

**2009 State of the State
of Gynecologic Cancers**

Seventh 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 of physicians who are trained in the comprehensive management of women with malignancies of the reproductive tract. Its purpose is to improve the care of women with gynecologic cancers by encouraging research and disseminating knowledge which will raise the standards of practice in the prevention and treatment of gynecologic malignancies, and cooperating with other organizations interested in women's health care, oncology and related fields. The Society's membership, totaling more than 1290, is primarily comprised of gynecologic oncologists, as well as other related medical specialists including medical oncologists, radiation oncologists and pathologists. SGO members provide multidisciplinary cancer treatment including chemotherapy, radiation therapy, surgery and supportive 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) was formed by SGO in 1991 as a 501(c) 3 not-for-profit organization whose mission is to ensure public awareness of gynecologic cancer prevention, early diagnosis and optimal 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.

To take a confidential risk assessment to learn about your risk for developing gynecologic and breast cancer, please visit GCF's Women's Cancer Network at www.wcn.org. There you can also find comprehensive information about each of the cancers unique to women.

The site 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.

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Fitness and Moving Forward

By Jenn Sommermann

Being fit truly saved my life, and maybe not in the way you would expect. I did not have cardiovascular disease, I had ovarian cancer. And, had I not had the body awareness to tell me something was different, I might not be writing this today.

I have always been an active person but didn't really consider myself an athlete until I turned 40 in 2004. My best friend decided since we both were turning 40, we needed to do a triathlon — an event that combines running, swimming and biking. We chose the Danskin triathlon in Seattle, an all women's race designed for first timers. Unlike my friend, I fell in love with the sport immediately and participated in four events that year. I had been bitten by the fitness bug and there was no turning back.

The next year, 2006, my passion for the sport literally saved my life. Without it, I would not have had the body awareness to detect my tumor, Stage III ovarian cancer. That was in December and treatment was scheduled to take place through June 2007. What of my triathlon season for the summer of 2007? Would I be able to compete in the races I had registered for? Would I be well enough to exercise through my treatment? No one knew. There is no exact science for this. “*Listen to your body,*” was what the doctors told me.

And this is my message to other women — “listen to your body.” If something doesn't seem right, speak up. Ask your doctor. If you have these recognized symptoms of ovarian cancer — bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, urinary symptoms (urgency and frequency) — ask that a diagnosis of ovarian cancer be considered. While most women with these symptoms will not have ovarian cancer, the hope is that for those who do, a diagnosis will be made sooner with the chance of cure is greater.

It took a solid year for me to get my strength back after my treatments. My recovery focused on moving forward and focusing on my fitness. I was determined to reclaim my body and my identity. I no longer wanted to be solely defined by my cancer.

I urge each of you to find a fitness program that is right for you, even if it is just a short walk every day. Not everyone will embrace triathlons, but we all need to learn to communicate with our bodies. And when it talks to you, please listen because it could literally save your life as did mine.

Jenn Sommermann is competing in 50 triathlons in 50 states to raise money for the Ovarian Cancer Research Fund.

Gynecologic Cancer Awareness Movement Weekend

November 6–8, 2009, Washington, DC

By G. Larry Maxwell, MD

As gynecologic oncologists, our lives are filled with clinical responsibilities, research activities and administrative obligations that must be balanced with our commitment to a strong and healthy family life. Limitations of time often prevent many of us from making a contribution to the specialty, while others find time to serve on committees or in leadership positions that facilitate the governance of our specialty's organizations. How can our specialty's membership at large, particularly those with time restrictions, make a meaningful contribution to the future of our specialty and the women we serve? ANSWER: by participating in the Gynecologic Cancer Awareness Movement (GCAM).

The GCAM Weekend, scheduled for November 6–8, 2009, in Washington D.C., will feature multiple events aimed at education of physicians, scientists and the public about issues concerning gynecologic cancer. The Society of Gynecologic Oncology will host a State of the Art Course for professionals that will focus on individualized patient care using molecular profiles for diagnostic tools and targeted biologic therapeutics.

For the first time, the Gynecologic Cancer Foundation will host three free concurrent survivor courses for survivors of cervical, endometrial and ovarian cancer, and their family and friends. Over 750 participants are expected and for those unable to attend.

The GCF Race to End Women's Cancer, the inaugural GCF Half Marathon/5K Run/1 Mile Walk, will provide an opportunity for over 2,000 participants to join together in a unique event honoring survivors and patients who battle gynecologic cancer, as well as to commemorate the memories of women that have lost their battle with their disease. A Surgeons Team of approximately 100 gynecologic oncologists is currently training for the event in an effort to honor the women they serve. An expo at the event will provide a forum for advocacy groups to disseminate educational materials to those in attendance.

The weekend of activities will climax in a post-race festival that will celebrate the Gynecologic Cancer Sisterhood of Survivorship. The band, "No Evidence of Disease," or N.E.D, consisting of six gynecologic oncologists, will provide musical entertainment. There will be an educational program and an opportunity to congratulate each individual who ran or walked to foster awareness about the prevention, early detection and optimal treatment of women's cancer.

The Gynecologic Cancer Awareness Movement Weekend represents an opportunity for gynecologic cancer healthcare providers and scientists to unite with survivors, and their families and friends, in an effort to promote gynecologic cancer education at an unprecedented level in our Nation's Capital.

Through unity and participation, our specialty's members can create awareness through a new approach that will positively impact our patients, our specialty and the public. It's time for us to stand up and make a difference.

Survivorship Teams

Women and Physicians Working Together to Improve Health and Well-Being After Gynecologic Cancer

By Diane C. Bodurka, MD

A 2007 study commissioned by the American Society of Clinical Oncologists predicts an 81% increase in people living with or surviving cancer by the year 2020. This translates to an estimated 19 million cancer survivors. According to the American Cancer Society, of the more than 80,000 women newly diagnosed with a gynecologic cancer next year, nearly 70%, or more than 50,000 women, will be cancer survivors.

Although the National Coalition for Cancer Survivors was founded in 1986, cancer survivors and survivorship have become a new priority for many, including patients, clinicians and elected officials. The term “survivor” has been expanded to include the moment of cancer diagnosis through the balance of life. Family members and caregivers are also impacted by the survivorship experience and are therefore included in this definition. Survivorship is defined as the period of health and well-being experienced by cancer survivors after cancer treatment. Recognizing the significance of this issue, the Institute of Medicine and Centers for Disease Control initiated a “Call to Action” and presented 23 needs which must be met in order to successfully address the issue of survivorship.

Survival rates are increasing for women with gynecologic cancers, including those with endometrial, ovarian, and cervical disease. More energy is now being devoted to assessing issues pertinent to survivors and focusing on quality of life (QOL), both during and after treatment. A recent study of more than 800 gynecologic cancer survivors asked women to rate key health issues important to them as survivors. The women ranked fatigue as the primary issue, followed closely by sexual problems, then bowel and urinary problems. Although many survivors report a high overall quality of life, more than 20% noted long-term side-effects from their cancer treatment including hearing loss, neurotoxicity and depression. More than half of the women surveyed indicated a strong interest in support groups, illustrating the importance of emotional and psychological well-being to their quality of life as cancer survivors.

Although the benefits of regular exercise to improving general health and well-being were first described many years ago, the impact of exercise upon cancer survivorship is a new and important topic of interest and research for both survivors and their healthcare providers. In terms of gynecologic cancers, most of the research on exercise and survivorship has focused on women with endometrial and ovarian cancer.

Endometrial cancer is the most common gynecologic cancer affecting women in the United States today. Of women with early stage endometrial cancer approximately 70% are obese, and obesity is a significant risk factor for the development of this disease. Unfortunately the number of women diagnosed with endometrial cancer each year is rising, and this increase in new cancers is likely related to the rising rates of obesity in the U.S. population. A recent study revealed that women with endometrial cancer who were obese had higher mortality rates from causes not related to their malignancy, such as heart disease and diabetes. Traditionally, research has focused upon finding ways to help women complete treatment safely in spite of these obesity-related illnesses. Now, investigators are focusing not only upon QOL during treatment, but also upon improving the overall health of these women after treatment. Interventions have been developed to decrease the impact of long-term treatment-related side effects. Programs which increase the rate of exercise in endometrial cancer survivors have recently been proven to be feasible, and exercise actually increased these patients’ overall health and quality of life. Practical interventions such as measuring physical activity with a pedometer, a device which counts the number of steps taken,

completing a food diary, participating in nutrition counseling and establishing support groups have improved the health and overall well-being, and increased the QOL of women with endometrial cancer. These practical steps to increase physical activity have also been studied in ovarian cancer survivors and been shown to be successful, again validating the importance of exercise, nutrition and emotional support in women who are gynecologic cancer survivors.

Nutrition is another key element of cancer survivorship. Women who have been treated with surgery and/or radiation can experience specific gastrointestinal-related side-effects including diarrhea, at times long after treatment has been completed. Identification of these bowel-related problems and having appropriate nutritional counseling and support is coming to the forefront of concerns for women with gynecologic cancer, and more research on the impact of nutrition on survivorship is needed. Research studies have shown that more than 90% of patients in gynecologic oncology clinics use complementary and alternative medicine approaches, both during and after their cancer treatment. No longer are patients or doctors satisfied with the limited data exploring the impact of alternative medicines upon cancer treatment and survivorship and this is yet another new research focus in gynecologic cancer.

Sexual health is another issue gynecologic cancer survivors have identified as a major area of concern, especially after treatment. Unfortunately, physicians and health care providers do not uniformly address sexual concerns with their patients, and women are often reluctant to raise such issues with their providers. A significant amount of work is currently underway to help improve the dialogue between patients and clinicians regarding this topic of such importance to gynecologic cancer survivors. Studies focusing on ways to identify and reduce treatment-related sexual health side effects are ongoing. A significant focus of recent research on the sexual and reproductive health of cancer survivors has been the use fertility-sparing treatments including surgery. For selected young women with early stage ovarian, endometrial, and cervical cancer fertility-sparing surgery has been shown to be a safe and viable option for cancer treatment that preserves a critical component of their ongoing quality of life.

We have entered an exciting time in the field of gynecologic oncology when women with gynecologic cancers are living longer and achieving a cure much more frequently than in the past. Such progress has led to a new focus on survivorship. Our challenge is to focus our ongoing and future research on identifying key issues important to gynecologic cancer survivors and meaningful interventions to address these concerns. When patients and clinicians work together as a “Survivorship Team,” women with gynecologic cancers will not only live longer, but also thrive with better overall health and quality of life.

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 80,000 new cases diagnosed and approximately 28,000 deaths from gynecologic cancers in the United States during 2009.¹

¹ American Cancer Society. Cancer Facts & Figures 2009. Atlanta: American Cancer Society; 2009.

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 before they become sexually active (currently recommended at 11 and 12 years of age) 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.

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. A recent study shows that even for women with HIV, thought to be at high risk for cervical cancer, appropriate screening with Pap tests may eliminate the increased risk.

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%. 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 (examination of the cervix using a magnifying device to see the cervix more clearly) 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.

Major educational efforts are being directed toward the appropriate approach to cervical cancer screening in adolescent girls (less than 21 years of age). Sexually active girls and young women frequently have HPV infections and will even have abnormal Pap tests. Many of these young women will have spontaneous resolution of their infections and abnormal Pap test without the need for their gynecologists to intervene. This is not the case for older women, and there is a growing concern that young women, less than 21 years of age, may be over treated for abnormal Pap tests that could have an impact on fertility. This topic will be addressed through several policy and consensus statements over the next few years.

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 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. A second vaccine was approved by the FDA in October 2009. 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 4,070 deaths in the United States during 2009.²

Advances in Cervical Cancer

Cervical cancer prevention and treatment efforts continue to demonstrate medical advances based on group efforts in both laboratory research and clinical trials. 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. Both of the existing HPV vaccines protect against infection with HPV types 16 and 18.

The results of several large clinical trials demonstrate the effectiveness of vaccines to prevent HPV infection and HPV related disease. When widespread vaccination has been achieved, cervical cancer should be reduced by over 70%. Because HPV vaccination 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, ideally before first intercourse, and young women age 13-26. Newer vaccines that provide immunity against a greater number of HPV types are under development with the hope of preventing over 90% of cervical cancer.

² American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2009.

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.

Clinical trials are currently ongoing to study the role of HPV vaccines in treating women already infected with HPV and women 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 vaccines that treat as well as prevent cervical cancer are important.

Progress continues to be made in developing better treatments for women with invasive cervical cancer. A fertility-sparing surgery called trachelectomy (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. In the past year several reports have described new approaches to these fertility-sparing surgeries. Traditionally performed through a vaginal incision, the procedure is now being done through abdominal incisions and by laparoscopic (minimally invasive) surgery. These advances are giving more young women in this country access to this new approach to the surgical management of cervical cancer that preserves an important part of their quality of life.

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 women who have minimally invasive surgery spend less time in the hospital and have less blood loss compared to women who have cervical cancer surgery with the standard “open” technique. However, because these techniques have only come into more widespread use in the last few years, there is little data on long-term effects on quality of life and late complications from minimally invasive surgery for cervical cancer currently available. A large, prospective clinical trial has begun that will attempt to answer these very important questions. This study may take many years to complete, but if successful will offer important information to optimize care and minimize side effects for women with early stage cancer.

For women with advanced-stage cervical cancers, treatment with a combination of radiation therapy and chemotherapy remains the standard of care. The National Cancer Institute issued a clinical alert in 1999 to emphasize the importance of combination therapy for the treatment of advanced cervical cancer. A long term follow-up of women who participated in the clinical trials that tested combination therapy confirms that those treated with radiation and chemotherapy continue to have a higher survival rate than women treated with radiation alone. Further, studies suggest that continued additional chemotherapy after radiation may improve survival even further. New studies have also identified alternative chemotherapy drugs that improve survival with potentially fewer harmful side effects from the drugs that have been traditionally used with radiation.

Recent advances in the ability to detect cervical cancer when it has spread outside of the pelvis include the new data demonstrating the accuracy of PET/CT scans to find disease that has spread away from the cervix, especially cancer located in lymph nodes outside the pelvis. Improved imaging of cervical cancer allows more accurate and targeted planning of the boundaries for radiation treatment, which minimizes effects of radiation on normal tissues. PET/CT scan has also been shown to be an accurate monitor of how a woman’s cervical cancer is responding to radiation treatment and can help detect recurrence before symptoms alert a woman or her gynecologic oncologist that the cancer may have returned.

A challenge in the treatment of cervical cancer has been the management of women who experience a recurrence of their cancer after being treated initially with surgery, or the combination of radiation and chemotherapy. Recent studies have shown that anti-cancer drugs known as biological agents, drugs that

block growth signals to cancer cells, may be effective against recurrent cervical cancer. Earlier this year the Gynecologic Oncology Group (GOG) reported the results of a clinical trial that showed a biologic agent called bevacizumab, that blocks new blood vessel growth in cancer, was effective in shrinking tumors in some women with recurrent cervical cancer. Based on the encouraging results of that trial, the GOG has recently opened a prospective randomized trial to find out if combining bevacizumab with chemotherapy will be effective in treating recurrent cervical cancer. It is hoped that new biologic approaches like these will play an important role in future clinical trials designed to improve the survival of women with recurrent cervical cancer.

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. A personal history of premenopausal breast cancer, or a family history of epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer or premenopausal breast cancer are important risk factors.

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 CA125 blood tests on an annual or biannual schedule, though the benefits of such screening is unproven. For most women, ultrasound and CA125 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 21,550 new cases diagnosed and approximately 14,600 deaths from ovarian cancer in the United States during 2009.³

³ American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2009.

Advances in Ovarian Cancer

Basic Biology

Over the past year there have been many important advances in ovarian cancer research. One of the most interesting discoveries is that some “ovarian cancers” — especially those in women with BRCA1 and BRCA2 genetic mutations — actually start in the fallopian tube. Researchers at Harvard Medical School found that most cancers detected in high-risk women who are having their tubes and ovaries removed to prevent cancer arise in the fallopian tube. These research groups also found possible precancerous areas in normal fallopian tubes of women who have the BRCA1 or BRCA2 gene. If additional research confirms that the fallopian tube is truly the origin of some “ovarian cancers,” then clinicians may need to change their approach to ovarian cancer screening and risk-reducing surgery.

Another basic science development was recently reported of importance to women with with ovarian cancer and the BRCA1 or BRCA2 gene. Tumor cells that have BRCA1/2 mutations are more sensitive to both platinum-based chemotherapy and a new class of drugs called PARP inhibitors. At the 2009 Society of Gynecologic Oncologists (SGO) Annual Meeting, research was presented that showed BRCA mutated tumor cells that initially could not make the BRCA protein were restored to normal BRCA protein expression through a second mutation to the gene. These double-mutated BRCA cancer cells were able to resist both platinum chemotherapy and the PARP inhibitors. This research may provide tools that allow clinicians to predict when ovarian cancer patients will respond to specific drugs. This furthers our ability to individualize cancer treatment based on the specific properties of a patient’s tumor.

Screening and Early Detection

Preliminary results from both the Prostate, Lung, Colorectal and Ovarian Cancer screening trial (PLCO) and the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) were reported in 2009. These are the two largest prospective randomized trials to evaluate screening for ovarian cancer.

In the PLCO trial, women who were screened for ovarian cancer with a yearly transvaginal ultrasound (TVS) and CA125 were compared to women who had no screening tests performed. Of the 34,261 postmenopausal women screened over a 4 year period, there were 89 invasive cancers diagnosed, 60 of which were detected by screening. Unfortunately, most of the cancers found by screening (72%) were late stage. The positive predictive value was less than 1% for TVS and only 2-3% for CA125, even by the fourth time a woman was screened. For each case of ovarian cancer detected by screening, 19 women had to undergo a surgical procedure.

In March 2009, the UKCTOCS trial published the results of their initial (prevalence) screening. Between 2001 and 2005 a total of 202,638 postmenopausal women were randomly assigned to three study groups: a) no screening; b) annual CA125 interpreted with a risk of ovarian cancer formula and with TVS as a secondary screen (multimodal screening [MMS]); or c) annual screening with TVS. The risk of ovarian cancer formula takes into account the baseline CA125, the patient’s age and rate of change in CA125 concentration. Screening led to surgery in 0.2% of women screened with MMS and in 1.8% of women screened with TVS alone. Primary ovarian cancers were detected in 42 of the MMS and 45 TVS screened patients. Early stage tumors were found in 47.5% of the MMS screened patients and 50.0% of the TVS screened patients. Although the initial results of screening by the MMS method are encouraging in terms of specificity and cancers being found in an early stage, more data is needed to determine if these approaches to screening reduce the number of women who die from ovarian cancer as well as how many women undergo unnecessary surgery to achieve the screening results.

One of the biggest challenges in screening for ovarian cancer is that the incidence in women over 50 is only 40 out of every 100,000 women. So, even with a perfect screening test, 2,500 women need to be screened to detect one case of ovarian cancer. This makes designing a cost-effective screening test a challenge. Investigators at the University of Washington are conducting a prospective trial of women presenting to primary care clinics. Women who agree to participate are offered a symptom screening questionnaire. Research has shown that over 80% of women with early stage disease and over 90% with advanced stage disease will have specific patterns of symptoms. Those patients who have symptoms which have been shown to be predictive of ovarian cancer are offered a CA125 and TVS for early diagnosis. By offering a 2-step screening process in which only 3-4% of women with symptoms actually undergo testing, as compared to 100% of all women, investigators hope to develop a cost effective method of screening with adequate specificity.

Ovarian Cancer and Treatment

Primary Surgery

Multiple investigators from a variety of institutions continue to report the importance of optimal cytoreduction in the overall prognosis of women with ovarian cancer. A recent report from Memorial Sloan Kettering Cancer Center and the Johns Hopkins Hospital has shown that when institutions adopt a programmatic shift in the surgical approach to ovarian cancer, including extensive upper abdominal and pelvic procedures to radically remove all visible cancer, the 5-year progression free survival for women with advanced ovarian cancer increases from 14% to 31%, and overall 5-year survival increases from 35% to 47%. These studies underscore the survival advantages for women with ovarian cancer when the initial surgical cytoreduction is performed by a gynecologic oncologist.

Intraperitoneal (IP) Chemotherapy

IP chemotherapy has been shown to improve survival in women with optimally debulked ovarian cancer compared to intravenous chemotherapy, but it also has been shown to cause significantly more toxicity. Research in IP chemotherapy this past year has focused on methods to reduce this toxicity. A study from the Mayo Clinic found that only one-third of patients could tolerate six cycles of the type of IP chemotherapy that was shown by the Gynecologic Oncology Group (GOG) to prolong survival in women with optimally cytoreduced ovarian cancer in a large Phase III randomized trial reported in 2006. At the 2009 SGO and American Society of Clinical Oncology (ASCO) meetings, researchers described experience with multiple alternative IP regimens which were administered to optimally cytoreduced women with acceptable toxicity. Investigators from the University of Washington found that survival in women in which Day 8 paclitaxel therapy was dropped and in women who received IP carboplatin was similar to what was seen in the GOG randomized trial. These preliminary studies provide encouraging results utilizing IP regimens that are better tolerated than the current IP standard of care. The GOG will soon open a new prospective randomized trial designed to identify an IP regimen that provides the survival advantage of the original GOG trial while minimizing toxicity.

Primary Chemotherapy

Recent advances were reported this year in both the timing of chemotherapy after primary surgery and the use of biologic agents in combination with standard chemotherapy. Several Phase I and Phase II studies presented at the 2009 ASCO and SGO meetings found that adding a biologic agent called bevacizumab (a monoclonal antibody that blocks new blood vessel formation in tumors) to primary treatment did not increase toxicity, even when given together with IP chemotherapy. In other studies, adding bevacizumab to intravenous chemotherapy resulted in favorable response rates, although results of

prospective randomized trials are needed before endorsing the use of bevacizumab as part of primary treatment. The GOG's Phase III randomized trial to determine whether adding bevacizumab to standard front-line paclitaxel and carboplatin therapy is beneficial for women with advanced ovarian cancer has recently finished enrolling participants and preliminary results are expected in the next one to two years.

Another interesting study presented at ASCO found that the timing of the initiation of chemotherapy following optimal cytoreduction was a significant factor associated with survival. Starting chemotherapy earlier after surgery was associated with an independent improvement of survival for those women following optimal cytoreduction, but not in women with residual disease. The data from this study suggests that there should be prompt initiation of chemotherapy in the immediate post-surgical period for optimally cytoreduced patients.

Ovarian Cancer and Maintenance Therapy

Maintenance therapy is defined as treatment given to women with ovarian cancer who are in remission after their primary surgery and chemotherapy in an effort to prevent their cancer from recurring. Long-term results the GOG/Southwest Oncology Group study of maintenance treatment with 12 cycles of monthly paclitaxel were recently reported. Although the initial results of this trial reported in 2003 showed women treated with 12 cycles of paclitaxel survived longer without progressive cancer than women treated with 3 cycles, the updated long-term data now demonstrate that overall survival was not significantly improved; women treated with 12 cycles of chemotherapy survived for 48 months compared to 53 months for those treated with 3 cycles..

Another trial evaluating the use of a monoclonal antibody to CA125 (oregovomab) as maintenance therapy for women with advanced stage ovarian cancer was recently reported. Over 300 women were randomized to receive either a placebo or the antibody treatment every few weeks as long as their cancer did not recur for up to 5 years. Although oregovomab was well tolerated and produced a significant immune response, there was no difference in survival between the treatment and placebo groups. Future research in immunotherapy will focus on other immune stimulating agents and the possibility of chemo-immunotherapy combinations.

Surveillance

At the 2009 ASCO meeting, a multi-institutional European trial on the utility of CA125 in monitoring women with ovarian cancer in remission after completion of primary therapy was reported. The study compared 265 women who began chemotherapy for recurrence after their CA125 levels began to rise with 264 women who waited to begin chemotherapy until they had symptoms. Although women who started treatment based on rising CA125 began chemotherapy an average of five months earlier, they did not live longer than women who started treatment after they developed symptoms. Quality of life was better in those who waited until the onset of symptoms before starting treatment. The trial was limited because it did not include a standard type of chemotherapy for all the participants and it did not address the role of secondary cytoreduction in the setting of recurrent disease. Despite its limitations, this study suggests that less frequent CA125 monitoring is acceptable, and waiting to initiate chemotherapy until the onset of symptoms is unlikely to be detrimental to most women with recurrent ovarian cancer. Keeping in mind that patients may derive psychological benefit from knowing their CA125 levels, physicians should discuss the pros and cons of CA125 surveillance, and the implications for subsequent treatment and quality of life.

Because most women also undergo periodic radiographic studies for surveillance, it is noteworthy that in April 2009 the Centers for Medicare and Medicaid Services (CMS) expanded coverage of CT/PET scans to include ovarian cancer. Over the past several years there have been a number of studies which show

that CT/PET scans are a useful tool for establishing ovarian cancer recurrence and helping clinicians identify appropriate patients for surgical intervention. CT/PET scans alter management in approximately 60% of women with suspected recurrent ovarian cancer. CMS now covers CT/PET scans for both initial and subsequent treatment. In general, most private payers will follow Medicare coverage policies.

Treatment of Recurrent Disease

For women with ovarian cancer that has recurred after initial treatment, significant advances were made this year towards identifying more effective and less toxic treatment options. At the 2009 ASCO meeting, results of the multi-center Phase III randomized trial comparing carboplatin/paclitaxel to carboplatin/liposomal doxorubicin in over 900 women with recurrent ovarian cancer were presented. These results showed that women treated with carboplatin/liposomal doxorubicin lived longer without their disease progressing (11.3 vs 9.5 months), and had fewer severe and long-lasting side effects, than women who received carboplatin/paclitaxel.

Multiple studies were presented over the past year at the SGO and ASCO meetings evaluating the role of the targeted agent bevacizumab in recurrent ovarian cancer. In trials that combined bevacizumab with topotecan, paclitaxel, or liposomal doxorubicin, over 50% of women with platinum resistant ovarian cancer had a response or stable disease with acceptable toxicity. Combining bevacizumab with low dose weekly chemotherapy also appears to be an effective strategy in women with platinum resistant ovarian cancer.

Another targeted therapy showing promise in the treatment of women with recurrent ovarian cancer is the use of PARP inhibitors in women with BRCA1 or BRCA2 gene mutations. PARP inhibitors prevent the repair of DNA which leads to cell death. At this year's ASCO meeting results from a Phase II trial using the oral PARP inhibitor, olaparib, in women with BRCA1 or BRCA2 gene mutations and chemotherapy resistant ovarian cancer showed an overall response rate of 33% with minimal side effects. Duke University researchers reported at this year's SGO meeting that 40% of non-hereditary ovarian cancers express the PARP protein, raising the possibility that PARP inhibitors may be useful for a select group of patients who are not BRCA1/2 gene mutation carriers.

Currently there are many ongoing trials evaluating novel biologic agents that block certain enzymes or other biologic pathways unique to cancer. Identifying which cancers utilize these specific enzymes and pathways is challenging, but holds significant promise for developing more individualized and effective treatments for women with ovarian cancer.

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

The majority of ovarian germ cell cancers are diagnosed in children and young women less than age 30. Germ cell cancers are highly curable with a combination of fertility sparing surgery (removing the affected tube and ovary) and chemotherapy, and only a few patients with very early stage low grade tumors can be cured without chemotherapy treatment.

However, recent research suggests that chemotherapy can be spared in additional patients. This year investigators in England published an interesting study which reported the outcomes of close follow-up after not giving chemotherapy in patients with Stage IA germ cell tumors. In this series, there were 37 patients with a median age of 26 (range 14–48 years). Patients had surgical staging and then were followed with regular tumor marker blood tests and imaging, but none were initially treated with chemotherapy. Recurrence rates for the nondysgerminoma tumors and dysgerminomas were 8/22 (36%) and 2/9 (22%), respectively, and all recurrences happened within 13 months. Of the 11 patients who had a recurrence, all but one was cured with chemotherapy. Over 50% of the women who underwent fertility sparing surgery

went on to have successful pregnancies. This study suggests that chemotherapy may be avoided in a significant number of these young women with germ cell tumors and that equivalent cure rates may be able to be obtained with early initiation of chemotherapy at the time of relapse. However, larger studies are needed to confirm these very interesting results.

In a study presented at the 2009 Society of Gynecologic Oncologists (SGO) Annual Meeting, fertility sparing surgery, even in women with advanced stage disease, was found to be a safe practice in women with ovarian germ cell tumors. In the 974 women with germ cell tumors studied, there was no negative impact on survival when the uterus or both ovaries were not removed. In another study evaluating SEER data in women with germ cell tumors, the authors found that Caucasian women had more favorable cancer cell types and were more likely to have complete surgical staging compared to African American women, but race alone did not predict survival.

Since most women with ovarian germ cell cancers are cured with surgery and chemotherapy, issues of survivorship are particularly important for this group of young women. A study from the Gynecologic Oncology Group (GOG) compared quality of life between women with treated germ cell tumors to controls (those who had never had cancer). A multivariate analysis found that compared to women in the control group, germ cell cancer survivors expressed more reproductive concerns and reported worse sexual functioning, but they also experienced a better appreciation of life circumstances and their emotional support. It is important for women with germ cell cancer and the providers who care for them to be aware of these survivorship concerns.

Advances in Stromal Cell Ovarian Cancer

The most common stromal tumors are granulosa cell tumors but what causes these tumors to develop on a molecular level is not known. Researchers in British Columbia recently found that almost all granulosa cell tumors have a specific mutation in a gene called FOXL2, a gene that makes a protein known to be critical for granulosa cell development. Investigators found that the FOXL2 mutation was present in 97% of adult granulosa cell tumors, 21% of thecomas (another type of stromal tumor) and absent in ovarian stromal tumors of other varieties. This mutation has such good sensitivity and specificity that it can help pathologists confirm that a tumor is a granulosa cell cancer when the diagnosis is not clear. The discovery that this mutated gene may be the cause of granulosa cell tumors could lead to the development of drugs that could target the function of the protein associated with the FOXL2 mutation and hopefully block the growth of ovarian granulosa cell tumors in patients.

Surgery to remove the primary site of cancer and staging to find out if there is spread to other sites has been the accepted standard treatment for women with ovarian stromal tumors. A recent study of the role of lymphadenectomy in women with stromal ovarian tumors was recently published by investigators at the M.D. Anderson Cancer Center. In their series of 58 women who underwent complete surgical staging with lymphadenectomy, none were found to have cancer that had spread to the lymph nodes, suggesting that it may be possible to omit pelvic and paraaortic lymph node dissection in these patients. The impact of leaving in place a woman's uterus and unaffected ovary as part of primary surgery for ovarian stromal tumors was reported by investigators at the 2009 SGO meeting. Looking at records from 268 women with ovarian stromal tumors in the large national SEER database, these investigators found that this type of fertility sparing surgery was commonly performed in younger women, but did not affect survival in women with ovarian stromal tumors.

While the majority of stromal ovarian tumors are cured with surgery alone, if these tumors do recur, they often respond poorly to chemotherapy agents. Recent studies have shown that stromal tumors with increased angiogenesis (blood vessel formation) and increased levels of a substance that promotes new

blood vessels, called vascular endothelial growth factor (VEGF), were associated with a higher risk of recurrence. Researchers from the M.D. Anderson Cancer Center recently published a retrospective review of eight women with recurrent granulosa cell tumors who were treated with bevacizumab, a drug that blocks new blood vessel formation. In this series, one patient had a complete response, two had a partial response and two had stable disease. While this study is very small, it appears that anti-angiogenesis drugs like bevicizumab have the potential to be effective in patients with ovarian stromal tumors.

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 that 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 40,610 new cases diagnosed in the United States during 2009, and more than 95 percent of these will be endometrial adenocarcinomas, with approximately 1600 cases of uterine sarcoma. Approximately 7,780 women will die from uterine cancer in the United States during 2009.⁴

Advances in Uterine Cancer

Endometrial adenocarcinoma, which accounts for 95% of the over 40,000 new cases diagnosed this year, is 4th most common cancer in women, with only lung, breast and colon cancer being more frequent. Fortunately, most endometrial cancers are diagnosed in an early stage and the potential for cure is great.

Having appropriate surgery is the critical factor in curing 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) by removing lymph nodes and collecting biopsies. Gynecologic oncologists are the specialists with specific training in the management of uterine cancers, and have the surgical expertise to perform hysterectomy and lymph node dissections. Many believe that complete staging, which describes if and how the cancer has spread beyond the original site, helps women with endometrial cancer best understand their chances of being cured. Patients identified with cancer confined to the uterus frequently require no additional therapy whereas those whose cancer has spread to the lymph nodes, ovaries, or within the abdominal cavity can be offered additional treatments, including radiation or chemotherapy, to reduce the chances of the cancer recurring.

During the past few years, advances in surgery for endometrial cancer have focused on improving benefits while reducing risks. Enhancing the use of minimally invasive surgery (laparoscopic and robotic) and defining which patients will benefit most from removing pelvic and para-aortic lymph nodes have been active research topics. Laparoscopic techniques are now being used by many gynecologic oncologists for the comprehensive surgical staging of endometrial cancer. A recently published survey of members of the Society of Gynecologic Oncologists (SGO) found that 87% of members who responded consider laparoscopic hysterectomy and staging an appropriate procedure for the treatment of endometrial cancer, and 43% reported staging endometrial cancer was the most commonly performed laparoscopic surgery in their practice. In a large 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 surgery (laparotomy). The number of lymph nodes removed and the frequency of lymph nodes identified with cancer spread (metastasis) were comparable between the two surgery groups, suggesting that the types of surgery had similar accuracy for staging. Survival and recurrence results will be available once patients have been followed for a longer period of time. It should be noted that laparoscopic surgery was shown to be more difficult in patients who were extremely overweight or who had a very large uterus,

Robotic assisted laparoscopic surgery (RALS) has been increasingly integrated into the management of endometrial cancer in an effort to address some of the challenges identified with both laparoscopy and open surgery. RALS adds to standard laparoscopy three dimensional, high definition visualization, and increased mobility and precision of hand movements for the surgeon. As with standard laparoscopic surgery, the use of RALS by gynecologic oncologists in the treatment of endometrial cancer is increasing. Twenty-four percent of the recent SGO survey responders reported using robotic surgery in their practices and 66% stated they would increase their use of this technique during the coming year. The experience with the use of RALS to stage endometrial cancer patients was reported by several groups

⁴ American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2009.

of gynecologic oncologists in 2008–2009. Although performed at a variety of different hospitals in geographic locations around the U.S, the results of these studies demonstrate that robot assisted laparoscopic surgery is technically feasible in the endometrial cancer population with results (amount of blood loss, operating times, complications and successful removal of lymph nodes) being the same or better when compared to patients treated by open or standard laparoscopic surgery. In addition, RALS may be superior in obese patients given the improved ability of the surgeon to see critical structures, including blood vessels and lymph nodes with this technology. Although the results of RALS use to stage endometrial cancer reported to date are encouraging, no prospective head-to-head comparison between open or laparoscopic procedures and robotic surgery has yet been reported.

In 2009, many gynecologic oncologists in the United States believe that the most accurate assessment of prognosis and appropriate treatment recommendations for women with endometrial cancer is made based on results of surgical staging that includes removal of pelvic and para-aortic lymph nodes (lymphadenectomy). Despite this commonly held perception among women's cancer specialists, lymph node dissection is performed in only 30–40% of all women having surgery for endometrial cancer in this country. There is controversy as to whether all, some, or none of the women having a hysterectomy to treat endometrial cancer should also have lymph nodes removed and the extent of the lymph node removal. Not in doubt, however, is the consensus that surgical removal of lymph nodes with pathologic review is the best available way to assess lymph node status. Detection of the spread of endometrial cancer to lymph nodes is one of the single most important predictors of outcome (recurrence and survival) for women with this disease. Women whose cancer has spread to the lymph nodes receive different treatments than those without spread. Debate has increasingly focused on identifying groups of patients who have the best chance to benefit from the surgical staging that removes lymph nodes.

Since the likelihood of spread to lymph nodes increases with the tumor grade and depth of penetration into the uterine wall, researchers have studied the effect of only performing lymph node removal in women with the highest risk of metastasis. In a prospective study of over 400 patients at one hospital 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 reported that about 20% of women with apparent early-stage endometrial cancer were at such low risk for spread that lymph node dissection could be safely omitted. 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 lymph node dissection 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. In 2009, two large prospective randomized European trials compared hysterectomy with or without removal of pelvic lymph nodes. In both trials, patients received radiation therapy irrespective of whether their cancer had spread to the lymph nodes. In both studies, patients who had surgery to remove lymph nodes in addition to hysterectomy had the same risk of cancer recurrence and the same survival as patients who did not have their lymph nodes removed. Experts have identified a number of strengths and weaknesses in how these trials were done, and others have questioned whether these results from a group of European women can be applied to the treatment of women with endometrial cancer in this country. Until further research clarifies the important issues raised by the European studies, women with endometrial cancer should discuss with their gynecologic oncologist the risks and benefits of performing or not performing a node dissection as part of their initial surgery.

What to do after surgery has also been an important research focus in endometrial cancer. For most patients with low-risk disease confined to the uterus, the risk of recurrence is low, less than 10%, and survival from this cancer is high, greater than 90%. For those patients without spread of cancer outside of the uterus but with certain high-risk features (age greater than 70, high tumor grade or deep muscle invasion) the chance of cancer recurrence is higher. The potential benefits of treatments in addition to

surgery have been studied in recent trials. Results of a randomized trial in over 400 patients that compared limited vaginal radiation therapy to more extensive pelvic radiation therapy showed lower recurrence similar survival and better quality of life in the patients treated with vaginal radiation.

The Gynecologic Oncology Group (GOG) recently opened a large trial to compare pelvic radiation therapy to vaginal radiation followed by 3 cycles of chemotherapy in this group of women with high-risk early stage endometrial cancer. This study will try to determine if there is a benefit to these early stage patients of chemotherapy after surgery. For patients with advanced disease, combination therapy of pelvic radiation followed by one of 2 types of chemotherapy has been evaluated 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 did not reduce the chance of cancer recurrence, and produced more side effects. Whether outcomes can be improved by adding radiation to chemotherapy versus using chemotherapy alone will be the focus of the next GOG study which will open soon. New drugs which focus on blocking specific growth signals of cancer cells are being actively studied in endometrial cancer. Experimental agents which block growth pathways (mTOR inhibitors) or interfere with blood vessel development in tumors (anti-angiogenesis agents) have shown the most promise in treating patients with endometrial cancer. Several new trials are ongoing in 2009 to evaluate these interesting new agents in the treatment of women with advanced or recurrent endometrial cancer.

Significant progress towards understanding the biology of endometrial cancers has been achieved by a large tumor banking study sponsored by the GOG. So far, nearly 4500 women with endometrial cancer nationwide have participated by donating portions of their tumor and blood obtained at the time of surgery so that researchers can identify promising biomarkers to predicting response and prognosis. These samples are being studied to answer important questions including why some cancers behave more aggressively and spread, and why some cancers respond better to other therapies. With these major advances in understanding what signals control endometrial cancer cells and development of new drugs to block specific growth signals, the future for endometrial cancer patients is promising and exciting!

Progress in the treatment of uterine sarcoma also has occurred recently as a result of prospective clinical trials. Results of a large randomized trial conducted in Europe showed that pelvic radiation therapy offered little benefit for patients with early stage uterine carcinosarcoma or leiomyosarcoma. The GOG published results from two studies of patients with carcinosarcoma suggesting that (1) chemotherapy (ifosfamide plus cisplatin) was preferable to whole abdominal radiation therapy in women with Stages I-IV disease, and (2) the combination regimen of ifosfamide with paclitaxel was better than ifosfamide alone in patients with advanced or recurrent disease. As a result, chemotherapy has taken a much larger role in the management of uterine carcinosarcomas.

At the 2009 American Society of Clinical Oncologists (ASCO) meeting, investigators from the GOG reported preliminary results in a small group of patients with advanced or recurrent carcinosarcoma disease treated with a regimen of carboplatin plus paclitaxel, similar to what is commonly used in ovarian cancer, showing promising response rates.

For patients with leiomyosarcoma, the two drug combination of gemcitabine and docetaxel demonstrated important activity in both first and second-line treatment of patients with metastatic disease. 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 GOG-sponsored prospective clinical trials has been very important for the recent advances in care of women with uterine cancer. GOG clinical trials currently available for enrollment can be found on GCF's Web site, the Women's Cancer Network, www.wcn.org.

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 many vaginal cancers are associated with HPV types 16 and 18, vaginal cancer can be prevented by vaccination with Gardasil® the vaccine that was approved by the FDA for this purpose in 2008.

Incidence: Vaginal cancer is very rare. It is estimated that there will be about 2,160 new cases diagnosed and 770 deaths from vaginal cancer in the United States during 2009.⁵ Vginal cancer accounts for about 3% 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 lose 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% of the tumors, and correctly demonstrated disease that involved tissues beyond the vagina in 88% 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.

⁵ American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2009.

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% in detecting sites of cancer beyond the pelvis with 73% 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, response 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, response 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.

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, reduce the risk of vulvar cancer. The HPV vaccine Gardasil® was approved by the FDA for prevention of HPV type 16 and 18 associated vulvar cancer in 2008. 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 3,580 new cases diagnosed and approximately 900 deaths from vulvar cancer in the United States during 2009.⁶ 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, or chronic swelling in the legs, is especially frustrating for patients and care-givers because there are few effective treatments, and it is difficult to study because it is underreported. The Gynecologic Oncology Group (GOG) recently reported a randomized control trial in 150 vulvar cancer patients investigating whether the use of a sealant sprayed on the area of lymph node dissection at the time of surgery could reduce this common complication. Although the study found that using the sealant did not prevent lymphedema, the completion of this trial does demonstrate the feasibility of studying ways to decrease the rate of this disabling complication. The GOG plans future trials to identify effective methods to prevent lymphedema in women having surgery for vulvar cancer.

⁶ American Cancer Society. Cancer Facts & Figures 2009. Atlanta: American Cancer Society; 2009.

One of the most significant recent advances is sentinel lymph node biopsy, which can improve detection of node metastases, and can reduce the risk of lymphedema in women having surgery for vulvar cancer. The sentinel lymph node is the node that is most directly connected to the main tumor through the lymph channels, and it is the most common site to which cancer cells spread. The sentinel lymph node 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 lymphedema in some patients.

At the 2009 American Society of Clinical Oncology (ASCO) meeting, the results from a much-anticipated GOG study designed to validate the use of sentinel lymph node biopsy in vulvar cancer were presented. Five hundred ten women with vulvar cancer were enrolled in the study. In each woman participating in the study, sentinel nodes, identified with both blue dye and radioactive dye, were removed and examined to look for tumor spread. During the same surgery, the rest of the lymph nodes in the groin area were removed and results compared with the findings in the sentinel lymph nodes. Sentinel nodes were successfully identified in over 95% of patients, confirming that this technique is feasible and safe in women with vulvar cancer. This study confirmed the findings of a large Dutch study published in 2008 that followed 202 women with negative sentinel lymph nodes for 2 years and concluded that sentinel lymph node biopsy is safe in many patients with vulvar cancer. Based on the encouraging results of these two large prospective trials, a woman with vulvar cancer should discuss with her gynecologic oncologist their experience and the risks of the procedure before proceeding with sentinel lymph node biopsy as part of her surgery.

Further supporting the concept that less radical surgery is safe for vulvar cancer patients, GOG investigators performed a secondary analysis of a previous trial to determine whether groin recurrence was associated with the removal of fewer lymph nodes at the time of original surgery. Among 113 patients who underwent groin dissection, nine had a recurrence in the groin, but there were no significant differences in node counts between patients who had recurrence in the groin and those who recurred outside the groin. Investigators concluded that variations in anatomy and other factors may make node counting an unreliable measure of surgical quality.

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 quality of life 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.

Legislative Update

Please support these following efforts by the gynecologic cancer community in the Federal legislative arena that are aimed at encouraging additional government support of gynecologic cancer research, education, prevention, early detection and treatment.

21st Century Cancer ALERT (Access to Life-Saving Early Detection, Research, and Treatment) Act of 2009 (S.717) Introduced by Senator Edward Kennedy (D-MA) would amend the Public Health Service Act to revise provisions related to the National Cancer Program to require the Secretary of Health and Human Services to award grants for research on cancer with a five-year survival rate of less than 50 percent, strengthen national tissue banks and prohibit ERISA plans from discriminating against participants and beneficiaries participating in cancer clinical trials and biomarker research.

Ovarian Cancer Biomarkers Research Act of 2009 (H.R. 1816/S. 755) Introduced by Congressmen Howard Berman (D-CA) and Ralph Hall (R-TX) and Senator Barbara Boxer (D-CA) 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 is being considered for inclusion as a section of S. 717, discussed above and its eventual U.S. House of Representatives companion bill.

Access to Cancer Clinical Trials Act of 2009 (H.R. 716/S. 488) Introduced by Congressman Steve Israel (D-NY) and Senator Sherrod Brown (D-OH) 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 is also being considered for inclusion in the broader cancer legislation, S. 717.

Reauthorization and Enhancement of Johanna's Law of 2009 (H.R. 2941) Introduced by Congresswoman Rosa DeLauro (D-CT), and Congressmen Sander Levin (D-MI), Darrell Issa (R-CA) and Dan Burton (R-IN), H.R.2941 would 1) reauthorize the existing programs under Johanna's Law for FY 2010-2012 at \$16.5 million and then for such sums in the subsequent years; and 2) authorize at least five grants in the first year to non-profit, private entities to carry out demonstration projects to test various gynecologic cancer outreach and education strategies. This section would have an authorization of \$15 million for FY 2010-2012 and then such sums there after.

Assuring and Improving Cancer Treatment Education and Cancer Symptom Management Act of 2009 Introduced by Congressman Steve Israel (D-NY) would amend the Social Security Act to provide Medicare coverage of comprehensive cancer patient treatment education services, and would require the NIH to expand research in the management of cancer treatments and side effects.

To educate your Members of Congress regarding the need for any of these pieces of legislations, please call the Capitol Hill Switchboard at 202.225.3121 and ask to be connected to their office. Ask for the staffer who handles health care issues and share with the staffer how important the legislation you are calling about is to you. 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.

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