (6.5%) [Slayton, 1987]
- Topotecan (10%) [Miller, 2005]
- Paclitaxel (18%) [Curtin, 2001]

Combination chemotherapy for uterine carcinosarcoma

• Ifosfamide vs Ifosfamide–cisplatin (n=197)
  – RR: 34% versus 56%*
  – PFS: 4 versus 6 months* [Sutton, 2000]

*p<0.05
Combination chemotherapy for uterine carcinosarcoma

- ifosfamide vs ifosfamide–cisplatin (n=197)
- OAS: 7.6 v. 9.4 months (RR=0.80, P = 0.07). [Sutton, 2000]

Combination chemotherapy for uterine carcinosarcoma

- ifosfamide to ifosfamide–paclitaxel–filgastrim (n=179)
  - RR: 29% and 45%*
  - PFS: 4 versus 6 months*
  - OS: 8 versus 14 months* [Homesley, 2007]*p<0.05

Combination chemotherapy for uterine carcinosarcoma

EORTC: cisplatin, Ifosfamide, doxorubicin

RR=56% (CR: 34%, PR: 22%)

Carboplatin-paclitaxel-PEG Doxorubicin for uterine carcinosarcoma:

- Pectasides, 2008: carboplatin/paclitaxel/liposomal-doxorubicin
  - (n=29) RR: 62%, PFS: 8.2, OS: 16.4 months

Carboplatin-paclitaxel for uterine carcinosarcoma: Retrospective studies & preliminary reports

- Toyoshima, 2004: RR 80% (4 of 5)
- Ramondetta, 2007: RR 64% (7 of 11)
- Hoskinds, 2008: 20 up-front tx, 11 recurrent
  - RR: 60% (12 of 20, CR 5, PR 7): Up-front
  - RR: 55% (6 of 11, CR 2, PR 4): recurrent
  - median PFS of 16 and 12 months

GOG 232B: Pac/Carbo

- Activated 5/31/05, closed 3/17/08
- N=55 enrolled, 9 excluded (2 not treated, 5 wrong pathology/site, 2 inevaluable), 46 evaluable
- Therapy: Paclitaxel 175 mg/m2 IV over 3 hours followed by carboplatin AUC = 6 IV over 30 minutes every 21 days until disease progression or adverse effects prohibit further therapy
### GOG 232B: 60% 6 or > cycles

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### AE's (CTCAE version 3): self limited marrow only.

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### Reported adverse events CTCAE version 3: 10% G3 neuropathy.

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Results: RR=54% (62% unconfirmed)

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<table>
<thead>
<tr>
<th>Complete Response*</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response*</td>
<td>19</td>
<td>41.3</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>11</td>
<td>23.9</td>
</tr>
<tr>
<td>Increasing Disease</td>
<td>6</td>
<td>13.0</td>
</tr>
<tr>
<td>Not evaluated for response</td>
<td>4</td>
<td>8.7</td>
</tr>
</tbody>
</table>

*Unconfirmed Response (no repeat imaging): CR=11 (24%), PR=16 (35%), ORR (59%)

Survival

Taxane/Platinum: The “Cytotoxic backbone”

- Ovarian Cancer
- Breast Cancer: Her-2+
- Lung Cancer
- Melanoma
- Uterine Cancer
- Cervix Cancer
- Bladder Cancer
- Head & Neck Cancers
- Adenocarcinoma of Unknown primary (Occult AdenoCa)
Matthew A. Powell, MD

**Taxane/Platinum Backbone**

- Nine common solid tumors have CT as an acceptable regimen for therapy. Why?
- Toxicity
- Ease of Administration
- Ease of combination with new agents

**232C: Carbo/Pac + BSI-201**

- Update to be provided

**Standard therapy: level of evidence**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel/Platinum</td>
<td>II</td>
</tr>
<tr>
<td>Ifos/Taxane</td>
<td>I</td>
</tr>
<tr>
<td>Gem/Taxane</td>
<td>O</td>
</tr>
</tbody>
</table>
GOG 161 vs 232B

Yellow: Ifos-Pac: Overall survival
--- --- : Carbo-Pac: Overall Survival

GOG 130E: A Phase II Evaluation of Gemcitabine and Docetaxel in the Treatment of Recurrent or Persistent Carcinosarcoma of the Uterus

• RR=8.3% (PRs only)
• All 24 with prior chemo

Toxicity

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel/Platinum</td>
<td>Marrow/neuropathy</td>
</tr>
<tr>
<td>Ifos/Taxane</td>
<td>Similar/worse</td>
</tr>
<tr>
<td>Gem/Taxane</td>
<td>Similar/worse</td>
</tr>
</tbody>
</table>
**Cost of Therapy**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cost $$$$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel/Platinum</td>
<td>Winner (Hoskins)</td>
</tr>
<tr>
<td>Ifos/Taxane</td>
<td>3 days + GCSF</td>
</tr>
<tr>
<td>Gem/Taxane</td>
<td>Non-generic +G</td>
</tr>
</tbody>
</table>

The winner: Paclitaxel plus Platinum

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Adding agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel/Platinum</td>
<td>232C Carbo/Pac + BSI-201</td>
</tr>
<tr>
<td>Ifos/Taxane</td>
<td>None: maxi-toxic?</td>
</tr>
<tr>
<td>Gem/Taxane</td>
<td>None: maxi-toxic?</td>
</tr>
</tbody>
</table>

Answering the question: GOG 261

**PROTOCOL GOG 261**

A RANDOMIZED PHASE III TRIAL OF PACLITAXEL PLUS CARBOPLATIN VERSUS SORAFENIB PLUS PACLITAXEL IN CHEMOTHERAPY- NAIVE PATIENTS WITH NEWLY DIAGNOSED STAGE IV PERSISTENT OR RECURRENT CARCINOSARCOMA (MIXED MESODERMAL TUMORS) OF THE UTERUS

NCT Version Date: August 16, 2009

**TREATMENT RANDOMIZATION**

**REGIMEN 1**
- Paclitaxel 175 mg/m² IV over 2 hr on day 1
- Carboplatin AUC 6 on day 1
- Repeats 6 weeks (see Section 5.2.1)

**REGIMEN 2**
- Sunitinib 50 mg PO daily day 1-21
- Paclitaxel 175 mg/m² IV over 2 hr on day 1
- Repeats 6 weeks (see Section 5.2.1)

GOG Support: Eligibilities or Pathogenetics

Activated 9/2006: Target accrual 424 patients over 5.5 years
Why Carboplatin / Paclitaxel?

- Now that GOG 218 [Carboplatin Paclitaxel plus Bevacizumab ] & GOG 229E (Bev in Endometrial) are positive trials?
- Phase I Ifos+Taxol +Bev in Uterine Carcinosarcoma?

Conclusion

- Given we care for patients with rare tumors, simplification of cytotoxic regimens is necessary to expedite future drug development.
- Carboplatin / Paclitaxel should be the standard cytotoxic regimen utilized in uterine carcinosarcomas.

Conclusion

- Carboplatin–paclitaxel is effective against uterine carcinosarcoma (MMMT) with response rates and survival similar to those achieved with ifosfamide doublets
- Advantage: more convenient, less requirement for growth factor support, cheaper?, likely less toxic, and potentially more easily combined with biologic therapies
Role of anti-angiogenesis and other targeted agents in corpus leiomyosarcomas

Martee L. Hensley, MD
Associate Professor of Medicine
Associate Attending Physician
Memorial Sloan-Kettering Cancer Center
Department of Medical Oncology
New York, NY

Dr. Martee L. Hensley is an Associate Attending physician at Memorial Sloan-Kettering Cancer Center and Associate Professor of Medicine at Weill College of Medicine at Cornell University. She graduated from Duke University School of Medicine and completed her medical residency training, and fellowship training in hematology and medical oncology, at The New York Hospital-Cornell Medical Center. She has Masters of Science in Epidemiology from Harvard School of Public Health.

Dr. Hensley joined the faculty of Memorial Sloan-Kettering Cancer Center in 1998 focussing her clinical and research efforts on gynecologic cancers. Her research interests include novel therapies for uterine sarcomas and for recurrent ovarian cancer. Dr. Hensley is active in the Gynecologic Oncology Group, serving as a committee member on the Uterine Corpus, Quality of Life, and Cancer Prevention and Control Committees. She is also active in the Sarcoma Alliance for Research through Collaboration (SARC). She serves as national principal investigator for several gynecologic sarcoma research studies.
Role of Anti-Angiogenesis and other Targeted Agents in Corpus Leiomyosarcoma

Martee L. Hensley, M.D.
Memorial Sloan-Kettering Cancer Center

I do not have any relevant financial relationships with commercial interests that pertain to the content of my presentation.

Disclosures

I have no financial disclosure relevant to this topic.

56 year old woman with
• Rapidly enlarging fibroid and post-menopausal bleeding
• TAH/BSO
• Uncomplicated post-operative course
• No major co-morbidities
• Histology shows:
56 year old woman with recent dx uterus-limited high grade LMS
- Develops new cough a few weeks after resection
- Key findings on CT chest/abdomen/pelvis are:

Recurrent uterine LMS
GOG progress report in LMS:

- Do any cytotoxics work?
- Can we identify targets in corpus LMS?
- What is the rationale for anti-angiogenesis treatment?
- What is the track record for targeted therapies in LMS?

Response rates in GOG phase II trials in advanced uterine LMS—cytotoxic therapy

<table>
<thead>
<tr>
<th>GOG phase II reference</th>
<th>Drug</th>
<th># prior regimens</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Look</td>
<td>gemcitabine</td>
<td>0-1</td>
<td>9/42 (20%)</td>
</tr>
<tr>
<td>Sutton</td>
<td>liposomal doxorubicin</td>
<td>0</td>
<td>5/32 (16%)</td>
</tr>
<tr>
<td>Gallup</td>
<td>paclitaxel</td>
<td>0-1</td>
<td>4/45 (9%)</td>
</tr>
<tr>
<td>Sutton</td>
<td>paclitaxel</td>
<td>0</td>
<td>3/33 (9%)</td>
</tr>
<tr>
<td>Thigpen</td>
<td>cisplatin</td>
<td>0</td>
<td>1/33 (3%)</td>
</tr>
<tr>
<td>Sutton</td>
<td>doxorubicin</td>
<td>0</td>
<td>7/28 (25%)</td>
</tr>
<tr>
<td>Sutton</td>
<td>ifosfamide</td>
<td>0</td>
<td>6/35 (17%)</td>
</tr>
<tr>
<td>Thigpen</td>
<td>etoposide IV</td>
<td>0</td>
<td>0/28 (0%)</td>
</tr>
<tr>
<td>Rose</td>
<td>etoposide PO</td>
<td>1</td>
<td>2/29 (7%)</td>
</tr>
<tr>
<td>Miller</td>
<td>topotecan</td>
<td>0</td>
<td>4/36 (11%)</td>
</tr>
<tr>
<td>Smith</td>
<td>trimetrexate</td>
<td>0-1</td>
<td>1/23 (4%)</td>
</tr>
<tr>
<td>Hensley</td>
<td>gemcitabine + docetaxel</td>
<td>0</td>
<td>15/42 (36%)</td>
</tr>
</tbody>
</table>

GOG 87L: RECIST response

<table>
<thead>
<tr>
<th>Best response</th>
<th>30 pts evaluable for response</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2/39</td>
<td>4.8%</td>
</tr>
<tr>
<td>PR</td>
<td>13/39</td>
<td>31%</td>
</tr>
<tr>
<td>SD</td>
<td>11/39</td>
<td>26.2%</td>
</tr>
<tr>
<td>POD</td>
<td>12/39</td>
<td>32%</td>
</tr>
</tbody>
</table>

Clinical Benefit Rate: 62%
19/38 (50%) patients received ≥ 6 cycles
GOG 87L: response duration, PFS

<table>
<thead>
<tr>
<th>Best response</th>
<th>Median duration</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + PR duration</td>
<td>6+ months</td>
<td>2.1-33.4+ months</td>
</tr>
<tr>
<td>SD</td>
<td>4.3 months</td>
<td>2.1-17.2 months</td>
</tr>
<tr>
<td>PFS</td>
<td>4.4+ months</td>
<td>0.4 – 34.2+ months</td>
</tr>
</tbody>
</table>

% pts Progression-Free at 12 weeks: 60%
% pts Progression-Free at 24 weeks: 41%

After fixed dose-rate gem-docetaxel

GOG progress report in LMS:
- Do any cytotoxics work?
- Can we identify targets in corpus LMS?
- Is there rationale for anti-angiogenesis treatment?
- What is the track record for targeted therapies in LMS?
Old targets/New Targets

<table>
<thead>
<tr>
<th>Target</th>
<th>Evidence</th>
<th>Potential Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER and PR</td>
<td>IHC+ in 40-80% of uLMS</td>
<td>aromatase inhibitors</td>
</tr>
<tr>
<td>VEGF</td>
<td>Higher VEGF is higher risk for POD; higher VEGF than in nl ut smooth muscle</td>
<td>bevacizumab, sunitinib, sorafenib, thalidomide, vandetanib, vorinostat</td>
</tr>
<tr>
<td>PARP</td>
<td>BRCA-1 protein (due to gene promoter methylation) absent in 29% of uLMS; thus PARP DNA repair pathway may be important</td>
<td>ABT-888, AZD2281 BSI-201, others</td>
</tr>
</tbody>
</table>


Aromatase Inhibitors in uLMS

- ER and PR + in 40-80% of uLMS
- Retrospective study of 34 patients
- Highly selected population
- 56% with no tumor mass >2 cm
- About 60% ER and/or PR positive
- PR 9%
- SD 35%

O’Cearbhaill, Hensley Gyn Onc, 2010

Aromatase Inhibitors in LMS

PFS longer among pts with ER/PR + LMS, but not necessarily attributable to the aromatase inhibitor

O’Cearbhaill, Hensley Gyn Onc, 2010
NCT00856050: Letrozole in Women With Advanced Estrogen/Progesterone Receptor Positive Uterine Leiomyosarcoma

- Phase II study at DFCI (Suzanne George, PI)
- Post-menopausal
- Measurable disease
- No limit on prior chemo and/or biologics

Old targets/New Targets—

<table>
<thead>
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<th>Evidence</th>
<th>Potential Agents</th>
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</thead>
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<tr>
<td>PARP</td>
<td>BRCA-1 protein absent in 29% uLMS</td>
<td>ABT-888, AZD2281 BSI-201</td>
</tr>
</tbody>
</table>

Leitao, Cancer 2004; Kallali, Appl IHC Mol Morphol 2004; McMeekin, Gyn Onc 2007; Arita Int J Gyn Ca 2005

GOG Phase II thalidomide in uLMS

- uLMS, 1-2 prior, measurable disease
- Oral thalidomide daily, target dose 1000 mg
- Primary endpoint PFS at 6 months OR objective response
- TRE: association of VEGF, bFGF, and Endothelial Protein C Receptor with outcome

McMeekin, Gyn Oncol 2007
**Association of plasma biomarkers with PFS and OS in uLMS treated on GOG phase II thalidomide study**

<table>
<thead>
<tr>
<th></th>
<th>PFS Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
<th>OS Hazard Ratio</th>
<th>97% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>3.5</td>
<td>1.5-7.8</td>
<td>0.003</td>
<td>4.7</td>
<td>1.6-13.8</td>
<td>0.005</td>
</tr>
<tr>
<td>sFGF</td>
<td>1.2</td>
<td>0.7-2.1</td>
<td>0.595</td>
<td>1.1</td>
<td>0.9-1.2</td>
<td>0.312</td>
</tr>
<tr>
<td>sEPCR</td>
<td>0.6</td>
<td>0.3-1.3</td>
<td>0.169</td>
<td>0.8</td>
<td>0.3-1.8</td>
<td>0.518</td>
</tr>
</tbody>
</table>

Objective Response: 0%

- % of patients progression-free at 6 months: 7% (2 patients)
- Median PFS: 1.9 months

_BUT_—Thalidomide did not decrease VEGF levels—maybe we had the wrong anti-VEGF agent

McMeekin, Gyn Oncol 2007

---

**GOG 231C: sunitinib, 1-2 prior uterine LMS**

Met first stage accrual goal of 19 patients in 7 months

- ORR 8%; PFS at 6 months = 17%

Hensley, ML, Gyn Oncol 2009

---

**Sorafenib phase II STS**

- Primary Objective: RECIST response rate for each stratum of STS pts treated with sorafenib
  - LMS accrued as a separate cohort in Simon 2-stage design
  - 0-1 prior treatments, measurable disease
- RECIST responses:
  - LMS 2.7% (1 PR / 37 patients)
  - LMS PFS 3.2 mo

Maki, J Clin Oncol 2009
Phase II aflibercept (VEGF-trap) in uLMS or carcinosarcoma

- 22/25 patients with uLMS had <1 prior therapy
- Aflibercept 4 mg/kg IV every 2 weeks
- CT for objective response every 8 weeks
- uLMS: 8 patients best response = SD
- 4/25 (16%) LMS patients had SD for >6 months
- Needed at least 2 patients PF at 6 months to proceed to second stage
- "moderately active" in uLMS

Townsley, Proc ASCO 2009

NSCLC Tax-Carb +/- Bev

<table>
<thead>
<tr>
<th></th>
<th>Tax-Carbo</th>
<th>Tax-Carbo-Bev</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (mo)</td>
<td>4.5</td>
<td>6.2</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>OS (mo)</td>
<td>10.3</td>
<td>12.3</td>
<td>P= 0.003</td>
</tr>
<tr>
<td>Response Rate</td>
<td>15%</td>
<td>35%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Sandler, NEJM 2006

Bevacizumab and Doxorubicin in STS

- Doxorubicin 75mg/m2 + Bev 15 mg/kg
- 1st line, measurable disease
- 11 of 17 patients had LMS
  7/11 uterine LMS
- 2/17 (12%) PR (expect 30% with dox)
- 6 patients (35%) with grade 2 or greater cardiotoxicity

D'Adamo, J Clin Oncol 2005

Take-home message:
1. VEGF-targeted agents may not always play well with others
2. Randomized trial design likely required to adequately assess their role
Gemcitabine-docetaxel + bev: safety

- Q 2 week gem-doce + bev 5 mg/kg
- Variety of STS histologies
- No prior chemotherapy
- 23 patients enrolled, 20 considered evaluable
- 8/20 objective responses (40%)
- 1 PTX, 1 bowel perforation

Rationale for Gem-Doce +/- Bev

- 4 prospective studies demonstrate high objective response rates to FDR gem-docetaxel
- Multiple studies (retrospective and prospective) showing association between VEGF pathway activity and poorer outcomes in uterine LMS
- Combinability of bevacizumab with non-anthracycline chemotherapy in lung, breast, colon
- One trial showing combinability of gem-doce-bev q 2 weeks in STS

GOG 0250: phase III gem-doce + placebo v. bevacizumab
GOG -250: gem-doce +/- bev for uterine LMS

Endpoints:
- Progression-free survival
- Objective response
- Overall survival
- Safety/tolerability

Accrual goals and study implications:
- 130 patients
- 25-30 patients/year
- Can the addition of bevacizumab improve median PFS from 4 months to 6.7 months?
- Definitive study for this research question
- Demonstrate ability of GOG to conduct phase III trials in this population

Other targets/Other trials

PARP inhibitors
- In vitro data for BRCA-1 dysfunction suggests role for PARP inhibition
- Combination of PARP inhibitor with alkylator likely most effective

HDAC inhibitors
- In vitro data showing uterine sarcoma cell line growth suppression
- Inhibition of histone deacetylation alters gene expression
- Under study in soft tissue sarcoma
- Concept submitted for phase II vorinostat in 231 series

GOG report card for uLMS

- Accrual of patients with this rare tumor to prospective phase II trials? A
- Identification of cytotoxic regimens with efficacy in uterine LMS? A
- Identification of potential targets for novel treatments? B
- Design and implementation of trials adding targeted strategies to effective cytotoxic backbone? A
- Accrual of patients to phase III trials with potential to change standard of care for uterine LMS? We need your help!

And the women with this disease need our answers
GOG Symposium
“New Frontiers in Cervical and Corpus Cancer”

Thursday, July 15, 2010
8 am – 3pm
Grand Ballroom/Liberty

The Gynecologic Oncology Group wishes to thank AMGEN ONCOLOGY for their grant support for this educational activity.
Save the date for these upcoming GOG semi-annual meetings!

January 28-30, 2011
Manchester Grand Hyatt
San Diego, CA
(Symposium - January 27)

July 15-17, 2011
Philadelphia Marriott Downtown Hotel
Philadelphia, PA
(Symposium - July 14)

January 27-29, 2012
Manchester Grand Hyatt
San Diego, CA
(Symposium - January 26)

July 27-29, 2012
Sheraton Hotel
Boston, MA
(Symposium - July 26)

January 25-27, 2013
Manchester Grand Hyatt
San Diego, CA
(Symposium - January 24)

July 19-21, 2013
Marriott River Center
San Antonio, TX
(Symposium - July 18)

January 24-26, 2014
Manchester Grand Hyatt
San Diego, CA
(Symposium - January 23)

July 18 - 20, 2014
Hyatt Regency Chicago
Chicago, IL
(Symposium - July 17)

January 23-25, 2015
Manchester Grand Hyatt
San Diego, CA
(Symposium - January 22)

Visit the GOG Website at www.gog.org for daily updates.