2008 State of the State of Gynecologic Cancers

Sixth Annual Report to the Women of America

Gynecologic Cancer Foundation

About the Society of Gynecologic Oncologists and the Gynecologic Cancer Foundation

The Society of Gynecologic Oncologists (SGO) is a national medical specialty organization for physicians trained in the comprehensive management of women's cancers. The Society's membership is comprised primarily of gynecologic oncologists — obstetricians/gynecologists with three to four years of additional, intensive training in the specific study of gynecologic cancers. SGO members provide medical and surgical care to women with ovarian, cervical, endometrial, vulvar and vaginal cancers. They are trained in surgery, chemotherapy, radiation therapy administration and supportive care in order to provide comprehensive patient care.

SGO's mission is to promote and ensure the highest quality of comprehensive clinical care through excellence in education and research in gynecologic cancers. The Society and its members share the long-term vision to eradicate gynecologic cancers.

For more information about SGO and the gynecologic oncology profession, please visit **www.sgo.org** or contact the Society at 312.235.4060.

The Gynecologic Cancer Foundation (GCF) is a 501(c) 3 not-for-profit organization whose mission is to ensure public awareness of gynecologic cancer prevention, early diagnosis and proper treatment. In addition, the Foundation supports research and training related to gynecologic cancers. GCF advances this mission by increasing public and private funds that aid in the development and implementation of programs to meet these goals.

For more information about GCF, its educational materials or research grants, please visit **www.thegcf.org** or contact GCF Headquarters by phone at 312.578.1439 or by e-mail at info@thegcf.org. For additional information on gynecologic cancers or for a referral to a gynecologic oncologist or a related specialist, please call the toll-free GCF Information Hotline at 800.444.4441.

For more information about women's cancers, visit GCF's Women's Cancer Network Web site: **www.wcn.org**. Log on for a confidential risk assessment to learn about your risk for developing gynecologic and breast cancers. Comprehensive information about each gynecologic cancer and breast cancer is available on the site. The site also provides the opportunity to locate a nearby gynecologic oncologist, a step women are urged to take if they suspect or have been diagnosed with a gynecologic cancer.

Table of Contents

A Letter and Greeting to the Women of America

The Gynecologic Cancer Foundation is pleased to publish the sixth edition of *The State of the State of Gynecologic Cancers: A Report to the Women of America*. This year's report may be the most important to date. In addition to providing readers with an update on advances made in each of the major gynecologic cancers during the past year, the report explains the importance of seeking care from a gynecologic oncologist when a reproductive cancer is suspected or diagnosed.

Our purpose is to help women achieve the best possible outcome from their gynecologic cancer diagnosis. It is our hope that what you learn from this report will help you and your healthcare provider make the right decision about your care.

I am especially pleased to share with you the following greeting from Congresswoman Rosa DeLauro (D-CT) who offers her personal experience with ovarian cancer and urges women to seek care from a gynecologic oncologist when a gynecologic cancer is suspected or diagnosed.

Sincerely,

Karl C. Podratz, MD, PhD
Chairman, Gynecologic Cancer Foundation

Dear Friends,

I am pleased to join The Gynecologic Cancer Foundation to welcome you to its annual State of the State of Gynecologic Cancers report to the women of America.

I write today not only in my official capacity as a Member of Congress, but as a foot soldier in this fight, one of more than a million gynecologic cancer survivors in the United States.

Twenty-two years ago, my life was forever altered when, during an unrelated doctor's visit, I was diagnosed with ovarian cancer. I had excellent doctors who detected the cancer by accident in Stage 1. Behind this country's remarkable cancer care delivery system are the doctors, the nurses and nurse practitioners who make it possible. My gynecologic oncologist was a partner and a guide in my battle against the disease.

We all know that cancer is an indiscriminate disease — it does not care about your age, your family, your sex, your race or your religion. Every woman is at risk of developing a gynecologic cancer. It reminds us that we are human and vulnerable. I was lucky. But the relentless professionalism and dedication of those in gynecological oncology at hospitals and research institutions across the nation have made that possible and narrowed the scope for luck.

There are countless researchers and doctors whose relentless and often unrecognized efforts have produced so many advances in cancer detection and treatment. I know that, simply put, their work saved my life. I underwent radiation treatment for two-and-a-half months. And I am proud to say that I have now been cancer-free for 22 years.

We have made great progress in the fight against cancer, but we have much further to go. In Congress, we worked years ago to create the National Breast and Cervical Cancer Early Detection Program, which provides access to critical breast and cervical cancer screening services for underserved women in the United States.

Congress has renewed that program through 2012. In the last 16 years, we have served 3 million women — an unquestionable success. Today, I sit on the House Appropriations Subcommittee on Labor-Health-Education and Human Services, where I have made funding biomedical research at the National Institutes of Health and the National Cancer Institute one of my top priorities.

Over the last decade, federal spending on cancer at those institutions has increased significantly. We made what I view as the single greatest bipartisan accomplishment since I came to Congress: a doubling of the NIH budget between 1998 and 2003. Unfortunately, since then, Congress has not maintained that infusion of resources. And so, we must keep at it. If we want to see serious improvements in health we need to make serious investments that pay dividends.

In 2006, we celebrated the approval of the first vaccine of its kind to guard women against cervical cancer — a medical breakthrough. Women around the country should learn of this advance and what it means to their lives, and the implications of HPV. We must work to ensure both the test and the vaccine are accessible and affordable to all women.

Last year, for the first time we funded powerful new outreach and research under Johanna's Law legislation I cosponsored to raise awareness about gynecologic cancers among women and their healthcare providers.

We know that more challenges lie ahead. Research. Outreach. Education. Screening. These make early detection possible. They make beating cancer possible. They are the powerful tools that give us real hope.

Today, I know I am one of the lucky ones. My life was given back to me and changed at the same time. I hope to see the day when cancer is prevented and no one has to go through what I and so many others have endured. In the meantime, I urge women to see a gynecologic oncologist should they suspect or be diagnosed with a gynecologic cancer.

Take advantage of this report: it is an outstanding resource. Together with our gynecologic oncologists, we will use every tool at our disposal to stand together and stand up against cancer.

Sincerely,

Rosa DeLauro
Member of Congress

Commonly Asked Questions

What are gynecologic cancers?

Gynecologic cancers are the uncontrolled growth and spread of abnormal cells originating in the female reproductive organs, including the cervix, ovaries, uterus, fallopian tubes, vagina and vulva.

What causes gynecologic cancers?

There are many factors that cause gynecologic cancers. Medical research has discovered that some classes of genes, called oncogenes and tumor suppressor genes, promote the growth of cancer. The abnormal function of these genes can be acquired (e.g., through smoking, aging, environmental influences) or inherited. Almost all cervical cancers and some cancers of the vagina and vulva are caused by a virus known as HPV, or Human Papillomavirus.

Can gynecologic cancers be prevented?

Screening and self-examinations conducted regularly can result in the detection of certain types of gynecologic cancers in their earlier stages, when treatment is more likely to be successful and a complete cure is a possibility. Diet, exercise and lifestyle choices play a significant role in the prevention of cancer. Additionally, knowledge of family history can increase the chance of prevention or early diagnosis by determining if someone may have a gene which makes them susceptible to cancer.

Who should treat gynecologic cancers?

Gynecologic cancers should be treated by a gynecologic oncologist.

A gynecologic oncologist is a board-certified obstetrician/gynecologist who has an additional three to four years of specialized training in treating gynecologic cancers from an American Board of Obstetrics and Gynecology-approved fellowship program. This subspecialty program provides training in the biology and pathology of gynecologic cancers, as well as in all forms of treatment for these diseases, including surgery, radiation, chemotherapy and experimental treatments.

How are gynecologic cancers treated?

Gynecologic cancers are treated by using one or more of the following: surgery, radiation therapy and/or chemotherapy. The choice of therapy(s) depends on the type and stage of the cancer.

Who is at risk?

Every woman is at risk for developing a gynecologic cancer. It is estimated that there will be about 78,000 new cases diagnosed and approximately 28,000 deaths from gynecologic cancers in the United States during 2008.[1]

[1] American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2008.

Gynecologic Oncologists: What Women Need To Know

By Beth Y. Karlan, MD

No one ever wants to hear the words, "I'm sorry, but the biopsy shows you have cancer." Yet in 2008, close to 80,000 U.S. women will be told that they have a cancer of the ovary, uterus, cervix, vulva and/or vagina. *What women need to know* is that their greatest chance for survival, future fertility and best quality of life may rest in their referral to a gynecologic oncologist, a specialist trained in treating reproductive cancers.

Gynecologic oncologists are physicians committed to the comprehensive treatment of women with cancer. After completing four years of medical school and four years of residency in obstetrics and gynecology, these physicians pursue an additional three to four years of training in gynecologic oncology through a rigorous fellowship program overseen by the American Board of Obstetrics and Gynecology. Gynecologic oncologists are not only trained to be skilled surgeons capable of performing wide-ranging cancer operations, but they are also trained in prescribing the appropriate chemotherapy for those conditions and/or radiation therapy when indicated. Frequently, gynecologic oncologists are involved in research studies and clinical trials that are aimed at finding more effective and less toxic treatments to further advance the field and improve cure rates.

Studies on outcomes from gynecologic cancers, especially ovarian cancer, demonstrate that women treated by a gynecologic oncologist have a better likelihood of prolonged survival compared to care rendered by non-specialists. Due to their extensive training and expertise, gynecologic oncologists often serve as the "team captain" who coordinates all aspects of a woman's cancer care and recovery. Gynecologic oncologists understand the impact of cancer and its treatments on all aspects of women's lives, including future childbearing, sexuality, physical and emotional well-being — and the impact cancer can have on the patient's whole family.

But there are only about 1,000 board-certified gynecologic oncologists in the United States. Women may need to ask their primary care provider for referral to a gynecologic oncologist if a gynecologic cancer is suspected since not all physicians are aware of the scope of practice of modern gynecologic oncologists. Women also can find a gynecologic oncologist by going online to www.wcn.org and clicking on the *find a doctor* button. This simple step may be the first stride forward to long-term survivorship and cure. It's important to start gynecologic cancer care with the right team and a winning game plan.

Cervical Cancer

State of Cervical Cancer

Cervical cancer is a cancer that begins in the cervix, the part of the uterus or womb that opens to the vagina. It is the part of the uterus that dilates and opens fully to allow a baby to pass into the birth canal. The normal cervix has two main types of cells: squamous cells that protect the outside of the cervix and glandular cells that are mostly inside the cervix which make the fluid and mucus commonly seen during ovulation. Cervical cancer is caused by abnormal changes in either of these cell types in the cervix, and is the only gynecologic cancer that can be prevented by regular screening and appropriate vaccination. Since nearly all cervical cancers are caused by persistent infection with the Human Papillomavirus (HPV), vaccinating women and young girls (best at 11 and 12 years of age) before they become sexually active leads to the greatest prevention of pre-cancer and cancer. Early vaccination along with regular Pap tests and HPV testing when recommended is now the best way to prevent cervical cancer. Cervical cancer usually affects women between the ages of 30 and 55, but has been found as early as the teen years.

Symptoms: Bleeding after intercourse, excessive discharge and abnormal bleeding between periods. Most women will have no symptoms and will be alerted by an abnormal Pap test.

Risk Factors: Infection with high-risk HPV has been shown to cause virtually all cervical cancers. However, HPV is very common and most women with HPV will never get any significant cervical disease. Other risk factors include smoking, weakened immunity due to HIV infection or taking medicines for chronic diseases, such as lupus, or following an organ transplant, and becoming sexually active at a young age. Failure to get regular gynecologic examinations with Pap testing takes away the opportunity for early diagnosis through cervical cancer screening.

Screening/Prevention: Over the last 50 years, routine use of the Pap test to screen for cervical cancer has reduced deaths from the disease by 74 percent. A Pap test is a standard way healthcare providers can check to see if there are any changes in the cervical cells that might cause concern. The Pap test involves looking at a sample of cells from the cervix under a microscope to see if there are any that are abnormal. It is a good test for finding not only cancer, but also finding cells that might become cancerous in the future.

Usually, healthcare providers perform the Pap test as part of a routine pelvic exam. It is important for women to know *if a Pap test was performed* because it is possible to have a pelvic exam without a Pap test. It is also important that women know and understand their Pap test results and follow through with any recommendations made by their healthcare provider. Most abnormal Pap tests will be followed by colposcopy and biopsy of any abnormal appearing areas on the cervix. Any pre-cancerous areas can then be seen and treated as recommended by the healthcare provider.

HPV testing is useful at certain times in combination with Pap testing. In non-adolescent women, HPV testing is done automatically when a Pap test is diagnosed as ASC-US (atypical squamous cells of undetermined significance). If high-risk HPV is present in these cells, then a pre-cancerous abnormality is more likely and colposcopy will be recommended. In women

over 30, HPV testing with a Pap test can determine who is not at risk of having pre-cancer of the cervix. A negative HPV test with a negative Pap test can allow Pap screening to occur in three years. Active research is underway to evaluate the role of HPV testing and HPV type-specific testing in primary cervical cancer screening.

One of the most significant advances in the fight against cervical cancer is the development of HPV vaccines. In June 2006, one of these vaccines, Gardasil®, was approved by the FDA for use in 9–26 year old women and girls. In large clinical trials, the vaccine was found to be very effective in protecting women from developing pre-cancerous lesions of the cervix, vulva and vagina. Early vaccination with regular screening, which includes a Pap test and HPV test when recommended according to standard guidelines, is now the most effective way to prevent cervical cancer.

Incidence: It is estimated that there will be about 11,070 new cases of invasive cervical cancer diagnosed and approximately 3,870 deaths in the United States during 2008.[2]

Advances in Cervical Cancer

Cervical cancer prevention and treatment efforts continue to demonstrate medical advances based on group efforts in basic, translational and clinical trials research. The most active area of research remains the continued development of HPV vaccines. Increasing knowledge of ways to prevent HPV infection and increase access to care are key to continuing advances in cervical cancer. Critical to the rapid progress made in recent years in cervical cancer prevention has been the detailed understanding that HPV is the cause of nearly every cervical cancer and pre-cancer.

Over 40 types of HPV have been identified in vaginal, vulvar and cervical diseases. Of these, approximately 15–18 are known to be cancer-causing types. Two types in particular, HPV 16 and 18, are the most common HPV types associated with cervical cancer. HPV 16 causes nearly 60 percent of all cervical cancers and HPV 18 causes an additional 10 to 20 percent. HPV types 16 and 18 are the most important HPV types to include in a vaccine designed to prevent the development of cervical cancer.

Last year's report on advances in cervical cancer discussed in detail the large clinical trials that demonstrate the effectiveness of vaccines to prevent HPV. With widespread vaccination, cervical cancer should be reduced by over 70 percent. Because the vaccine is so effective at preventing cervical pre-cancer and cancer, especially if given to girls before they become sexually active, several medical organizations, including the Advisory Committee on Immunization Practice, the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncologists recommend routine vaccination of young girls 11 and 12 years of age and young women age 13–26, ideally before first intercourse. Newer vaccines that provide immunity against a greater number of HPV types are under development with the hope of preventing over 90 percent of cervical cancer.

[2] American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2008.

More girls and young women need to be vaccinated to achieve this goal. The barriers remain access to care, patient and provider education, and attitudes toward the HPV vaccine. The HPV vaccine is available through most public health facilities and government sponsored insurance programs. Most private insurers will provide some coverage for the cost of the HPV vaccine, but availability also may be a challenge.

Clinical trials are currently ongoing to study the role of HPV vaccines in treating women already infected with HPV who have cervical cancer. These vaccines work differently and are more complex than the vaccines for prevention. But since cervical cancer is far from being fully eradicated, clinical trials of therapeutic vaccines are important.

Progress continues to be made in developing better treatments for women with invasive cervical cancer. Fertility-sparing surgery (removing the cervix and cancer but keeping the uterus to allow a woman to carry a pregnancy) continues to be an option for select women with early-stage cervical cancer. Outcome data from over 500 women treated with fertility-sparing surgery recently have been reported in the literature. Surgery was effective with a recurrence of the tumor in only 4 percent of patients. Pregnancy occurred in 70 percent of the women who tried to get pregnant, and of those, 70 percent delivered in the third trimester.

For women treated for early-stage cancer with radical hysterectomy, research on the use of minimally invasive surgery by laparoscopy or robotically assisted laparoscopy continues. Results from small retrospective trials show shorter hospitalization and less blood loss with minimally invasive surgery compared to standard "open" techniques. However, data on long-term effects on quality of life and late complications from surgery are lacking.

For women with advanced-stage cervical cancers, treatment with a combination of radiation therapy and chemotherapy remains the standard of care. Improved radiation technology called intensity-modulated radiotherapy, or IMRT, allows the radiation oncologist to deliver high doses of radiation to the tumor and lower doses to the normal surrounding organs with fewer side-effects than standard radiation therapy. Advances in the ability to detect cervical cancer when it has spread outside of the pelvis include the evolving data demonstrating the sensitivity and specificity of PET/CT scans in identifying disease that has spread away from the cervix, especially tumors located in lymph nodes outside the pelvis. Improved imaging of cervical cancer allows more accurate and targeted planning of the fields for radiation treatment. PET/CT can also be used to monitor response to treatment and detect recurrence. In one recent study, post-treatment PET/CT scans were able to predict survival based on response of pre-treatment lymph node disease. Further studies will help define the benefits and limitations of this radiologic test in the management of primary and recurrent cervical cancer.

The Gynecologic Oncologist and Cervical Cancer

Cervical cancer is a complex disease that often requires a multidisciplinary approach to optimize treatment for best outcomes. Because of the years of subspecialty training, the gynecologic oncologist has the unique skill set necessary to properly diagnose, stage and direct the treatment of patients with cervical cancer. For women with early-stage cervical cancer, the gynecologic oncologist is uniquely qualified to perform the highly specialized procedure of radical hysterectomy. Gynecologic oncologists have pioneered fertility-sparing minimally invasive surgical approaches, including robotic surgery, to improve the quality of life

and minimize side-effects of treatment for women with cervical cancer. For women with advanced-stage disease, the gynecologic oncologist has the unique ability and qualifications to individualize care plans while working with the multidisciplinary team, including the radiation oncologist. Gynecologic oncologists are specially trained to prescribe and administer the chemotherapy that is specifically timed with radiation therapy in advanced-stage cervical cancer. Lastly, gynecologic oncologists are critical providers of follow-up care for women after treatment for cervical cancer, as early detection of a recurrence in the central pelvic area may be cured with a specialized operation called a pelvic exenteration, which is the most complex operation for which the gynecologic oncologist is trained. Gynecologic oncologists are active and productive researchers, and have been the leaders in designing and performing many of the clinical and translational trials that have produced the advances in prevention and treatment that are described in this report.

For more information about cervical cancer, visit the Gynecologic Cancer Foundation's National Cervical Cancer Public Education Campaign Web site at wwww.cervicalcancercampaign.org.

Ovarian Cancer: Epithelial

State of Epithelial Ovarian Cancer

Ovarian cancer, the seventh most common cancer among women, usually starts on the surface of the ovary in cells that are called epithelial cells. About 85 percent to 90 percent of ovarian cancers are epithelial ovarian cancers.

Symptoms: Bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly and/or urinary symptoms (urgency or frequency).

Women with ovarian cancer report that symptoms are persistent and represent a change from normal for their bodies. The frequency and/or number of such symptoms are key factors in the diagnosis of ovarian cancer. Several studies show that even early-stage ovarian cancer can produce these symptoms.

Women who have these symptoms almost daily for more than a few weeks should see their doctor, preferably a gynecologist. Prompt medical evaluation may lead to detection at the earliest possible stage of the disease. Early-stage diagnosis is associated with an improved prognosis.

Several other symptoms have been commonly reported by women with ovarian cancer. These symptoms include fatigue, indigestion, back pain, pain with intercourse, constipation and menstrual irregularities. However, these other symptoms are not as useful in identifying ovarian cancer because they are also found in equal frequency in women in the general population who do not have ovarian cancer.

Risk Factors: The risk of epithelial ovarian cancer increases with age, especially around the time of menopause. A family history of epithelial ovarian cancer is one of the most important risk factors. Infertility and not bearing children are also risk factors for getting ovarian cancer, while pregnancy and the use of birth control pills decrease the risk.

Screening/Prevention: Currently, there is no widely accepted and effective screening test for epithelial ovarian cancer. High-risk women may be candidates for screening using transvaginal ultrasound and CA 125 blood tests on an annual or biannual schedule, though the benefits of such screening is unproven. For most women, ultrasound and CA 125 screening is not recommended because false positive results can lead to unnecessary surgery.

Incidence: Ovarian cancer ranks fifth in cancer deaths among women and causes more deaths than any other reproductive cancer. It is estimated there will be about 21,650 new cases diagnosed and approximately 15,520 deaths from ovarian cancer in the United States during 2008.[3]

Advances in Ovarian Cancer

Prevention and early detection have continued to be an area of progress this year with studies in women who are at the highest risk for developing ovarian cancer because they carry a mutation in the BRCA1 or BRCA2 genes. Understanding that no single test or combination

[3] American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2008.

of tests has proven useful in screening for ovarian cancer in the general population, researchers studied the effectiveness of combining transvaginal pelvic ultrasound with the CA 125 blood test to screen for ovarian cancer in women with known BRCA gene mutations. Results of screening 120 women with BRCA mutations over a 4.7 year period were presented at the 2008 meeting of the American Society of Clinical Oncology (ASCO). Abnormal test led to surgery in 6 percent of women, with 4 women found to have ovarian cancer, 3 women were found to have early-stage disease and 1 woman had advanced-stage disease. The researchers concluded that screening with ultrasound and CA125 was effective for some women with BRCA mutations, but not as effective as prophylactic surgery to remove the fallopian tubes and ovaries before cancer develops.

For women with BRCA1 or BRCA2 mutations who have already developed ovarian cancer, encouraging preliminary results using a new biologic agent were reported by another group of researchers at the 2008 ASCO meeting. AZD2281, a member of a class of drugs called "PARP inhibitors" that when given by mouth blocks the pathway used by BRCA mutated cells to repair DNA damage, was able to shrink or keep ovarian cancer from growing in 46 percent of 50 patients with recurrent disease. Advances in the early detection and treatment of ovarian cancer such as those described above in women with inherited genetic risk, may ultimately lead to similar progress for the woman in the general population at average risk for developing ovarian cancer.

The ability to detect ovarian cancer early in the general population centers on the identification of biomarkers that can be used to screen women at average risk for developing the disease. Progress in this effort has been made during the past year. In presentations at the 2008 Annual meeting of the Society of Gynecologic Oncologists and the 2008 ASCO meeting, preliminary results of a multi-center, prospective double-blind study of biomarkers HE4 and CA 125 measured in over 500 women undergoing surgery for a pelvic mass were reported. Researchers found that in post-menopausal women, 94 percent of ovarian cancers were correctly placed in a high-risk group before surgery based on HE 4 plus CA 125 results and 75 percent of benign masses were correctly placed in the low-risk group.

In a second study with preliminary results reported at the 2008 ASCO meeting, the same group of researchers found HE4 correlated with CA 125 as a marker of response or recurrence in women with known ovarian cancer, and was a more useful marker for some women with a recurrence in whom CA 125 was not elevated. Although encouraging, the results of these HE4 studies and similar studies of other serum proteins have not yet identified an accurate ovarian cancer screening test for use in the general population. Significant national resources must be directed to support ongoing and to encourage new "bench" research to identify biomarkers for ovarian cancer. Even greater resources must be directed towards completing the large, population-based clinical trials necessary to validate their use as tools for early detection for disease in the average-risk woman.

In addition to evidence described elsewhere in this report showing improved survival for women with ovarian cancer whose primary surgery is performed by a gynecologic oncologist, advances in developing better treatments for ovarian cancer in the past year include changes in the dose and timing of giving standard chemotherapy drugs, as well as new studies of targeted biologic agents.

Improved outcomes for women with advanced ovarian cancer were reported in preliminary results of a prospective randomized trial comparing conventional to dose-dense (higher dose delivered over shorter time) paclitaxel and carboplatin at the 2008 ASCO meeting. In a study of over 500 patients, researchers reported women treated with paclitaxel every week were 30 percent less likely to have progression of their disease than women who were given paclitaxel according to the conventional every 3 week schedule. In the *2007 State of the State of Gynecologic Cancers in America*, we noted the encouraging results of treating ovarian cancer with biologic agents that block new blood vessel growth, or angiogenesis. During the past year, final results of the Gynecologic Oncology Group (GOG) Phase II study of the anti-angiogenesis agent bevacizumab in women with recurrent ovarian cancer were published, as well as results of two additional Phase II studies in women with recurrent ovarian cancer, all demonstrating the ability of a drug that blocks angiogenesis to shrink and prevent new growth of recurrent ovarian cancer. The GOG is testing the benefit of adding bevacizumab to standard paclitaxel and carboplatin chemotherapy for women with primary ovarian cancer in a Phase III prospective randomized trial, GOG 218, which should complete enrollment of patients in the next 18 months.

During the last year, research conducted by the gynecologic oncology community has advanced our understanding of epithelial ovarian cancer with respect to hereditary/genetic risk factors and early detection. Progress has been made in the search for better treatments with information about new ways to deliver standard chemotherapy drugs and the use of biologic agents that target specific pathways critical for cancer cell growth. Together with the evidence described below that maximal first surgical effort by an appropriately trained specialist improves survival in ovarian cancer, these advances will move us closer to the goal of eliminating death and suffering from this disease.

The Gynecologic Oncologist and Ovarian Cancer

It is important for women who are found to have a pelvic mass suspicious for cancer to be aware of the specialty of gynecologic oncology. Over the past five years, educational efforts directed towards physicians and the public have focused on raising awareness of the importance of referral of women with known or suspected gynecologic cancer to a gynecologic oncologist. This is critically important for women with ovarian cancer because, as the data demonstrates, women initially treated by a gynecologic oncologist have improved outcomes and are more likely to receive standard therapy.

As described in the first section of this report, a specialist in gynecologic oncology has completed residency training in obstetrics and gynecology and an additional 3–4 year fellowship of subspecialty training in gynecologic oncology. These additional years of subspecialty training provide the unique set of surgical skills required to provide appropriate and comprehensive care for women with gynecologic cancers. The benefits of this specialized training is highlighted in the study results reported below.

An analysis of SEER data for patients treated between 1992–1999 by Earle et al., demonstrates the lack of specialist care given to women with ovarian cancer in the United States.[4]

[4] Earle CC, Schrag D, Neville BA et al. Effect of surgeon specialty on process of care and outcomes for ovarian cancer patients. J Natl Cancer Inst 98:172-80, 2006.

Reporting on over 3,000 women aged 65 and older who underwent primary surgery for ovarian cancer, the authors found that only 33 percent were treated by a gynecologic oncologist, while the remainder were operated on by non-specialists in either general gynecology or general surgery. When patients had their initial surgery performed by a gynecologic oncologist, they were more likely to undergo the appropriate and recommended procedures. Surgical treatment of early-stage disease should consist of thorough staging procedures, including lymph node removal and multiple biopsies of peritoneal surfaces. Debulking (cytoreductive) procedures are needed for adequate treatment of patients with advanced-stage disease. In addition, this study noted that the administration of postoperative chemotherapy when indicated was significantly more likely to happen when patients had their initial surgery performed by a gynecologic oncologist.

Other authors have reported similar findings. Goff reported on over 10,000 women in nine states undergoing surgery for ovarian cancer.[5] Among the most important factors for receiving appropriate surgical management were surgeon specialty of gynecologic oncologist and the volume of cases performed by the surgeon annually. In a separate report, this same author found that the performance of appropriate staging procedures in cases of suspected early-stage disease, including lymph node removal, were less likely to occur when women had surgery in a low volume centers and the surgery was performed by a non-gynecologic oncologist.[6]

Current state of the art in the surgical treatment of advanced-stage ovarian cancer includes initial surgical resection of the maximal volume of disease in patients who are able to undergo such surgery. This stems from long-held observations and supporting data that indicates the relationship between the smallest amount of residual disease and longest survival. In addition, recent studies also demonstrate the important correlation between the surgical effort and the amount of residual disease — greater surgical effort, including bowel resection and removal of cancer from the upper abdomen, results in smaller residual tumor volumes. Because of the recognized importance of the aggressiveness of the initial surgical resection in advanced ovarian cancer, it is unlikely that a randomized trial will ever be performed on this subject. However, two recent retrospective studies demonstrate the importance of surgical approach to ovarian cancer on the outcomes of both residual disease and overall survival.

Aletti et al., demonstrated the impact of surgeon tendency to employ a more aggressive surgical approach to advanced-stage ovarian cancer. The authors found a strong correlation between the use of radical procedures during surgery and the resultant lower volume of residual disease. These procedures include bowel resection, splenectomy and removal of tumor from the diaphragm — procedures requiring the unique surgical skill set acquired in the training of a gynecologic oncologist. For those patients operated on by surgeons who most often tended to use these radical surgical procedures to remove disease, the median survival time was more than twice as long (5.9 years vs. 2.5 years) compared to those women operated on by surgeons least likely to

[5] Goff BA, Matthews BJ, Larson EH et al. Predictors of comprehensive surgical treatment in patients with ovarian cancer. Cancer 109:2031-42, 2007.

[6] Goff BA, Matthews BJ, Wynn M et al. Ovarian Cancer: patterns of surgical care across the United States. Gynecol Oncol 103:383-90, 2006.

employ such procedures.[7] The authors observed that the primary determinant of overall survival in the subset of patients with most extensive disease was the performance of radical surgical procedures to achieve optimal cytoreduction.

Similar conclusions regarding the impact of a more aggressive surgical approach were reported by Eisenhauer et al., when reporting the effect of altering the surgical approach to ovarian cancer.[8] Beginning in the year 2000, the gynecologic oncologists at one institution made a determined effort to employ upper abdominal surgical resection in the treatment of ovarian cancer. Comparison of the outcomes between patients treated during the 3 years prior to those patients treated during the 3 years after the change in approach demonstrated significantly higher rates of optimal cytoreduction. More importantly, the group having surgery during the more recent 3 year period also experienced improved overall survival compared to those operated on before the change in approach. These results were obtained with satisfactory outcomes in terms of minor and major operative complications.

Unfortunately, the survival benefit of more radical surgical approaches to ovarian cancer is not currently experienced by most women in the United States. In reporting on 10,432 women with ovarian cancer treated across nine states, Goff found that patients treated by gynecologic oncologists were significantly more likely to undergo cytoreductive procedures compared to those treated by non-specialists. However, only 52 percent of patients were treated by high-volume surgeons who performed at least 10 ovarian cancer cases annually. Moreover, over 30% of patients were not treated by gynecologic oncologists.[9]

In an analysis of state cancer registry data, Chan et al., found only 34 percent of patients received care by a gynecologic oncologist, but those who did had a longer 5 year disease-specific survival compared to those patients who were not treated by a gynecologic oncologist.[10]

In aggregate, the data if quite convincing. The specialty of gynecologic oncology has made significant advances in the safe employment of radical surgical procedures aimed at reducing volume of disease even in advanced cases as illustrated in the studies described above. The specialty has focused intense effort through research and continuing education to improve the rates of complete and optimal cytoreduction for patients nationally. Treatment by the appropriate cancer specialists — a gynecologic oncologist — is the essential first step in ensuring that a woman with ovarian cancer experiences the improved survival afforded by optimal initial surgical effort. Additionally, the likelihood of receiving the recommended standard of care chemotherapy is highest when patients care has included a gynecologic oncologist.

[7] Aletti G, Dowdy S, Gostout BS et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. Obstet Gynecol 107:77-85, 2006.

[8] Eisenhauer EL, Abu-Rustum NR, SonadaY, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. Gynecol Oncol 103:1083-1090, 2006.

[9] Goff BA, Matthews BJ, Larson EH et al. Predictors of comprehensive surgical treatment in patients with ovarian cancer. Cancer 109:2031-42, 2007.

[10] Chan JK, Kapp DS, Shin JY, Husain A, Teng NN, Berek JS, Osann K, Leiserowitz GS, Cress RD, and O'Malley C. Influence of the gynecologic oncologist on the survival of ovarian cancer patients. Obstet Gynecol ;109:1342-50, 2007.

Ovarian Cancer: Germ Cell and Stromal Cell

State of Germ Cell and Stromal Cell Cancers

Germ cell and stromal cell ovarian cancers are rare ovarian cancers. Germ cell cancer starts in the cells that form eggs in the ovary and stromal cell cancer begins in the cells that produce female hormones and hold the ovarian tissues together.

Symptoms: Germ cell and stromal cell cancers can cause pain or discomfort at the beginning stages. Stromal cell cancers can secrete hormones like estrogen or testosterone, and cause symptoms of abnormal uterine bleeding, new onset acne and facial hair growth. Germ cell cancers can become very large and can cause pain or abdominal distension. Some germ cell cancers may produce HCG, the pregnancy hormone, leading to a false positive pregnancy test.

Risk Factors: There are no known risk factors for stromal cell cancer, although there is recent data suggesting that alterations in certain chromosomes may be associated with stromal cell cancers. Rare chromosome abnormalities can cause delayed puberty and menstruation, and an increased risk for germ cell cancers.

Screening/Prevention: There are no known prevention measures for germ cell and stromal cell cancers. Abnormal enlargement of an ovary might be noticed at the time of an annual pelvic examination, increasing the chance for early diagnosis and treatment. Girls who have not started menstruating by age 15 should be evaluated and part of this evaluation should include an analysis of the chromosomal abnormality that could predispose to a germ cell cancer.

Incidence: Only about five percent of ovarian cancers are stromal cell cancers and less than five percent of ovarian cancers are germ cell cancers. Stromal cell cancers are the most common hormonally active tumors. Germ cell cancers are usually found in adolescent girls and young women, with the average age of diagnosis being 18 years. Stromal cell cancers can be diagnosed at any age, with the average age of diagnosis being 45.

Advances in Germ Cell Ovarian Cancer

In 2007, investigators reported a detailed description of germ cell tumor and stromal cell tumor occurrences in the United States by analyzing data in the Surveillance, Epidemiology, and End Results (SEER) national cancer database. Findings from the stromal cell review are discussed in the following section. Using data from 1988–2001, it was reported that patients diagnosed with germ cell cancers later in life fared worse than those diagnosed at a younger age. As expected, patients with advanced-stage tumors and tumors that resembled the yolk sac, a structure seen in the early stages of a developing embryo, had a worse outcome than those patients diagnosed at an earlier stage and without yolk sac appearance of their tumor. Importantly for those patients in whom the uerus and normal ovary were not removed, survival was identical to girls and women who had more extensive surgery, including removal of the uterus, and both tubes and ovaries. Thus, in girls and women with early-stage germ cell cancer who want to have children in the future, conservative surgery that preserves their ability to become pregnant is an appropriate and reasonable option.

A vital area of investigation relates to the quality of life experienced by patients following diagnosis and treatment for germ cell tumors, particularly since this cancer is often diagnosed in women and girls at a young age. Important data regarding the quality of life experienced by survivors of ovarian germ cell cancers was reported in 2007. Patients from four previous Gynecologic Oncology Group (GOG) trials, along with patients enrolled in similar trials through The University of Texas M.D. Anderson Cancer Center, were contacted to participate in this study. At a median of 10 years following their chemotherapy, 132 patients were evaluated for their physical, psychosocial, sexual and spiritual function. In this group of patients, all of whom completed chemotherapy for ovarian germ cell cancers, function in all categories was better in patients who reported better self-confidence and social support. Sexual function was better in younger and married survivors. Neurologic toxicity was common in all patients requiring chemotherapy with platinum drugs and was the strongest factor affecting physical function in the women participating in this study.

These data suggest that clinicians caring for patients with ovarian germ cell cancers should be sensitive to social support and self-confidence in order to promote the highest quality of life following cancer treatment. In a study comparing these women with a matched set of women without ovarian germ cell cancers matched for age, race and education, of those women who remained potentially fertile after surgery, the majority (88 percent) had menstrual cycles. Compared with those women without cancer, cancer survivors experienced greater reproductive concerns and less sexual pleasure, but had a better ability to establish and maintain close relationships.

Currently, researchers are investigating novel approaches to the treatment of patients with ovarian germ cell cancers. Along with the investigation of high-dose chemotherapy with stem cell transplantation, other agents, such as those that target specific cancer-causing changes, are being investigated in clinical trials. Two such agents are sunitinib and bevacizumab, which block the formation of new blood vessels (angiogenesis), thereby limiting tumor growth and spread. These agents are currently being studied in patients with ovarian germ cell cancers.

Advances in Stromal Cell Ovarian Cancer

Stromal cell cancers of the ovary are rare, accounting for only about five percent of all ovarian cancers. Stromal cancers tend to be slow growing tumors and, although they are less likely to recur, they display less sensitivity to chemotherapy when recurrences are detected. These tumors can recur 10 to 15 years or more after first diagnosis. The most common type of stromal cell cancer is granulosa cell tumor. A special subtype, the juvenile granulosa cell tumor principally occurs in girls, whereas the more common adult type may occur at any age, most commonly in the postmenopausal age group.

In 2007, investigators reported data regarding the factors that impact survival of women diagnosed with stromal cell ovarian cancer. Using data from the SEER database, it was recognized that patients diagnosed with stromal cell cancers at an earlier age and with earlier stage disease had a better survival than those patients diagnosed after the age of 50. The age difference was most apparent in patients with early-stage tumors. As with germ cell tumors, the investigators found that in those patients in whom the uterus and unaffected ovary were not removed, survival was identical to that of patients who had more extensive surgery,

including hysterectomy and removal of both ovaries. This is important and good news for girls and women with stromal cell tumors who wish to maintain the option of future pregnancy.

In patients with ovarian granulosa cell tumors, response to therapy has been evaluated using a blood test called inhibin. Rising inhibin levels offer a clue that a granulosa cell tumor may be growing or may have recurred after a period of remission. Scientists have described two different but related inhibin component parts referred to as inhibin A and inhibin B. Recently, investigators have demonstrated that inhibin B may be a better indicator for granulosa cell tumor. In blood samples obtained at the time of first diagnosis, inhibin B levels were elevated in 89 percent of patients while inhibin Alevels were elevated in 67 percent. Though this is a small study, it may lead to better diagnostic testing for this rare tumor.

The Gynecologic Oncologist, and Ovarian Germ Cell and Stromal Cell Tumors

Both ovarian germ cell and stromal cell tumors are rare cancers that can frequently affect women during their reproductive years. Most of these tumors are highly curable, but detailed and specific knowledge regarding the principles of both surgical and chemotherapeutic treatments are required to ensure a woman's best chance for cure with preservation of reproductive function, if so desired. Gynecologic oncologists, because of their 3 to 4 year specialty fellowship training, are uniquely qualified to care for women suffering from these rare ovarian cancers. A recently published analysis of 613 patients with malignant ovarian germ cell tumors from the SEER database revealed the overall rate of lymph node metastasis was 18 percent, with a variance according to the specific cell type of the tumor, and was as high as 28 percent in women with dysgerminoma. Presence of lymph node metastasis was a predictor of poor survival and the authors conclude that lymphadenectomy as part of primary surgical therapy may play an important role in decision making about adjuvant therapy.[11]

For stromal cell tumors of the ovary, a recent review confirms the importance of surgery for staging of primary disease, and for debulking of recurrent disease, particularly for adult granulosa cell tumors.[12] Given the importance of primary surgical staging, including decisions about the risk-benefit ratio of lymphadenectomy in malignant ovarian germ cell tumors, fertility-preservation, when indicated, and complex decision-making regarding type and schedule of adjuvant therapy (chemotherapy or radiation therapy), treatment by the appropriate specialist — a gynecologic oncologist — is critical to ensuring the best outcome for women with malignant ovarian germ cell and stromal cell tumors.

[11] Kumar S, Shah JP, Bryant CS, Imudia AN, Cote ML, Ali-fehmi R, Malone JM, and Morris RT. The prevalence and prognostic impact of lymph node metastasis in malignant germ cell tumors of the ovary. Gynecol Oncol 110:125-132, 2008.

[12] Colombo N, Parma G, Zanagnolo V, and Insinga A. Management of ovarian stromal cell tumors. J Clin Oncol 25:2944-2951, 2007.

Uterine Cancer: Endometrial Adenocarcinoma and Uterine Sarcomas

State of Uterine Cancer

The endometrium is the lining layer of the uterine cavity and most uterine cancers begin because of cancerous changes in the lining. In the most common type of uterine cancer, called endometrial adenocarcinoma, cells in the endometrial lining grow out of control, may invade the muscle of the uterus and sometimes spread outside of the uterus (ovaries, lymph nodes, abdominal cavity).

Uterine sarcomas represent a type of uterine cancer in which malignant cells form in the muscle of the uterus (leiomyosarcoma) or in the network of support cells in the uterine lining (endometrial stromal sarcomas and carcinosarcomas). Accounting for fewer than five percent of all uterine cancers, uterine sarcomas are much less common than endometrial cancer, but have a much more aggressive clinical behavior. These cancers can spread quickly to distant sites.

Symptoms: The most common warning sign for uterine cancer is abnormal vaginal bleeding, and recognition of this symptom often affords an opportunity for early diagnosis and treatment. In older women, any bleeding after menopause may be a symptom of uterine cancer. Younger women should note irregular or heavy vaginal bleeding because they may be symptoms of uterine cancer. Sarcomas can also produce pelvic pain or pressure. In addition, a rapidly growing fibroid, especially during the post-menopausal period, should raise the suspicion of a leiomyosarcoma.

Risk Factors: Risk factors for endometrial cancer include use of estrogen without progesterone, obesity, diabetes, hypertension, tamoxifen use and late menopause (after age 52). Women who have not been pregnant also have a higher risk for endometrial cancer. A strong family history of endometrial or colon cancer may signal an inherited risk for getting endometrial cancer. Sarcomas are twice as common in black women as in women of other racial and ethnic groups, and having pelvic radiation therapy increases the risk of developing this rare type of uterine cancer.

Screening/Prevention: Women with postmenopausal bleeding or heavy, prolonged or unexpected bleeding during the menstruating years should have a biopsy of the endometrium to check for uterine cancer. For women without symptoms, there are no screening tests that are recommended on a routine basis. The Pap test is designed to find cervical cancers and its precursors, not endometrial cancer. Women can decrease their risk of endometrial cancer by exercising regularly, keeping blood sugar and blood pressure under control, and maintaining a healthy weight. Taking progesterone, either alone, or in combination with estrogen in birth control pills, lowers the risk of endometrial cancer. Progestin can prevent cancer from developing in women who have irregular menstrual cycles and infertility. There are no known methods to prevent uterine sarcoma.

Incidence: Cancer of the uterus is the most common reproductive cancer. It is estimated that there will be about 40,100 new cases diagnosed in the United States during 2008, and more than 95 percent of these will be endometrial adenocarcinomas, with approximately 1600 cases of uterine sarcoma. Approximately 7,470 women will die from uterine cancer in the United States during 2008.[13]

Advances in Uterine Cancer

Due to the different behaviors of the varied types of uterine cancer, this discussion will focus on the most common type, endometrial adenocarcinoma, which accounts for 95 percent of the over 40,000 new cases diagnosed this year. Endometrial cancer is one of the more common cancers in women, with only lung, breast and colon cancer being more frequent, and because most endometrial cancers are diagnosed in an early stage, the potential for cure is great.

Surgery is the most important factor in achieving a cure for a woman with endometrial cancer for two reasons: (1) it removes the primary site of the cancer (hysterectomy), and (2) it looks for spread of cancer outside the uterus (staging) that will determine prognosis and need for additional treatment. A complete staging procedure performed by a gynecologic oncologist will allow most patients with uterine cancer to have confidence in their prognosis and avoid the use of adjuvant therapy. During the past year, advances in surgery for endometrial cancer have focused on improving the benefits while reducing the risks of staging by defining which patients will benefit most from removing pelvic and paraortic lymph nodes and expanding the use of minimally invasive techniques (laparoscopy).

Laparoscopic techniques (minimally invasive surgery) are now being used by many gynecologic oncologists for the comprehensive surgical staging of endometrial cancer. A recent survey of members of the Society of Gynecologic Oncologists (SGO) found that 49 percent of those surveyed use laparoscopic surgery to stage their patients. In a recently completed prospective, randomized clinical trial, the Gynecologic Oncology Group (GOG) found patients whose endometrial cancer was staged by laparoscopy had shorter hospital stays, fewer serious complications, and better quality of life outcomes compared to those who were staged by traditional open laparotomy. Survival and recurrence results will not be available until all patients have been followed for 5 years. Some patients in the GOG study were not able to have complete staging laparoscopically because their uterus was too large, they were extremely overweight or experienced other medical problems.

The results of using robot-assisted laparoscopic surgery to stage endometrial cancer in these types of patients was reported by two groups of researchers at the 2008 annual meeting of the Society of Gynecologic Oncologists. Preliminary results of a retrospective study comparing 56 patients who had robotically-assisted laparoscopic hysterectomy (RALH) to 106 who had open hysterectomy, found operating time was longer, but length of stay, blood loss and postoperative complications were lower for patients who had RALH. Retrospectively comparing outcomes for 49 obese and extremely obese women with endometrial cancer who had robot-assisted laparoscopic staging versus 33 women who had standard laparoscopic staging, another group of researchers found shorter operating time, less blood loss, shorter hospital stay and higher numbers of lymph nodes removed in the robotically-staged group.

[13] American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2008.

Accurate prognosis and appropriate treatment recommendations for women with endometrial cancer can only be made based on results of surgical staging that includes removal of pelvic and paraortic lymph nodes (lymphadenectomy). Since the likelihood of spread to lymph nodes increases with the clinical extent of disease, researchers have studied the effect of limiting lymphadenectomy to those patients with the highest risk of metastasis. In a single hospital, prospective trial of over 400 patients where risk of lymph node spread was based on an assessment of tumor size, grade, and depth of invasion into uterine muscle made during surgery, researchers presenting at the 2008 SGO Annual Meeting reported that about 20 percent of women with apparent early-stage endometrial cancer were at low risk and could safely avoid lymphadenectomy. In a retrospective study of over 12,000 patients with endometrial cancer from a state tumor registry, another group of researchers at the 2008 SGO Annual Meeting found that lymphadenectomy was associated with improved survival for both low risk and intermediate risk patients, implying that even patients in the low-risk group derived benefit from full surgical staging.

Recent advances in treatment given to patients with endometrial cancer after surgery, or adjuvant therapy (chemotherapy or radiation therapy) have occurred during the past year based on the results of two prospective randomized, clinical trials. Having shown in a previous trial that radiation prevents cancer recurrences in the vagina and pelvis but does not improve survival compared to no treatment for women with Stage I endometrial cancer, the PORTEC investigators in Europe compared vaginal radiation therapy to whole pelvic radiation to determine which was better for preventing recurrence and quality of life. Presented at the 2008 meeting of the American Society of Clinical Oncology (ASCO), the preliminary results of the 400 patient, PORTEC-2 trial showed lower vaginal recurrence, similar survival and better quality of life for patients treated with vaginal radiation. The researchers concluded vaginal radiation should become the standard of care for in women with intermediate-risk endometrial cancer after primary surgery. A more selective use of vaginal radiation and tumor directed radiation is now advocated along with chemotherapy for women with Stage III or IV disease who are at high risk for death due to recurrent endometrial cancer after primary surgery based on results presented at the 2008 SGO Annual Meeting by the GOG. In a randomized trial of over 500 patients, adding paclitaxel to the standard chemotherapy regimen of doxorubicin plus cisplatin after radiation therapy and surgery in these patients increased side-effects but did not improve survival.

Progress in the treatment of uterine sarcoma has also occurred during the past year as a result of prospective clinical trials. Although not showing a statistically significant advantage, the GOG concluded that combination ifosfamide based chemotherapy should be studied in future trials of adjuvant therapy of carcinosarcoma based on a trend towards lower recurrence and mortality compared to abdominal radiation therapy. Ifosfamide and paclitaxel is currently the most active regimen for carcinosarcomas. For patients with leiomyosarcoma, the two drug combination of gemcitabine and docetaxel became the new standard of care for both first and second-line treatment of metastatic disease with the publication of two GOG Phase II studies showing tumor shrinkage in 36 percent and 27 percent of patients respectively. To improve survival for women with leiomyosarcoma, the GOG soon will activate a prospective randomized trial adding an angiogenesis inhibitor to gemcitabine and docetaxel. Enrollment of patients in these prospective clinical trials by gynecologic oncologists has been very important for the recent improvements in care of women with uterine cancer.

The Gynecologic Oncologist and Uterine Cancer

The staging system adopted by the International Federation of Gynecology and Obstetrics in 1988 classifies endometrial cancer by whether tumor has spread to the fallopian tubes and ovaries, lymph nodes, peritoneal cavity or the upper abdomen. Thus accurate staging of endometrial cancer can only be done by surgery that takes washings of the pelvis, removes pelvic and para-aortic lymph nodes, and examines the upper abdomen in addition to removing the uterus, ovaries and tubes. Through their 3 to 4 years of fellowship training, gynecologic oncologists develop the unique surgical skills necessary to perform complete therapeutic and staging surgery for women with endometrial cancer.

As noted above, an important benefit for the patient is that pathologic information provided by complete and accurate surgical staging is used to determine prognosis and need for additional therapy in women found to have high-risk intrauterine factors for recurrence, or evidence of cancer that has spread outside of the uterus. Perhaps as important as determining which patients do need additional treatment after surgery, thorough surgical staging of an endometrial cancer patient may allow for the avoidance of adjuvant radiation therapy. Cost-effectiveness analysis has demonstrated that avoiding additional treatment, when appropriate for Stage I patients, reduces costs by 31 percent and had minimal effect on survival, but prevents complications from over-treatment.[14]

That primary surgical staging by a gynecologic oncologist in women with endometrial cancer decreases the use of adjuvant radiation therapy was demonstrated in the "real-world" setting by two recent studies. Using data from a community-based health system, Roland et al found that complete surgical staging by a gynecologic oncologist reduced the use of adjuvant radiation therapy by 100% in the patients at lowest risk for recurrence.[15] In a 2005 survey of SGO members that documented that 71 percent of responders performed complete surgical staging of their endometrial cancer patients, Naumann et al also found radiation therapy was recommended less often for endometrial cancer patients by SGO members in 2005 compared to 1999, and vaginal cuff radiation was preferred when necessary.[16] Thus the balance of risks, benefits and costs for additional treatment after surgery may be best decided by the gynecologic oncologist. The additional 30 minutes required for the thorough surgical staging of an endometrial cancer patient may avoid adjuvant radiation therapy. Without surgical staging, the lack of confidence that the patient truly has only Stage I cancer may lead to over-treatment.

One explanation of why survival is improved after surgical staging by a gynecologic oncologist is the possibility of removal of microscopic metastatic disease that is not detectable by standard pathologic assessment. Three recent retrospective studies, each describing a single institution's experience, suggest a potential therapeutic benefit of lymphadenectomy in primary surgery for early endometrial cancer based on improved survival observed in high-risk patients who had

[14] Fanning J, Hoffman, ML, Andrews SJ, Harrah AW, and Feldmeier JJ. Cost-effectiveness analysis of the treatment ofr intermediate risk endometrial cancer: postoperative brachytherapy vs. observation. Gynecol Oncol 93;632-636, 2004.

[15] Roland PY, Kelly FJ, Kulwicki CY, Blitzer P, Curcio M and Orr JW. The benefits of a gynecologic oncologist: a pattern of care study for endometrial cancer treatment. Gynecol Oncol 93;125-130, 2004.

[16] Naumann RW, and Coleman Rl. The use of adjuvant radiation therapy iin early endometrial cancer by members of the Society of Gynecologic Oncologists in 2005. Gynecol Oncol 105;7-12, 2007.

complete surgical staging.[17,18,19] In a retrospective study of over 12,000 women with early endometrial cancer in the SEER database, Chan and colleagues found extensive lymph node resection was associated with improved survival in intermediate/high risk patients.[20] For women presenting with Stage III or IV endometrial carcinoma, retrospective reports suggest the amount of disease left after primary surgery is an important determinant of survival and an aggressive cytoreductive approach similar to that employed for patients with advanced ovarian carcinoma is recommended.[21,22]

Gynecologic oncologists have the unique training and skills to provide complete surgical staging for women with early endometrial cancer, and resection of metastatic disease for women who present with advanced disease. In 1999, the Society of Gynecologic Oncologists Outcomes Committee documented the ability of gynecologic oncologists to safely and effectively perform complete surgical staging on patients with endometrial cancer. In a pilot project of 300 patients undergoing complete surgical staging, the mean length of stay in the hospital was 3.3 days, the operative time was 119 minutes and 8 patients required blood transfusions.[23] A more recent patterns of care study in a community-based health system found gynecologic oncologists provided care for less than half of over 200 consecutive patients with endometrial cancer, but completed surgical staging more frequently than other providers with similar short hospital stay and low complication rates as was observed in the SGO pilot project.[24]

Having care by a gynecologic oncologist benefits women with endometrial cancer through the provision of comprehensive surgical staging which gives important information about their risk for cancer recurrence. Armed with this knowledge, the patient and her gynecologic oncologist can make informed and appropriate choices about whether to get radiation therapy or chemotherapy after surgery. Gynecologic oncologists have been and will continue to be leaders in clinical trials to expand the use of minimally invasive surgical techniques and develop new treatments for women with advanced and recurrent disease.

---

[17] Abu-Rustum NR, Iasonos A, ZhouQ, Oke E, Soslow RA, Alektiar KM, Chi DS, and Barakat RR. Is there a therapeutic impact to regional lymphadenectomy in the surgical treatment of endometrial carcinoma? Am J Obstet Gynecol 198;457.e1-457.e6, 2008.

[18] Cragun JM, Havrilesky LJ, Calingaert B, Synan I, Alvarez Secord A, Soper JT, Clarke-Pearson DL and Berchuck A. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. J Clin Oncol 23:3668-3675, 2005.

[19] Bristow RE, Zahurak ML, Alexander CJ, Zellars RC, and Montz FJ. FIGO stage IIIC endometrial carcinoma: resection of macroscopic nodal disease and other determinants of survival. Int J Gynecol Cancer13;664-672, 2003.

[20] Chan JK, Cheung MK, Huh, WK, Osann K, Husain A, Teng NN, and Kapp DS. Therapeutic role of lymph node resection in endometrioid corpus cancer, a study of 12,333 patients. Cancer 107;1823-1830, 2006.

[21] Bristow, RD, Zerbe MJ, Rosenshein NM, Grumbine FC, and Montz, FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol 78; 85-91, 2000.

[22] Lambrou NC, Gomez-Marin O, Mirhashemi R, Beach H, Salom E, Almeida-Parra Z and Penalver M. Optimal surgical cytoreduction in patients with Stage III and Stage IV endometrial carcinoma: a study of morbidity and survival. Gynecol Oncol 93;653-658, 2004.

[23] Kennedy AW, Austin JM, Look KY, and Munger CB. The Society of Gynecologic Oncologists Outcomes Task Force Study of Endometrial Cancer: Initial Experiences. Gynecol Oncol 79;379-398, 2000.

[24] Roland PY, Kelly FJ, Kulwicki CY, Blitzer P, Curcio M and Orr JW. The benefits of a gynecologic oncologist: a pattern of care study for endometrial cancer treatment. Gynecol Oncol 93;125-130, 2004.

Vaginal Cancer

State of Vaginal Cancer

Vaginal cancer originates in the vagina, usually in the squamous epithelium (lining). It is usually diagnosed in older women and radiation is the most common treatment.

Symptoms: Vaginal cancer, especially at precancerous and early stages, may not cause any symptoms. Common symptoms of more advanced stages include bleeding, pain, or problems with urination or bowel movements.

Risk Factors: Risk factors for vaginal cancer include HPV (Human Papillomavirus) infection, smoking, age (60 years and older), and prior treatment for cervical or vulvar cancer. The daughters of women who took DES (a hormone medication used many years ago to prevent miscarriage) while pregnant are at increased risk for both vaginal and cervical cancer.

Screening/Prevention: Many precancerous conditions and early vaginal cancers can be detected through routine pelvic exams and Pap tests. Because the FDA approved cervical cancer vaccine offers protection against HPV types that are also associated with many vaginal cancers, vaccination may reduce the risk of vaginal cancer.

Incidence: Vaginal cancer is very rare. It is estimated that there will be about 2,210 new cases diagnosed and 790 deaths from vaginal cancer in the United States during 2008.[25] Vaginal cancer accounts for about 3 percent of reproductive cancers.

Advances in Vaginal Cancer

Because of its rarity, it is not possible to conduct large clinical studies in patients with vaginal cancer, comparing one form of treatment with another. Therefore, much of what is understood in vaginal cancer treatment is borrowed from clinical trials in related other cancers, including vulvar and cervical cancer.

Although most women with vaginal carcinoma are past child-bearing years, many women with DES-associated vaginal cancers are young. Standard treatments for vaginal cancer can cause young women to loose the option of having children, but a recent report showed that fertility-sparing surgery is possible in carefully selected patients even when the vaginal tumor extends to and requires removal of the cervix. Another advance in surgical therapy for vaginal cancer includes the adoption of a minimally invasive approach. Surgeons are demonstrating that laparoscopic techniques for surgical evaluation with lymph node biopsy may be utilized to select patients with localized disease for tumor excision, or to precisely define radiation treatment fields to permit protection of normal organs during radiation treatment.

Visualizing vaginal cancer with imaging tests can be difficult because of the other organs located near the vagina in a woman's body including the uterus, bladder and rectum. One recent study evaluated magnetic resonance imaging (MRI) of vaginal cancer and showed that MRI correctly identified over 95 percent of the tumors, and correctly demonstrated disease that involved tissues beyond the vagina in 88 percent of patients. MRI staging correlated very well with survival. Thus, for patients with advanced disease, staging may allow a treatment plan to be enacted without need for surgery.

[25] American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2008.

Positron emission tomography (PET) in combination with MRI (or CT scans) may be an even better method to image vaginal cancer. A recent study evaluated PET prior to a planned radical surgery to remove recurrent cervical or vaginal cancer. PET was found to have a sensitivity of 100 percent in detecting sites of cancer beyond the pelvis with 73 percent specificity. These findings are particularly important for women with vaginal cancer because PET imaging may, in a non-invasive fashion, identify otherwise non-detectable metastasis, sparing some patients unnecessary surgical procedures and allowing others to receive radiation treatment to a smaller area.

Most patients with vaginal cancer are treated with radiation therapy. Radiation therapy alone is an effective treatment for early vaginal cancer; however, results with radiation therapy for more advanced vaginal cancers are not uniformly good and better treatments are needed. For some cancers, if chemotherapy is given along with radiation therapy, cancer control rates and survival significantly improve. Similar to results seen in large clinical trials of women with cervical cancer, a recent study shows that by giving chemotherapy at the same time as radiation to women with vaginal cancer, cancer control rates and survival are improved with an acceptable level of side-effects.

It is hoped that the integration of PET with other new imaging methods may improve the accuracy of surgery or radiation treatment planning, resulting in improved survival and reduced treatment-related side-effects for women with vaginal cancer. The addition of simultaneous chemotherapy can also improve the effectiveness of radiation therapy for this disease. Since HPV is a risk factor for many vaginal cancers, it is hoped that the widespread use of HPV vaccines will reduce the incidence of this rare gynecologic cancer in the future.

The Gynecologic Oncologist and Vaginal Cancer

Vaginal cancer is a very rare type of gynecologic cancer that requires special expertise to make the diagnosis, evaluate the extent of disease and develop a plan for treatment. Gynecologic oncologists undergo 3 to 4 years of specialty fellowship training to acquire the skills needed to evaluate and treat all gynecologic cancer including vaginal cancer. Every woman with known or suspected vaginal cancer should seek treatment from the appropriate specialist — a gynecologic oncologist — to ensure she has the best chance for cure.

Vulvar Cancer

State of Vulvar Cancer

Vulvar cancer is caused by the growth and spread of abnormal cells within the skin of the labia and perineum.

Symptoms: Itching, burning, bleeding, pain, or a new lump or ulcer in the genital area are common symptoms.

Risk Factors: Infection with Human Papillomavirus (HPV) is a common cause of vulvar cancer in young women. Vulvar cancer in older women is associated with chronic vulvar irritation from any source.

Screening/Prevention: Protection from infection with HPV (Human Papillomavirus), including an HPV vaccination, may reduce the risk of vulvar cancer. Examination of the vulva for changes by a woman at home or by her gynecologist during her yearly pelvic exam may lead to early detection of vulvar cancer. Suspicious or unexplained changes on the vulva should be biopsied.

Incidence: Vulvar cancer is uncommon. It is estimated that there will be about 3,460 new cases diagnosed and approximately 870 deaths from vulvar cancer in the United States during 2008.[26] Vulvar cancer is usually diagnosed in the early stages and is most often cured with surgical treatment.

Advances in Vulvar Cancer

Although vulvar cancer can often be cured with surgery, the side-effects of the procedures traditionally used to treat this rare cancer have a major impact on quality of life. Advances in surgical techniques and strategy have improved the lives of women with vulvar cancer by preserving sexual function, reducing surgical wound complications and reducing the condition of chronic swelling of the legs, called lymphedema. These advances have been achieved by performing less radical surgeries that preserve more of the normal tissue of the genital area.

Results from a recent study showed that cure rates for women with early-stage vulvar cancer treated with less radical surgery today are as good as the survival seen in women treated with the more extensive procedures that were standard 20 years ago. In spite of these improvements in surgery for vulvar cancer, problems remain, including accurate identification of patients whose cancer has spread to the groin lymph nodes and the lymphedema that results from inguinal femoral lymphadenectomy. Lifelong lymphedema is especially frustrating for patients and care-givers when it occurs in patients with lymph nodes free of cancer. To find new ways to treat this frustrating complication, the Gynecologic Oncology Group (GOG) has recently activated GOG trial 236, a prospective randomized Phase III trial comparing a new device for manual therapy for lymphedema that results from treatment for a gynecologic cancer.

One of the most significant advances in surgical oncology, sentinel lymph node biopsy, offers the potential to improve detection of node positive patients and reduce the risk of lymphedema. The sentinel lymph node is the node that is most directly connected to the tumor through the lymph channels, and it is the most common site to which cancer cells spread. The sentinel lymph node

[26] American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2008.

can be found with a technique called lymphatic mapping. This strategy has been used successfully in patients with breast cancer and melanoma to improve the detection of metastatic disease, and avoid extensive lymph node resection and the associated lymphedma in selected patients.

This is a landmark year in the care of women with vulvar cancer because a large study has found that sentinel lymph node biopsy is safe in patients with vulvar cancer. A group of Dutch investigators designed a study in which patients with early-stage vulvar cancer had lymphatic mapping and sentinel node biopsy performed by a skilled team of doctors including a nuclear medicine specialist, a pathologist and a gynecologic oncologist. Each hospital had to perform at least 10 cases that were reviewed by the primary investigators before they could enroll a patient on this study. They assumed that with the standard surgery the risk of a recurrence in the groin following a standard lymphadenectomy with negative nodes was 2 percent. They constructed a statistical design to ensure the safety of patients enrolled in the study. If the sentinel node was positive, the patient received additional treatment. They followed 202 sentinel node biopsy negative patients for 2 years. Eight patients relapsed in the groin (2.9 percent). Six of these patients died of the relapse in spite of additional treatment. The authors had suggestions that they believe could reduce the relapse rate to 2.3 percent about the same as has been seen in earlier studies using standard surgery for lymph node removal in the groin. A second large study sponsored by the GOG and conducted in North America is near completion.

Patients with vulvar cancer should ask their gynecologic oncologist about sentinel lymph node biopsy. It could be that only half the patients with vulvar cancer are good candidates for the sentinel lymph node procedure. The patient and her gynecologic oncologist should have a candid conversation about her risk tolerance and experience before proceeding with sentinel node biopsy.

Another area of progress in the treatment of vulvar cancer is the use of a combination of types of therapy for more advanced-stage tumors. This strategy holds great promise for patients who have large tumors or disease that has spread to lymph nodes. Results from a recent analysis of five vulvar cancer trials in women with advanced-stage cancer showed that treating women with the combination of chemotherapy and radiation before surgery can shrink the size of the tumor and reduce the extent of surgical resection. This strategy helps preserve organ function for patients who might have lost rectal, bladder or sexual function from surgical therapy alone. Another new technology being studied in the treatment of vulvar cancer is intensity modulated radiation therapy (IMRT). IMRT allows the radiation oncologist to vary the intensity of each beam of energy both in space and time, and provide a dose that more closely conforms to the contours of the tumor, with less dose of radiation to normal tissues. A recent report of combining IMRT with chemotherapy for patients with locally advanced vulvar cancer before surgery showed good tumor response and lower toxic effects to normal tissues.

The Gynecologic Oncologist and Vulvar Cancer

Gynecologic oncologists spend 3 to 4 years in specially designed fellowship training to acquire the surgical and diagnostic skills to care for women with all gynecologic cancers, including vulvar cancer. Because of the rarity of vulvar cancer and the particular challenges with regards to radical surgery on the vulva, including preservation of form and function as well as the requirement for removal of lymph nodes from the groin as part of staging, all women with vulvar cancer should receive care from the appropriate specialist — a gynecologic oncologist — in order to ensure their best chance for cure.

Legislative Update

Please support the gynecologic cancer community in its Federal legislative efforts aimed at encouraging additional government support of gynecologic cancer research, education, prevention, early detection and treatment.

Ovarian Cancer Biomarkers Research Act of 2007 (H.R. 3689/S. 2569) Introduced by Congressmen Howard Berman (D-CA) and Ralph Hall (R-TX) and Senators Barbara Boxer (D-CA) and Elizabeth Dole (R-NC), this bill would amend the Public Health Service Act to authorize the Director of the National Cancer Institute to make grants for the discovery and validation of biomarkers for use in risk stratification for, and the early detection and screening of, ovarian cancer. This bill currently has 77 cosponsors in the House of Representatives and 17 cosponsors in the Senate.

Comprehensive Cancer Care Improvement Act of 2007 (H.R. 1078/S. 2790) Congresswoman Lois Capps (D-CA) and Senator Mary Landrieu (D-LA) introduced this legislation that provides for coverage of comprehensive cancer care planning under the Medicare program, and improves the care furnished to individuals diagnosed with cancer by establishing a Medicare hospice care demonstration program and grants for cancer palliative care and symptoms management programs, provider education, and related research. This bill has 108 cosponsors in the House of Representatives and four cosponsors in the Senate.

Cancer Screening, Treatment & Survivorship Act of 2007 (H.R. 2353/S. 1415) Introduced by Congresswoman Janice Schakowsky (D-IL) and Senator Tom Harkin (D-IA) this legislation seeks to amend the Public Health Service Act and the Social Security Act to improve screening and treatment of cancers; provide for survivorship services; and similar other purposes. This bill has 98 cosponsors in the House of Representatives and 13 cosponsors in the Senate.

Access to Cancer Clinical Trials Act of 2007 (H.R. 2676/S. 2999) Congresswoman Deborah Pryce (R-OH) and Senator Sherrod Brown (D-OH) introduced this bill to amend the Public Health Services Act, the Employee Retirement Income Security Act of 1974, and the Internal Revenue Code of 1986 to require group and individual health insurance coverage and group health plans to provide coverage for individuals participating in approved cancer clinical trials. This bill has 35 cosponsors in the House of Representatives and two cosponsors in the Senate.

Medicare Cervical Cancer Screening and Detection Coverage Act of 2007 (H.R. 4055) Introduced by Congresswoman Rosa DeLauro (D-CT), the bill would amend title XVIII (Medicare) of the Social Security Act to provide for Medicare coverage of screening tests for Human Papillomavirus (HPV) associated with a higher risk of cervical cancer.

To educate your Members of Congress regarding the importance of these proposed pieces of legislation, please call the Capitol Hill Switchboard at 202.225.3121 and ask to be connected to his or her office. Ask to speak with the staff handling healthcare issues and share with the staff how important the legislation you are calling about is to you, patients and their families and friends. Ask them to follow-up with you regarding the Member of Congress' decision to cosponsor the bill.

If you have any questions or need additional information, please do not hesitate to contact SGO Director of Government Relations, Jill Rathbun at jill_rathbun@galileogrp.com.

Acknowledgements

We would like to thank that following members of the Society of Gynecologic Oncologists (SGO) for contributing to the *State of the State of Gynecologic Cancers* sixth annual report. These individuals generously shared their knowledge and expertise regarding the latest information and advances in gynecologic cancers to make this report as accurate and timely as possible. Each of these physicians and gynecologic cancer specialists is actively involved in clinical practice and research to develop innovative treatments for gynecologic cancers.

Medical Editor

Carol L. Brown, MD
Associate Attending Surgeon
Memorial Sloan-Kettering Cancer Center
New York, NY

Editor

Marsha Tanner Wilson, MPH
Director of Communications
Gynecologic Cancer Foundation
Chicago, IL

Contributors

William A. Cliby, MD
Associate Professor
Gynecologic Surgery
Mayo Clinic
Rochester, MN

Beth Y. Karlan, MD
Director, Gynecologic Oncology
Professor of Obstetrics & Gynecology
Cedars-Sinai Medical Center-UCLA
Los Angeles, CA

Charles Levenback, MD
Associate Professor
The University of Texas M.D. Anderson Cancer Center
Houston, TX

Carolyn Muller, MD
Division Director of Gynecologic Oncology
University of New Mexico
Albuquerque, NM

Joan Walker, MD
Professor & Section Chief of Gynecologic Oncology
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Gynecologic Cancer Foundation

Awareness. Education. Research.

230 W. Monroe, Suite 2528
Chicago, IL 60606
312.578.1439
info@thegcf.org
www.thegcf.org
www.wcn.org

230 W. Monroe, Suite 710
Chicago, IL 60606
312.235.4060
sgo@sgo.org
www.sgo.org

Content developed by the Gynecologic Cancer Foundation. Printing made possible by AMGEN.

SOS-E-2008