

2011 State of the State of Gynecologic Cancers

Ninth Annual Report to the Women of America

FOUNDATION FOR
WOMEN'S CANCER



Gynecologic Cancer
Awareness • Research • Education

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A Letter to the Women of America

The Foundation for Women's Cancer, formerly the Gynecologic Cancer Foundation, is pleased to publish a special 20th anniversary edition of the *State of the State of Gynecologic Cancers: Ninth Annual Report to the Women of America*.

Since the Foundation was established by the Society of Gynecologic Oncology in 1991, significant progress has been made in the prevention, early detection and optimal treatment of gynecologic cancers. We have asked leading experts to chronicle the 20 years of advances for each of the gynecologic cancers. Dr. John Curtin, President of the Society offers an opening article that describes the role and contributions of the Society of Gynecologic Oncologists in advances made by the Society during this period.

The Foundation's commitment to serve women affected by a gynecologic cancer is unwavering. A decision to change our name was a result of an increasing body of knowledge about risk factors and prevention strategies available to women to allow them to improve their gynecologic health.

We will continue to annually publish the exciting research and its impact on clinical practice to inform women and their families about the strides being made. In keeping with our new name and emerging science, we also will broaden our programs with the hope of reaching all women in America with critical information about how to maintain their gynecologic health.

Sincerely,

A handwritten signature in black ink, appearing to read "D. M. Gershenson". The signature is fluid and cursive, with a long horizontal flourish extending to the right.

David M. Gershenson, MD
Chairman, Foundation for Women's Cancer

Twenty Years of Progress: The Society of Gynecologic Oncology

By John P. Curtin, MD, President, Society of Gynecologic Oncology

While the Society of Gynecologic Oncology (SGO) and its membership have remained steadfast in their commitment to women's cancer care, much has changed and evolved within the Society over the past 20 years. To begin with, we as a Society have committed ourselves to the following powerful vision and mission statements for the organization:

VISION: To Eradicate Women's Cancer

MISSION: To Promote the Highest Quality of Comprehensive Clinical Care through Education and Research in the Prevention and Treatment of Gynecologic Cancers

Twenty years ago such ambitious statements would seem far reaching. But with the medical and technological advances in treatment and prevention, which our membership has led, both may be attainable in our lifetime.

Looking back there are key areas in which SGO has made tremendous strides over the past two decades. These include the enhanced Annual Meeting on Women's Cancer™, the growth and evolution of our membership model, and our organizational changes.

Twenty years ago the Annual Meeting on Women's Cancer was much different in its composition and organization than today. Even ten years ago, in 2000 the attendance was 1061 with few, if any, international attendees. To present an abstract at the meeting, a potential participant had to be invited by an SGO member. The meeting was largely attended by Society members only. In recent years, our Annual Meeting averages a total attendance of approximately 1,800 of which nine percent are non-members, including 12 percent international attendees. An open submission process, fostered by a global Call for Abstracts, has dramatically increased the volume and diversity of the scientific studies presented. The Annual Meeting also has taken on a truly international flavor with presentations and posters from all over the world, and dedicated sessions for our international guests. All of these changes have served to strengthen the Annual Meeting and unite women's cancer care specialists from across the world to join in our mission and vision.

Growth in our membership has been another major area of incredible change over the past 20 years. In 1991, the SGO had a membership of approximately 545, which was primarily comprised of full members (then defined as American Board of Obstetrics and Gynecology certified gynecologic oncologists only). Today our membership totals more than 1450. In 2005 the Society, in an effort to engage and groom emerging gynecologic oncologists to learn and network within the Society, expanded its membership to allow Candidate and Fellow membership categories. While international members could always join in the Associate and Fellow categories, they were only extended full voting rights category in 2011. SGO took a major step toward better reflecting the face of gynecologic oncology by creating a new membership model that embraces a host of women's cancer care professionals including medical oncologists, oncology radiologists, nurses, pathologists, social workers, nurse practitioners and residents, as well as welcoming select colleagues from across the globe as International Members in 2010.

This change in our membership led to another major transformation for the Society: the change in its name from the Society of Gynecologic Oncologists to the Society for Gynecologic Oncology. This subtle, but important revision announced earlier this year signaled a commitment to truly embrace our new, inclusive membership model and to support our positioning as the voice of gynecologic oncology.

Our desire to be the leader in women's cancer care had led to a host of organizational changes over the past 20 years as well. The decision to create a standalone entity with a dedicated professional staff led to the Society's move from SmithBucklin, a Chicago-based association management company in January 2006. Over the past 20 years, we have evolved into a very open, transparent organization with more than 250 member volunteers participating on our various committees, task forces and workgroups. SGO changed its election process to allow self-nomination and is currently reviewing the existing process to determine if open elections are a viable option to include even more members in leadership positions.

Ever mindful of our position as the voice of the profession, we have actively advocated with legislators and federal agencies to research funding and essential reimbursement in Washington, DC, hiring a dedicated government relations director and Capitol Hill lobbyist to represent SGO and our patients' interests. We established a Clinical Practice Committee to create and distribute practice guidelines and bulletins aimed at educating other women's health providers about important treatment and prevention methodologies for gynecologic oncology. And, we are working diligently to create a quality and outcomes database that will assist us in not only setting standards for the emerging new care models, but also effectively set clinical pathways that will greatly improve and impact patient care.

Perhaps the biggest organizational change, and one that will surely impact the Society's next 20 years, is the decision to restructure SGO from a 501(c)(3) to a dual 501(c)(6) and 501(c)(3) entity. With the enormous socio-economic demands on the profession, and based on the Society's ambitious mission and vision, it became strategically obvious that SGO needed to be able to perform certain functions that its current structure prohibited. By reorganizing our structure to a 501(c)(3) and 501(c)(6), SGO will not only be able to continue to provide excellent continuing medical education programming for women's cancer care professionals, but also embark on heightened public policy and advocacy programming, work to establish practice and treatment guidelines, as well as delve into public education and awareness program to increase the knowledge of these diseases and our unique role in their prevention and treatment.

As the Society continues to evolve, it remains steadfast in its commitment to the women battling with gynecologic cancers. It is our hope that every change we make moves us one step closer to our ultimate goal of eradicating women's cancer here in the United States and across the globe.

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 specialist with advanced training and demonstrated competence, such as 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 83,000 new cases diagnosed and approximately 28,000 deaths from gynecologic cancers in the United States during 2011.¹

¹ American Cancer Society. *Cancer Facts & Figures 2011*. Atlanta: American Cancer Society; 2011.

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 are on the outside of the cervix and glandular cells which make the fluid and mucus commonly seen during ovulation that are mostly on the inside of the cervix. 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 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 and potentially exposed leads to the greatest prevention of pre-cancer and cancer. Early vaccination (currently recommended at 11 or 12 years of age) 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 abnormal precancerous or cancer cells will be identified by screening with a Pap test and HPV testing when indicated.

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 cervical disease that would require some sort of treatment. 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 that includes Pap testing takes away the opportunity for early diagnosis through cervical cancer screening. Even in women with HIV, previously thought to be at risk for cervical cancer, appropriate screening with Pap tests may eliminate this 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 over 70%. 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. Recently, guidelines for cervical cancer screening have changed. It is now recommended that for normal women, annual Pap tests might lead to more procedures and more treatment, but not pick up more cancers. So, the guidelines are increased intervals for screening in normal women with no history of prior Pap abnormalities. Also, the American College of Obstetricians and Gynecologists published revised guidelines recommending cervical cancer screening before age 21 should be avoided because it could lead to unnecessary and potentially harmful overtreatment in a group of women at very low

risk for developing cervical cancer. It is also important that women know and understand their Pap test results and follow through with any recommendations made by their healthcare provider. Some abnormal Pap tests will be followed by colposcopy (examination of the cervix using a magnifying device to see the cervical 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 a healthcare provider.

Current cervical cancer screening guidelines support the use of HPV testing 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 is 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 five years. Active research is underway to evaluate the role of HPV testing and HPV type-specific testing in primary cervical cancer screening. In some developed countries, HPV-based screening has already begun. By this approach, if the HPV test is positive, then a Pap will be performed. This approach has been shown to improve identifying those women most at risk, while minimizing procedures, treatment, and potentially harm in those women who can continue to be screened at recommended intervals.

One of the most significant advances in the fight against cervical cancer is the development of HPV vaccines.

HPV vaccines are now routinely recommended for all 11 and 12 year old girls. One of the vaccines is also routinely recommended for 11 and 12 year old boys. These vaccines can be given as young as age 9 and up to age 26. 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 12,710 new cases of invasive cervical cancer diagnosed and approximately 4,290 deaths in the United States during 2011.²

Screening and Prevention of Cervical Cancer

There has been ground-breaking work with regards to the prevention and treatment of cervical cancer in the past twenty years. The regular use of Pap smears to screen for cervical cancer, discovered by Dr. George Papanicolaou over 50 years ago, rapidly decreased the incidence of what was the most common cancer that affected women in the United States in the early 20th century. Routine use of the Pap smear has reduced cervical cancer deaths by nearly 75%. A Pap smear is a standard way healthcare providers can check to see if there are any changes in the cervical cells that might cause concern. This 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.

With the explosion of new molecular technologies in the 1970's and 1980's, Harold zur Hauzen was one of the first to link infection with a common virus, Human Papillomavirus (HPV), to cervical cancer. This discovery led to his winning the 2008 Nobel Prize in Physiology and Medicine. Establishing this link was critical to allow for a better understanding of the natural history of cervical cancer. Scientists, epidemiologists and physicians then teamed up to utilize knowledge about the natural history from HPV infection to cancer in order to implement new technologies that allowed for early detection in a much more sensitive way than a Pap smear alone. Current cervical cancer

² American Cancer Society. *Cancer Facts & Figures 2011*. Atlanta: American Cancer Society; 2011.

screening guidelines include HPV testing at certain times in combination with Pap testing in order to determine who is at low risk of having pre-cancerous cells of the cervix. Also, a negative HPV test with a negative Pap test can allow for Pap-based screening to occur at much less frequent intervals in a safe fashion. Globally, there are large multi-institutional trials underway that are evaluating the role of HPV testing for primary cervical cancer screening. Also, there are other tests and molecular technologies that are being explored that may further assist medical professionals in triaging those women who need more intervention versus those women who can be safely observed.

One of the most significant advances in the fight against cervical cancer is the development of cancer prevention vaccines that protect against the cause of cervical cancer, HPV. In June 2006, after over a decade of clinical trials in tens of thousands of girls and women, one of these vaccines was approved by the FDA for use in 9–26 year old women and girls. In large clinical trials, HPV vaccines were found to be very effective in protecting women from developing precancerous lesions of the cervix, vulva and vagina. It was a monumental milestone not only for cervical cancer, but for all cancers as this is the first vaccine that is approved for preventing cancer. When widespread vaccination has been achieved, cervical cancer should be reduced by over 70% in the future.

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 Oncology, recommend routine vaccination of young girls 11 and 12 years of age, ideally before first intercourse, and young women age 13–26. As a result of more recent clinical trials, one of the prophylactic HPV vaccines has also been recommended for boys and young men as well in order to protect them from genital warts and HPV-associated anal cancer. Newer vaccines that provide immunity against a greater number of HPV types are under development and carry the promise of preventing over 90% of cervical cancer. Early vaccination with regular screening, which includes a Pap smear and HPV test when recommended according to standard guidelines, is now the most effective way to prevent cervical cancer.

Treatment of Cervical Cancer

Advances in radiation therapy and our understanding of the biology of cervical cancer led to clinical trials that combined chemotherapy with radiation therapy in the 1980's. In laboratories, the synergy that occurred with this combination of chemotherapy and radiation was found to lead to very potent cell death in cervical cancers. This 'radiosensitizing' chemotherapy concomitant with radiation therapy was then translated from the laboratory to large-scale clinical trials, mostly led by the Gynecologic Oncology Group (GOG). These trials were such a success that the National Cancer Institute issued a clinical alert in 1999 to emphasize the importance of combination therapy for the treatment of locally-advanced cervical cancer. For women with advanced-stage cervical cancers, treatment with a combination of radiation therapy and chemotherapy remains the standard of care. Long term follow-up of women who participated in the clinical trials that tested this combination therapy confirms that those treated with radiation and chemotherapy continue to have a higher survival rate than women treated with radiation alone. Furthermore, recent and currently ongoing studies suggest that continued additional chemotherapy after radiation may improve survival even further. There are a number of clinical trials that are investigating whether the addition of targeted therapies *in addition* to concomitant chemoradiotherapy will improve survival even further, or potentially minimize the side effects from the drugs or radiation therapy.

Novel immunotherapies or treatment vaccines have been developed in recent years. Clinical trials are currently ongoing to study these targeted therapies in women already infected with HPV and in 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. Additionally, the potential of medically-managing cervical cancer, which is historically treated with radical surgery in the early stages, has clear clinical advantages.

Due to surgical advances that have been made in the past two decades, there are now better treatments for young women with early stage invasive cervical cancer. 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. Traditionally performed through a vaginal incision, the procedure is now being done through abdominal incisions, and by laparoscopic (minimally invasive) and robotic-assisted surgical approaches. These advances are giving more young women worldwide access to surgical management of cervical cancer that preserves an important part of their quality of life.

Ovarian Cancer: Epithelial

State of Epithelial Ovarian Cancer

Ovarian cancer, the ninth most common cancer among women in the United States, is generally grouped with primary peritoneal and fallopian tube cancers. About 85 percent to 90 percent of ovarian cancers resemble the glandular inner surface lining of the upper genital tract structures (fallopian tube, uterus, and cervix). These are classified as epithelial ovarian cancers, although their origin remains controversial.

Symptoms: Bleeding, 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 21,990 new cases diagnosed and approximately 15,460 deaths from ovarian cancer in the United States during 2011.³ High grade serous cancers represent approximately 85% of ovarian cancer deaths.

³ American Cancer Society. *Cancer Facts & Figures 2011*. Atlanta: American Cancer Society; 2011.

Advances in Epithelial Ovarian Cancer

Epithelial ovarian cancer (EOC) is really a heterogeneous set of diseases, with not only a diverse group of microscopic cell types but also biologic differences within each microscopic type. During the last year several important findings have been made regarding the molecular “classification” of EOC which may have implications in terms of disease development and treatment. At the 2011 meeting of the American Society of Clinical Oncology, researchers identified genes which appeared to be active among 363 EOC tumors. They identified six “genetic” subgroups which were significantly related to microscopic cell type and predicted prognosis. Clear cell and mucinous cancers were found in distinct genetic categories, while serous and endometrioid cancers were distributed among the remaining four genetic groups. Within the group of serous (most common microscopic type) cancers, they were able to classify the serous cancers into three subgroups with different prognoses; one of these subgroups was defined by activation of genes related to tumor angiogenesis, the process by which cancers stimulate the formation of a new blood supply from surrounding normal host tissue. In an article published in June 2011 in the journal *Nature*, scientists in The Cancer Genome Atlas (TCGA) Research Network reported on complete analysis of genes activated in 500 serous cancers. They demonstrated at least four distinct molecular subtypes of serous cancers. Among these groups they found 108 genes associated with poor survival and 85 associated with prolonged survival compared with the average. Finally, they searched for genes whose activity might possibly predict the effectiveness of specific targeted biologic treatments which have effects on specific mechanisms of cancer progression. This search identified 68 genes that could be targeted by Food and Drug Administration approved or experimental anti-cancer drugs. In particular, they noted that over 50% of tumors expressed genes which indicated these cancers could be susceptible to the class of drugs under investigation known as poly ADP ribose polymerase (PARP) inhibitors. Other studies identified that two genes (ARID1A and HINF1B) may be of importance specifically in the development of clear cell cancers, a subtype which appears to be relatively resistant to standard chemotherapy agents. These findings could lead to new strategies for treatment.

Studies have shown more favorable outcomes when gynecologic oncologists are involved in initial management. When such referrals are made, standards of diagnosis, staging and treatment are upheld more often. Three studies over the last year suggest that referrals to gynecologic oncologists are not made in many cases and that potentially this may lead to substandard care. One study reported at the Society of Gynecologic Oncology (SGO) Annual meeting, demonstrated that in a survey of over 3000 primary care physicians, the majority do not recommend direct referral to a gynecologic oncologist for women with a mass suspicious for ovarian cancer. This may contribute to the high rates of non-comprehensive surgery for patients with ovarian cancer in the United States. Consistent with this observation, in another study reported at the same meeting, it was found that only 39% of 8,000 women with EOC in the Medicare population received both surgery and at least six (standard number) cycles of chemotherapy as part of their initial management. Finally, a study published in the journal *Cancer* based on approximately 4,500 women with EOC in the Medicare population, 72% underwent surgery. Those who underwent surgery varied according to region, and was less likely in women who were non-white, older and had more advanced stage disease. Of importance, the death rate in these women also varied according to region, and access to surgery, which explained some of that variation. The overall conclusion of this research is that improving access to initial management involving a gynecologic oncologist, including access to surgery, may improve outcomes including survival. Continued public support for this initiative is paramount.

Several treatment advances have been made in the last year. As mentioned earlier, in selected cases of presumed advanced EOC, initial management with some chemotherapy (neoadjuvant chemotherapy or NACT) prior to standard interval surgery, and followed by completion of chemotherapy may be appropriate. Results of a randomized, controlled Phase III European trial published in the *New England Journal of Medicine*, demonstrated that this approach in unselected women with suspected advanced EOC led to a similar overall survival but slightly reduced complication and post-operative mortality rate, compared with the group undergoing initial surgery followed by chemotherapy. At the 2011 Annual Meeting of the Society of Gynecologic Oncology (SGO), two retrospective institutional studies suggested that in selected patients there might be further advantage for NACT with interval surgery. One study demonstrated that for 221 women with Stage IV (disease spread beyond the abdominal cavity) cancers, the rate of complete surgical resection and post-operative death rate were 27% and 0%, respectively, for those receiving NACT and interval surgery compared with 8% and 5%, respectively, for those undergoing the traditional treatment sequence. Although there was no overall survival difference between the two groups, in the subgroup with cancer spread to the liver, survival averaged 43 months for those treated with NACT with interval surgery compared with 27 months for those undergoing surgery as an initial step in management. In another study examining over 28,000 women in the Nationwide Inpatient Sample, the post-operative major complication and mortality rates for initial surgery increased with age, particularly after age 70. Taken together, the body of evidence at this point shows no statistically significant difference in overall survival for women undergoing NACT with interval surgery compared with those undergoing initial surgery followed by all chemotherapy given after surgery, but does suggest that NACT with interval surgery may be a safer or a more rational approach in selected women with more extensive cancers or with high risk of major complications based on factors such as advanced age, multiple medical problems or malnutrition.

It is known that tumor angiogenesis, the process by which cancers stimulate the formation of new blood and lymphatic vessels in order to more effectively grow and spread, is fundamental to the progression of EOC. Angiogenesis involves two phases, the initiation phase where new vessel formation takes place, and the maturation phase, where newly formed vessels stabilize and gain function. Several anti-angiogenic agents have been investigated in clinical trials, most directed against a growth factor made by tumors called factor vascular endothelial growth factor (VEGF), which is involved principally in the initiation phase of angiogenesis. In the last year, results of three Phase III trials of the drug bevacizumab and antibody that blocks VEGF have demonstrated significant prolongation of progression free survival (PFS, the time during which cancers have demonstrated no evidence of growth or spread) when administered with standard chemotherapy followed by continuation of bevacizumab. Two of these trials (GOG 0218 and ICON 7) were conducted in a total of 3,401 women with newly diagnosed cancers and the third (OCEANS) was conducted in 484 women with recurrent disease. The effect of bevacizumab on overall survival in women with EOC remains to be determined, as complete results are needed. However, preliminary results show no evidence of a decrease in overall survival. The major side effect that has been demonstrated for bevacizumab is high blood pressure which requires medical management in between 20 to 25% of women treated, and this effect seems to be related to the duration of treatment. However, in the vast majority of patients with bevacizumab-associated high blood pressure, this problem can be effectively managed without discontinuation of treatment. Other potentially life-threatening side effects that may be related to bevacizumab have been uncommon. These include worsening of low white blood cell counts in association with chemotherapy treatment, stroke, heart attack and gastrointestinal perforation (full thickness ulcer in the wall of the stomach, small intestine or colon). In these trials, the risk of gastrointestinal perforation, although approximately double the rate in the bevacizumab treatment groups compared to the groups receiving chemotherapy alone, occurred in fewer than 3% of women. At

the 2011 SGO meeting, GOG 0218 investigators presented results indicating that independent risk factors for gastrointestinal perforation other than bevacizumab included removal of any bowel segment (particularly colon) with reconnection, at the time of initial ovarian cancer surgery (two-fold increase in risk) and history of inflammatory bowel disease (Crohn's disease or ulcerative colitis). At the 2011 annual meeting of the American Society of Clinical Oncology (ASCO), investigators presented updates for GOG 0218 and ICON 7, and the initial results of OCEANS. For GOG 0218, an independent review of radiologic data confirmed the investigator assessed progression free survival results that were initially presented one year ago.. For ICON 7, a subgroup analysis of poor prognosis patients revealed evidence of a PFS and overall survival benefit for the group receiving bevacizumab; however, this is a retrospective, unplanned analysis. Although it is somewhat problematic to compare results of different trials, the results of OCEANS indicated a more pronounced PFS difference between bevacizumab treated versus untreated patients. This may possibly relate to the duration of bevacizumab, which in OCEANS was until evidence of cancer progression, while for GOG 0218 and ICON7 was until a defined number of treatments even if patients' cancers had not yet progressed. Results of Phase II trials with other angiogenesis inhibitors in women with recurrent EOC demonstrated response rates worthy of further clinical investigation. The investigational regimens were aflibercept a drug that binds and blocks VEGF given with the taxane docetaxel , and cabozantinib, an orally administered drug that blocks the activity of VEGF and other angiogenic growth factors by interfering with the receptors (proteins on the cell surface to which growth factors bind) on microscopic new vessels were also presented at ASCO in 2011. Phase II trials of other anti-VEGF agent called aflibercept when given with the taxane docetaxel in 49 patients with recurrent disease demonstrated a response rate worthy of further clinical investigation. Several Phase III trials of angiogenesis inhibitors are ongoing, including studies of three agents like cabozantinib (pazopanib, BIBF 1120 and cediranib), and of the drug AMG 386, which inhibits the maturation phase of angiogenesis.

Another extremely important area of exploration involves the class of anti-cancer drugs poly ADP ribose polymerase (PARP) inhibitors. DNA is the genetic code in all of our cells and is wound up into our 46 chromosomes. Each DNA molecule is actually composed of two juxtaposed chains and is constantly exposed to insults which cause mechanical breaks in these chains. Each mechanical break in one of the two chains of DNA is usually repaired by the enzyme PARP. In the absence of PARP, these breaks can involve not only one chain but also the paired chain as well. Double chain breaks are repaired through separate enzymes involved in the process called homologous recombination repair (HRR). Accumulated double chain DNA breaks are incompatible with cell survival and lead to a process called programmed cell death. Fortunately, normal cells have these backup methods to repair DNA breaks. However, it is been discovered that some cancer cells have defects in HRR, including EOC cancer cells in women who have hereditary breast-ovarian cancer syndrome involving mutations in the genes BRCA1 and BRCA2. Both of these genes are involved in HRR. As presented by multiple research groups in the last year, It is also been shown that tumor cells from women with high grade serous and endometrioid EOC may have impaired HRR even in the absence of hereditary BRCA1 and BRCA2 mutations. For example, two independent groups demonstrated defective BRCA1 and BRCA2 genes in only the cancer cells of patients without hereditary BRCA1 or BRCA2 mutations. Another group published results in the *Journal of Clinical Oncology* indicating that a simultaneous analysis of all gene activity in cancer cells from patients with EOC might identify multiple types of defective genes that could impair HRR. Since defective HRR function in these cases is found only in the cancer cells, treatment of women with PARP inhibitors can lead to programmed cell death in the cancer cells since they have no ability to repair DNA breaks, while normal cells are relatively spared since they still have normal HRR function. The PARP inhibitor olaparib is the most extensively studied PARP inhibitor in women with ovarian cancer.

At the 2010 meeting of the European Society of Medical Oncology (ESMO), investigators reported on a Phase II randomized study showed that olaparib was not superior to the known active chemotherapy drug PEGylated liposomal doxorubicin (PLD) in patients with recurrent EOC; however, there was no evidence that olaparib was inferior. At the 2011 ASCO meeting, results of the Phase II randomized trial of olaparib versus placebo in women with recurrent serous EOC who were in unmaintained partial or complete response following the last platinum containing chemotherapy regimen, showed a significantly prolonged PFS (65% reduction in the risk of progression) in favor of olaparib, and the drug was well tolerated. Overall survival data were too immature for analysis. Multiple PARP inhibitors are under investigation. Research results related to this promising area of PARP inhibitors raise many important questions. Perhaps the most important question is how to best identify women with EOC whose tumors have evidence of HRR. For now, such testing remains investigational. However, at the 2011 ASCO meeting, investigators reported on a study in which all women with non-mucinous EOC regardless of family history were tested for hereditary BRCA1 and BRCA2 mutations. The overall frequency was 13%. This rate is common enough to suggest that BRCA testing should be implemented in all women with non-mucinous EOC. Even though PARP inhibitors are considered experimental at this time, the results of BRCA testing at this time can have implications in terms of personal risk of breast cancer, and risk of breast and ovarian cancer in unaffected family members.

One of the major goals of research has been the identification of effective treatment options for women with platinum resistant EOC. Recently, receptors for folate (vitamin B9) have shown promise as a target for anticancer therapy. Folate is absorbed by all cells in the body through a generic cell surface transport process. However, a specific receptor for folate called folate receptor alpha is rarely present on normal cells. When circulating folate binds to these receptors, the cells are stimulated to grow. Research has shown that approximately 80% of non-mucinous EOC tumors have folate receptors. A therapeutic antibody called farletuzamab, which binds to and blocks the activity of folate receptors, is currently under investigation in a Phase III trial. EC 145 is a designer drug including folate linked with a highly toxic chemotherapy drug in the Vinca alkaloid family. Circulating EC 145 is relatively non-toxic, and the Vinca alkaloid can only be toxic once the link has been broken. The link can only be broken if the drug is internalized into cells. Also, EC 145 cannot be internalized in the same way that circulating folate is normally absorbed into cells since it is too large a molecule. However, the folate portion of EC 145 can bind to folate receptors and be brought into cells by the receptors after binding. Then, the link between the folate and the Vinca alkaloid is broken, and the Vinca alkaloid can have its toxic effect in that specific cell. Final results of a Phase II randomized trial were presented at ASCO 2011 meeting and demonstrated a significant delay in PFS for women with platinum resistant (with cancer that has recurred or progressed with 6 months from the completion of a platinum chemotherapy regimen) EOC receiving EC 145 in combination with PLD versus PLD alone. A Phase III trial is planned.

Another example of an advance in the management of platinum resistant EOC is based on the principle of PEGylation. This involves attaching the strands of the polymer polyethylene glycol to molecules (such as doxorubicin, in the case of PLD) that can help to meet the challenges of improving the safety and effectiveness of many therapeutics. PEGylation results in multiple drug molecules attached to each other (polymerized), leading to increased drug delivery to cancer tissue that is highly angiogenic with relative sparing of normal tissue. This can increase selective effectiveness of the chemotherapy drug while diminishing side effects. In this case the target is the enzyme topoisomerase-I, and enzyme that is involved in normal coiling and uncoiling of DNA during cell division. This enzyme is particularly active in rapidly dividing cells, such as cancer cells. However, not all rapidly dividing cells in the body are cancer cells, and therefore the drugs that block topoisomerase-I may have unacceptable side effects. The traditional topoisomerase-I inhibitor approved in the treatment of women with recurrent EOC is topotecan; this drug has been

somewhat limited because of side effects, but it is still used widely in clinical practice. Recently, scientists have developed a new formulation in which the topoisomerase-I inhibitor, in this case irinotecan, is PEGylated. Results of the Phase II trial presented at ASCO 2010 meeting showed that the drug NKTR 102 was effective in 21% of study patients with platinum resistant EOC. At the ASCO 2011 meeting results of the second Phase II trial involving 71 women with platinum resistant EOC showed a similar response rate. The limiting side effect of native [??] irinotecan is diarrhea, and the rate of significant diarrhea requiring any form of hydration when NKTR 102 was administered every three weeks was 18%, much lower than what would be expected with native irinotecan.

As discussed above, drugs in the platinum family have historically been considered a staple of EOC therapy. The reason why some EOC cells are or become resistant to platinum agents has received a great deal of attention. One of the main mechanisms for platinum resistance appears to be “silencing” of some genes in cancer cells whose activity is normally required for platinum to be effective against the same cells. This silencing is caused by a process called methylation by which the DNA in these genes is chemically coated and becomes inactive. Results of two early phase clinical trials with agents known to reverse methylation in combination with carboplatin for patients with platinum resistant EOC were reported during the last year. The first, whose results were published in the journal *Cancer*, was a Phase I/II study of the hypomethylating drug azacitadine, and the second, presented at the ASCO 2011 meeting, was a Phase II trial of decitabine. Both studies showed preliminary evidence that hypo-methylated agents can partially restore sensitivity to platinum therapy. During the last year, new insights on resistance and sensitivity to chemotherapy were gleaned from two presentations at SGO 2011 Annual Meeting. In one study of women with serous EOC, it was found that specific minor hereditary alterations (polymorphisms) in the gene known as XPC were associated with long initial PFS after platinum-based therapy independent of known prognostic factors. XPC is a gene involved in DNA repair. Another study evaluated the presence of cancer stem cells (populations of parent tumor cells within a cancer that are relatively inactive but in an unpredictable way may start growing and dividing into active cancer cells). Cancer stem cells are known to be relatively resistant to chemotherapy. In this study, researchers found that the proportion of cancer stem cells was higher in recurrent EOC than in corresponding initially diagnosed tumors from the same women. This supports the idea that cancer stem cells represent a portion of an initially diagnosed EOC that can survive relatively effectively after exposure to chemotherapy compared to other cancer cells. The future challenge will be to identify methods to either selectively attack stem cells or at least suppress their conversion into active cancer cells. Finally, another strategy which may improve sensitivity to platinum-containing therapy is based on the observation that the time from completion of initial platinum-based therapy is directly related to a ability of women with recurrent EOC to respond to subsequent platinum containing regimens. It has been proposed that the use of non-platinum regimens in the management of first recurrence may improve overall outcome by extending the “platinum-free interval.” A Phase III randomized trial under development of the non-platinum combination PLD plus the investigational chemotherapy agent trabectedin versus PLD plus carboplatin in women with recurrent EOC and initial platinum free interval of between 6 and 12 months, will soon begin to answer this question.

Immunologic therapy, involving methods to stimulate the immune system to recognize and destroy cancer cells, is hoped to be an important future component of treatment for EOC. Many early phase trials of cancer vaccines or immune system stimulators are in progress. At the ASCO 2011 meeting, investigators reported on the results of a Phase II/III study (MIMOSA) with the antibody abagovomab, which has features resembling the tumor associated protein CA125 and therefore may serve as a vaccine. Unfortunately, in the 888 women who were in complete remission following primary therapy for advanced EOC, no difference in PFS was seen in women receiving

abagovomab compared with those receiving placebo. These results, according to scientific critiques, point out the complexity of immunologic therapy. It was noted in the discussion of the study results that in order for immunologic therapies to be successful, three components are necessary at minimum: 1) specific tumor-related components (antigens) which can be recognized as foreign by the immune system; 2) effective presentation of antigens to the immune system by antigen presenting cells (e.g. dendritic cells); and 3) reversal of immune-suppression by activating cancer-destroying cells of the immune system. In the abagovomab trial, only the first component was addressed in the study design, and it is unclear that CA125 is a rational antigen for future studies. Trials which incorporate all three components are in development.

It would seem likely that diagnosis of women with EOC at earlier stages would lead to improvements in survival rates. However, this principle has been difficult to prove in research. Certainly, most women with symptoms (including abdominal bloating, gastrointestinal symptoms, and pelvic pressure) will be found to have advanced stage cancers. Results from a case-control study (type of controlled retrospective study) involving over 1,400 women with EOC from Australia demonstrated that once cancers caused symptoms, shortening the time to diagnosis did not greatly alter stage of disease at diagnosis or survival. As discussed earlier, the discovery of methods to detect EOC in early stages and thereby improve survival rates has been a major challenge. At the ASCO 2011 meeting investigators reported on results from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer randomized screening trial involving 8,216 women aged 55–74 years randomly assigned to receive either annual screening with CA125 blood tests for 6 years and transvaginal ultrasound for 4 years, versus usual care without screening. Unfortunately, this study showed that this screening strategy did not reduce ovarian cancer mortality in women from the general population in this age group, and there was evidence of harm from diagnostic evaluation following a false positive screening test with respect to the number of unnecessary surgeries in the screening group.

The results of this and many other studies on screening have been disappointing for several reasons. First, EOC is a heterogeneous set of diseases likely with multiple mechanisms of cancer development. Second, EOC is not as prevalent a disease as, for example breast, colon or prostate cancer where screening has been shown to be effective in the general population. Third, the biology of disease development for most EOC, namely high-grade serous cancers, seems to develop more explosively than in a stepwise manner, so that the transitions between early-stage and advanced stage tumors may be extremely rapid and therefore not amenable to screening methods that are employed once or twice per year. It may be more frequent or even continuous screening with more specific (while still ultra-sensitive) methods will be necessary to demonstrate benefit. Recently, investigators have hypothesized that multiple blood tumor markers in combination with CA125 (which by itself appears to be insufficiently sensitive or specific) may improve specificity and sensitivity of detecting EOC. However, there is conflicting evidence on this point.

Underscoring this conflicting evidence are results of two studies reported during the last year. In one study reported at the ASCO 2011 meeting, the panel of the markers CA125, CA15.3, CA72.4, CA19.9, and HE4 applied retrospectively to women with or without EOC demonstrated increased sensitivity for the detection of EOC compared with CA125 alone, while maintaining specificity of 98%. In contrast, another study with a similar design published in the journal *Cancer* demonstrated that the addition of 7 completely different markers known to be elevated in the blood of women with EOC did not improve sensitivity for early detection of EOC beyond CA125 alone.

Perhaps in the case of EOC a more useful strategy than attempting to detect cancers that have already developed in an early stage would be to the identification more women at high risk for the development of EOC with the subsequent application of known methods of prevention (e.g. risk-reducing surgery, as discussed in the very beginning of this section). One way to study risk of ovarian cancer development is to conduct studies looking at heritable genetic changes other than those in the BRCA genes. Two studies reported during the last year, one at the 2001 meeting of the American Association for Cancer Research and the other at the SGO 2011 meeting, demonstrated subtle polymorphisms in sets of genes are highly predictive of risk. High grade serous cancers, the most common EOC subtype, resemble the surface lining of the fallopian tubes. Multiple studies in women from hereditary ovarian cancer families undergoing risk-reducing surgery have revealed pre-cancerous microscopic abnormalities in the inner lining of the fallopian tubes which could be the initial site of serous cancer development. The fallopian tube is lined by an internal glandular surface known as serous epithelium, and, as discussed above, the majority of ovarian cancers are advanced, high grade serous carcinomas. Scientists have theorized that cells with these early microscopic abnormalities can physically break off from the fallopian tube lining, drift away and become entrapped underneath the surface of the ovary where they can develop into an invasive cancer. In other words, a woman could develop a serous ovarian cancer which initially arises from microscopically abnormal cells in the fallopian tube. As an alternative, these microscopic fallopian tube abnormalities might not be directly connected to ovarian cancer development but might serve as a coincidental indicator that a woman is likely to develop ovarian cancer. At the SGO 2011 meeting, researchers showed that 43% of 21 women with advanced serous cancers had pre-cancerous lesions (serous tubal intraepithelial carcinoma) in their fallopian tubes. Furthermore, the molecular abnormalities associated with cancer initiation were indistinguishable in the tissue from these pre-cancerous lesions and their invasive serous carcinoma tissue, indicating possibly a common origin.

Another study published in the journal *Cancer* examined molecular indicators of cancer causation (defects in p53, a tumor suppressor protein; and K-67, a marker of cell growth) in fallopian tube surface lining. The study showed that these molecular alterations that precede cancer development were present more often in women with BRCA1 and BRCA2 hereditary mutations than women without this risk factor. In the TCGA study reported in June 2011, mutations in the gene for the p53 tumor suppressor protein that would knock out p53 function were present in 96% of serous cancers. It is thought that mutations in this gene occur in the pre-cancerous phase and leads to cancer causation in affected cells. Just as the serous subtype appears in some way to be linked to the fallopian tube, the endometrioid subtype (second most common type of EOC) appears to be linked to microscopic abnormalities within endometriosis (a commonly benign condition in which deposits of inner uterine lining tissue implants along the pelvic and abdominal surfaces, preferentially forming masses beneath the ovarian surface). Studies are ongoing to determine how we can use information on hereditary genetic variations in multiple genes or abnormalities in the fallopian tubes or in endometriosis to predict the risk of EOC development and thus allow effective primary prevention to decrease the incidence of the disease overall.

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 and become a cancer. This cancer may invade the muscle of the uterus and sometimes spread outside of the uterus to ovaries, lymph nodes, and the abdominal cavity.

Uterine sarcomas represent a rare 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 generally 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 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. Black women are also more likely to develop endometrial cancers that are more aggressive and thus comprise a group whose mortality from this disease is disproportionate to the rest of the population.

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 43,470 new cases diagnosed in the United States during 2011, and more than 95 percent of these will be endometrial adenocarcinomas, with approximately 1600 cases of uterine sarcomas. Approximately 7,950 women will die from uterine cancer in the United States during 2011.⁴

Advances in Uterine Cancer

Endometrial adenocarcinoma, which accounts for 95% of the over 43,000 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.

Prior to 1989 the staging system for endometrial cancer was a clinical staging system based on preoperative characteristics that took into account clinical features like the size of the uterus and cervical involvement. The current staging system was the result of a GOG trial (GOG 33) that demonstrated that we could more accurately determine outcome and future treatment by surgically staging patients to determine the site of any spread. The main contribution of this staging system was that we now could avoid additional therapy in most patients. Therefore, 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 collecting biopsies and removing lymph nodes when indicated. Gynecologic oncologists are the specialists with specific training in the management of uterine cancers, and have the surgical expertise to perform a hysterectomy and lymph node dissection. 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.

In a large prospective, randomized clinical trial of over 2500 women with presumed early stage endometrial cancer, 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. Long-term results of this GOG trial reported at the 2010 annual meeting of the Society of Gynecologic Oncologists, showed there was no difference in recurrence or survival rates between women staged by laparoscopy or open surgery. Although laparoscopic surgery was more difficult in patients who were extremely overweight or who had a large uterus, the favorable survival results and lower complication rates with laparoscopic staging seen in this trial establish minimally invasive surgery as a safe and effective option for the standard treatment of early endometrial cancer.

⁴ American Cancer Society. *Cancer Facts & Figures 2011*. Atlanta: American Cancer Society; 2011.

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. Continued experience with the use of RALS to stage endometrial cancer patients reported by several groups of gynecologic oncologists in 2010 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. Although outcomes from the use of robotic surgery to stage endometrial cancer continue to be encouraging, no head-to-head comparison of robotic surgery to either standard laparoscopy or open surgery was reported in 2010.

In 2010, 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.

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.

An important advance in the surgical staging of endometrial cancer is the incorporation of sentinel node mapping to identify the first (sentinel) nodes in the lymphatic chain that are at highest risk of having cancer spread. Identification and removal of these nodes can potentially avoid the side effects experienced by patients having a more extensive lymph node dissection including lymphedema (swelling of the lower extremities). Sentinel lymph node mapping involves the injection of either a radioactive solution or a blue dye into the cervix at the start of surgery that then travels to the closest group of lymph nodes that drain the uterus. The surgeon then identifies these sentinel nodes in the pelvis, using either a radiation probe or by visualizing the blue dye, and

removes only the sentinel lymph nodes during the staging surgery. Although no large prospective trials of sentinel node mapping in endometrial cancer have been performed, results from small single-institution studies seem to indicate that this procedure is feasible and accurate in detecting the sentinel node. Larger studies are needed to determine whether sentinel node mapping is accurate for detecting if endometrial cancer has spread to the lymph nodes

Patients at High-Risk for Recurrence and Clinical Trials to Determine Best Treatment Options

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 less than 10%, and survival is greater than 90%. This group of patients typically requires no further therapy. For those patients 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 alone.

The Gynecologic Oncology Group (GOG) recently opened a large prospective randomized 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, GOG-0249 is currently enrolling patients, and will try to determine if there is a benefit to these early stage patients of chemotherapy after surgery.

There is also controversy regarding whether chemotherapy, radiation or chemotherapy and radiation in combination are better if the patient has disease outside of the uterus. A recent study was completed by the GOG that demonstrated for the first time that chemotherapy was better than radiation in some patients with locally advanced endometrial cancer. For women with advanced stage endometrial cancer whether outcomes can be further improved by adding radiation to chemotherapy versus using chemotherapy alone is the focus of two new studies. One is a GOG (GOG 258) study and the other is being done in Europe (PORTEC 4). Both trials are open and accruing patients. GOG-0258, is currently open and will enroll over 800 patients whose stage III or IVA endometrial cancer has been optimally debulked with surgery to compare the recurrence-free and overall survival of those treated after surgery with cisplatin and tumor volume-directed radiotherapy followed by carboplatin and paclitaxel to the survival of those patients treated after surgery with carboplatin and paclitaxel alone. The PORTEC trial will compare radiation alone against radiation plus chemotherapy. Once these two trials are done we should have a much better idea of when these modalities are best used in the treatment of endometrial cancer.

New drugs that focus on blocking specific growth signals of cancer cells are being actively studied in endometrial cancer. Experimental agents that 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 clinical trials evaluate these interesting targeted agents in the treatment of women with advanced or recurrent endometrial cancer. Recently opened for enrollment, GOG trial-0248 ongoing GOG trial is designed to determine the response rate in patients with advanced, persistent, or recurrent endometrial carcinoma treated with the mTOR inhibitor temsirolimus with or without hormonal therapy comprising megestrol acetate and tamoxifen citrate. As we learn more about the genetic make up

of cancers through new research initiatives like The Cancer Genome Atlas (TCGA) we should be able to more accurately target the abnormalities of specific cancers and directly treat the identified abnormality within that cancer

Significant progress towards understanding the biology of endometrial cancers has been achieved by a large tumor banking study sponsored by the GOG. More than 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. Also there on going research through this database to determine the best way to screen the general population for an inherited form of endometrial cancers. Some women are at very high risk for developing this disease because they and some members of their families have Lynch Syndrome. This is a specific genetic abnormality that prevents repair of mistakes that occur during cell division. Cancers associated with Lynch syndrome are colon, endometrial, ovary, stomach and some types of bladder cancers. If you have a family history of any cancers in several family members or in family members at a young age you may want to ask your physician to evaluate you more thoroughly.

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 promising preliminary results in a small group of patients with advanced or recurrent carcinosarcoma disease treated with a regimen of carboplatin plus paclitaxel. . Based on these results, the GOG recently launched a trial of over 400 patients with newly diagnosed or recurrent uterine carcinosarcoma to determine if treatment with paclitaxel and carboplatin has similar effects on survival when compared to treatment with paclitaxel and ifosfamide In addition, the study will determine if side effects, specifically neurotoxicity and infection, are more favorable as well as quality of life are improved with the combination paclitaxel and carboplatin compared to that of paclitaxel and ifosfamide.

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 these patients, the GOG recently opened GOG protocol -0250 a prospective trial that randomizes women with advanced or recurrent leiomyosarcoma to receive docetaxel and gemcitabine alone or in combination with the angiogenesis inhibitor bevacizumab.

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 Foundation for Women's Cancer website, foundationforwomenscancer.org.

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. A quadravalent HPV vaccine () and a bivalent vaccine () have been approved by the FDA for this purpose. Examination of the vulva for changes by a woman at home or by her gynecologist during her yearly pelvic exam may lead to the detection of preinvasive disease or early 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 4,490 new cases diagnosed and approximately 950 deaths from vulvar cancer in the United States during 2011.⁵ Vulvar cancer is usually diagnosed in the early stages and is most often cured with surgical treatment.

Vulvar Cancer

Cancer of the vulva is a rare tumor with the most recent cancer statistics reporting that approximately 4,000 women in the United States are afflicted annually. Fortunately, it is highly curable if detected at an early stage; however, treatment can have significant adverse effects on body image, sexual function, as well as bladder and rectal function. Lower extremity lymphedema, a form of chronic swelling which results from the disruption of lymphatic drainage in the groin, is a long-term complication and is, for the most part, irreversible. Much of the purpose of clinical trials has been to improve overall survival while minimizing the impact of treatment on organ function and quality of life.

Background

One hundred years ago, vulvar cancer was considered a fatal disease. The suffering endured by patients and caregivers was horrific. Patients typically died from locally progressive disease that eroded into the rectum, vagina, bladder and pubic bone. This was an era before antibiotics and blood transfusions were available. Surgical techniques and pain management were rudimentary compared with current standards.

⁵ American Cancer Society. *Cancer Facts & Figures 2011*. Atlanta: American Cancer Society; 2011.

A major breakthrough occurred in the 1890s when Dr. William Halsted described radical mastectomy for the treatment of advanced breast cancer. This innovative surgical strategy consisted of complete resection of the primary organ, regional lymph nodes, and intervening lymphatic channels and remained the standard for the treatment of breast cancer through the 1970's. The procedure was adapted to vulvar cancer patients and radical vulvectomy represented a huge advance in surgery and undoubtedly saved the lives of many patients. Unfortunately, survivors of radical vulvectomy suffered from a high incidence of wound infection and wound breakdown. Long-term complications, including diminished body image and sexual function as well as chronic lymphedema, were a heavy burden on survivors.

Over the following decades, medical advances included antibiotics, transfusion medicine, critical care medicine and improved surgical techniques which reduced the morbidity and mortality of radical vulvectomy. Pioneers such as Robert Morris and Philip DiSaia introduced more limited procedures such as hemi-vulvectomy and wide radical excision respectively which reduced short-term and long-term complications.

It is important to note that social norms then, as now, impact patient interactions with healthcare providers. One hundred years ago, the shame associated with vulvar or breast complaints made it very difficult for women to alert physicians to symptoms associated with vulvar cancer including a growing lesion, malodorous discharge and bleeding after intercourse. Feelings of shame rooted in a history of sexual abuse, insensitive treatment by a healthcare provider, and the personal nature of the complaints remain barriers to early detection and treatment of gynecologic cancers today.

In the 1960–70's, investigators focused on identifying patients who did not require lymphadenectomy. This was an era prior to the creation of multi-institution co-operative groups, so most published research was in the form of single institution series and expert opinion. The effort to omit lymphadenectomy in selected patients was conducted by trial and error at large academic centers. Unfortunately, a single institution experience can lead to an incorrect conclusion and may lack the statistical power to justify major changes to standard treatment paradigms. This effort led to the creation of the Gynecologic Oncology Group (GOG) in 1970 by gynecologic oncologists from 11 institutions. The organization has now grown to over 50 member institutions and more than 160 affiliates. The GOG has played a critical role in advancing the care of women with vulvar cancer since its inception.

In the years after its founding, the GOG conducted surgical pathologic studies that established the linkage between depth of invasion and lymph node metastases,, the role of pelvic radiation therapy in patients with groin metastases [6], and the utility of concurrent chemoradiation to avert pelvic exenteration in patients with advanced tumors involving the vagina and rectum.

Just as the Halsted's radical mastectomy proved to be the catalyst for dramatic change in the treatment of vulvar cancer, a surgical innovation with a dramatic impact on the management of vulvar cancer in the last 20 years came from an unlikely source. In the late 1970's and early 1980's a Paraguayan urologist, Dr Ramon Cabanas, described a technique to identify the first draining lymph node in patients with penile carcinoma. This was the first modern description of sentinel lymph node biopsy (SLNB). Many investigators, notably Dr. Donald Morton from Santa Monica, CA, studied patients with cutaneous melanoma, simplified lymphatic mapping and SLNB making it widely available to surgeons and gynecologic oncologists. The first description of SLNB in patients with vulvar cancer was in 1994, marking the start of a new era in the care of women with vulvar cancer.

Treatment of Vulvar Cancer Today

The early 1990's were notable by the publication of multiple single institution series describing patients managed with SLNB. Early experience at centers like The University of Texas MD Anderson Cancer Center in the United States [11], and Groningen University Medical Center in the Netherlands established the feasibility of SLNB in patients with vulvar cancer. In addition to establishing feasibility, an accurate estimate of the false negative rate was critical to compare SLNB to the existing standard treatment, inguinal femoral lymphadenectomy. The primary question was: if a patient has a SLNB and the lymph node is carefully examined by a pathologist and found to be free of cancer cells, what is the chance that one of the 7–10 remaining non-sentinel lymph nodes which are left in place will actually have metastatic cancer? When the SLN is falsely negative, the patients relapse rate and mortality is high, and all of the benefits of SLNB, avoiding lymphadenectomy and lymphedema, are negated. Although the results of the single institution trials were very promising, clinicians around the world were hesitant to abandon the tried and true standard for lymphadenectomy without larger studies.

Two large multi-institutional trials were commenced to answer this question. The first conducted in the Netherlands enrolled 400 patients over 7 years. In this study, patients with a negative SLNB were closely observed for relapse. The GOG enrolled over 500 patients over 9 years who underwent SLNB followed by lymphadenectomy. These studies had sufficient power to reach their respective statistical end points and demonstrated remarkably similar findings. Patients' who have a new vulvar cancer of less than 4 cm in size and have normal preoperative imaging, can undergo wide excision and SLNB with a less than 3% risk of groin relapse if the SLN is free from metastatic disease. The standardization of SLNB for vulvar cancer averts thousands of unnecessary surgical procedures and their attendant side effects each year.

Future Challenges

The last 20 years of vulvar cancer research has achieved a major milestone — the incorporation of SLNB into the management of women with vulvar cancer. Nevertheless, major challenges remain to improve outcomes. What is the most appropriate management for patients with lymph node metastases? The Dutch GROINS investigators and the GOG are joining together to enroll patients in a trial that incorporates radiation therapy for patients with groin lymph node metastases. What is the role of targeted agents in the treatment of vulvar cancer? A recent study suggests that the addition of the tyrosine kinase inhibitor, erlotinib, compared to chemotherapy, results in improved response rates to treatment. Will HPV vaccines designed to reduce the incidence of cervix cancer have a similar benefit in reducing the incidence of vulvar cancer? What is the role for sexual health counselors and therapists for the treatment of post-traumatic stress symptoms frequently observed in vulvar cancer survivors? What is the best management for patients who have lymphedema?

Summary

The last 20 years of clinical trials in patients with vulvar cancer have established the utility of sentinel lymph node biopsy in selected patients with small primary tumors. This approach will limit complications for a large proportion of patients who do not have metastatic disease. Continued progress will depend upon improving treatment outcomes for patients with metastatic or recurrent disease.

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