

2014 State of the State of Gynecologic Cancers

Twelfth Annual Report to the Women of America

FOUNDATION FOR
WOMEN'S CANCER



Gynecologic Cancer
Awareness • Research • Education

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The Foundation for Women's Cancer is a 501(c)3 not for profit organization whose mission, in concert with SGO, is to support research, education and public awareness of gynecologic cancer prevention, early diagnosis and optimal treatment.

A Letter to the Women of America

As I began to write the preface to the Foundation for Women's Cancer 12th Annual Report to the Women of America, I decided to compare this year's report to the first report written in 2003.

It is heartening to see the progress that has been made during this 12-year period. For example, the first cervical cancer vaccine was still in the clinical trial stage in 2003. Now there are two effective vaccines, and boys have been included in the vaccination recommendations, making the hope that cervical cancer can be totally prevented one step closer to reality.

In 2003, no identified cluster of symptoms associated with ovarian cancer had been identified, and little was known about ovarian cancer hereditary risk factors. The knowledge that has been accumulated since the first report was written allows women to be alert to symptoms and have access to an algorithm that can define individual risk. This represents a significant step forward in potentially reducing risk and/or enabling an early diagnosis and thus an improved prognosis for the most lethal gynecologic cancer. Moreover, in October 2014, the Society of Gynecologic Oncology issued a position statement recommending that all women diagnosed with epithelial ovarian, fallopian tube and peritoneal cancer receive genetic counseling and offered genetic testing.

Importantly, the recent FDA approval of olaparib, a PARP inhibitor, for women with recurrent ovarian cancer who are BRCA positive is the first therapy approved for a specific population of ovarian cancer patients, officially welcoming the era of personalized therapy.

With respect to uterine or endometrial cancer, treatment advances continue. However, while obesity was listed as a risk factor in 2003, only now do we appreciate the significance of this risk factor and have accelerated our efforts to so inform women. Additionally, bleeding after menopause, the most common uterine cancer symptom, is not recognized by all women as a possible sign of this cancer. Thus we must redouble our educational efforts to combat this lack of knowledge.

While the treatment for vaginal and vulvar cancers has remained static, the relationship between these two cancers and infection with the human papillomavirus again offers hope of reducing the number of these relatively rare cancers through widespread adoption of the HPV/cervical cancer vaccine.

These advances have been made through the efforts of clinicians and basic scientists who work tirelessly to lessen the burden of these cancers. Critical to their success is the willingness of women to participate in clinical trials. We respectfully dedicate the *2014 State of the State of Gynecologic Cancers: Twelfth Annual Report to the Women of America* to the thousands of women who have participated in a clinical trial.

Lastly, we again thank the gynecologic oncologists who volunteered their time to provide the information contained in this year's report.

Sincerely,



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

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 91,000 new cases diagnosed and approximately 28,000 deaths from gynecologic cancers in the United States during 2013.¹

¹ American Cancer Society. *Cancer Facts & Figures 2013*. Atlanta: American Cancer Society; 2013.

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 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 vaccination and regular screening. 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 exposed is the greatest prevention strategy against 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 can be identified by screening with a Pap test and HPV testing.

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 develop any cervical disease that would require 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 include cervical cancer screening takes away the opportunity for early diagnosis and treatment. Even in women with HIV, previously thought to be at risk for cervical cancer, appropriate screening with Pap tests and HPV 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 more than 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. Healthcare providers will occasionally 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 to include increased intervals for screening in these women. 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. Recently the management guidelines have also been updated. These updates include more conservative management of equivocal abnormalities in young women. 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. 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 30 and over, HPV testing in combination 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.

Recently, the Society of Gynecologic Oncology (SGO) and the American Society for Colposcopy and Cervical Pathology (ASCCP) issued an Interim Guidance Report after the U.S. Food and Drug Administration (FDA) approved an HPV test as a “primary,” or first, test performed for cervical cancer screening. The test detects DNA from 14 high-risk HPV types, including types 16 and 18, which are responsible for 70 percent of cervical cancers.

The Interim Guidance Report recommends:

- Primary HPV testing can be considered for women starting at age 25.
- Women under age 25 should continue to follow current guidelines that recommend cytology alone beginning at age 21.
- Women with a negative primary HPV test result should not be retested again for three years. This is the same screening interval recommended under current guidelines for a normal cytology test result.
- An HPV test positive for HPV 16 and 18, two types associated with a higher risk of future disease, should be followed with colposcopy, a test that allows the doctor to examine the cervix under illumination and magnification.
- A test that is positive for HPV types other than 16 and 18 should be followed by reflex cytology testing.

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 12,360 new cases of invasive cervical cancer diagnosed and approximately 4,020 deaths in the United States during 2014.²

² American Cancer Society. *Cancer Facts & Figures 2014*. Atlanta: American Cancer Society; 2014.

Advances in Cervical Cancer

A continuing challenge in the treatment of cervical cancer is finding effective therapy for women whose cancer recurs after being treated initially with surgery, or the combination of radiation and chemotherapy. In 2009, the 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 recently completed GOG protocol 240, a prospective randomized trial designed to study the effect of combining bevacizumab with paclitaxel/cisplatin vs. topotecan/paclitaxel chemotherapy on survival in women with recurrent cervical cancer. Results of this trial, presented as one of the lead presentations at the American Society of Clinical Oncology (ASCO) in 2013, showed nearly a 30% improvement in survival when compared non-bevacizumab containing regimens. This led to an NCI alert on the results of this trial and ultimately, FDA approval of this drug for recurrent cervical cancer. The survival advantage identified in this trial is the largest significant survival improvement in recurrent cervical cancer patients in more than two decades.

Another active area of research in cervical cancer remains in prevention, including the continued development and implementation of both the current preventative HPV vaccines as well as therapeutic targeting vaccines, and updates in screening and management. Increasing knowledge of ways to prevent HPV infection and increase access to care are key to continuing these advances. 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 precancer.

More than 40 types of HPV have been identified in vaginal, vulvar and cervical diseases. Of these, approximately 14 are known to be cancer-causing types. Two types, HPV 16 and 18, are the most common HPV types associated with cervical cancer. HPV 16 causes nearly 60% of all cervical cancers and HPV 18 cause an additional 10 to 20%. 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 FDA approved HPV vaccines protect against infection with HPV types 16 and 18. Recently, the FDA approved a new vaccine for both boys and girls that protects against nine types of HPV, five more types than previously approved by the FDA. This new vaccine has the potential to prevent up to 90% of cervical, vaginal, vulvar and anal cancers.

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 more than 70%. These high vaccination rates have already been achieved in some developed countries, but the rates is disappointingly low in the United States. Recent reports of vaccine registries shows that while vaccine use in the United States is increasing, only a small number of young girls and boys have received all 3 doses of vaccines. The barriers remain access to care, patient and provider education, and attitudes toward the HPV vaccine. The HPV vaccine is available through almost all public health facilities and government sponsored insurance programs. Essentially all private insurers will provide coverage for the cost of HPV vaccines for those in the recommended age range. Educational efforts, including efforts by the Foundation for Women's Cancer, are ongoing. Of note, all professional stakeholder organizations recommend routine use of HPV vaccines in young women. Because HPV vaccination is so effective in 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 girls ages 11 and 12 years (ideally before first intercourse), and young women ages 13–26. Also, vaccination in boys

is recommended as well. Recently, the American Cancer Society convened the first meeting of the National HPV Vaccination Roundtable, consisting of 65 national organizations, whose purpose is to increase vaccination rates among 11 and 12 year olds.

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 HPV vaccines that are routinely recommended for prevention. These therapeutic vaccines in development work by boosting a woman's immune response to recognized HPV. Since cervical cancer is far from being eradicated, clinical trials of vaccines that treat as well as prevent cervical cancer are important.

There have been recent changes to the terminology as to how cervical biopsies, as well as biopsies of other lower genital tract precancerous lesions such as vulva and anus, are read. This standardized terminology assists pathologists and clinicians in knowing which biopsies might be precancerous. Also, there has been an increase in the amount of sensitive testing that pathologists might use to assist them in determining which biopsies will need more treatment. The new terminology also takes these new sensitive tests into account.

Progress continues to be made in developing better treatments for women with 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, when cervical cancer is often diagnosed, access to surgical management that can allow them to preserve their fertility at the prime of their reproductive life.

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 women 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 new, targeted chemotherapy drugs that improve survival with potentially fewer harmful side effects than the drugs that have been traditionally used.

Ovarian Cancer: Epithelial

State of Epithelial Ovarian Cancer

Ovarian cancer is the ninth most common cancer among women in the United States, and is generally grouped with primary peritoneal and fallopian tube cancers. About 85 to 90% of ovarian cancers are classified as epithelial ovarian cancers.

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

Women with ovarian cancer report that symptoms are persistent and show a noticeable deviation from the normal way their body feels. Unfortunately these symptoms are quite nonspecific, and can mistakenly be blamed on weight gain, age, heartburn or irritable bowel syndrome. Several studies show that even early-stage ovarian cancer can produce these symptoms, so women should be vocal with their physicians about any new symptoms in an effort to make a diagnosis as soon as possible.

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 diagnosis of disease at its earliest, most treatable stage. Early-stage disease is associated with an improved prognosis. However, it is not definitively known that all cancers progress from an early stage to a late one. It may be that the most aggressive cancers move to other sites very quickly, and that is why later stage is associated with a poor prognosis. And perhaps cancers detected at an earlier stage are more slow growing. Therefore diagnosis at a later stage does not necessarily imply that an early cancer was missed.

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. The mean age at diagnosis is 62. 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 developing 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 also important risk factors.

Screening/Prevention: Currently, there is no widely accepted or effective screening test for epithelial ovarian cancer. High-risk women, such as those with a strong family history known BRCA mutation or Lynch syndrome, may be candidates for screening using transvaginal ultrasound and CA 125 blood tests on an annual or biannual schedule, though the benefits of such screening is unproven. For most women, ultrasound and CA 125 screening is not recommended because false positive results can lead to unnecessary surgery. More details on screening are described on page 8.

Incidence: Ovarian cancer ranks fifth in cancer deaths among women and causes more deaths than any other reproductive cancer. It is estimated that there will be about 21,900, new cases diagnosed, and approximately 14,270 deaths from ovarian cancer in the United States during 2014.³ However, the death rates from ovarian cancer have declined by 2% per year from 2005 to 2009.

Advances in Ovarian Cancer

Etiology and Biology

Remarkable advances in the understanding of the biology of ovarian cancer have been made over the last few years. Appreciation for these concepts has provided a more rational approach to prevention, screening and treatment of ovarian cancer, and continues to be the foundation for future discoveries.

Recent evidence suggests that ovarian cancer should be classified into 2 distinct categories: Type I ovarian cancers encompass essentially all epithelial ovarian cancers that are not high-grade papillary serous cancers and include endometrioid, clear cell and transitional carcinomas; and low-grade serous cancers. Low-grade serous tumors may arise from tumors of low-malignant potential (sometimes called borderline tumors), thus supporting a genetic continuum of tumor progression. They are usually genetically stable, grow more slowly, and therefore more likely to be diagnosed in early stage. However, they are actually less responsive to chemotherapy due to their slow growth pattern. They lack p53 and BRCA mutations, but are known to frequently harbor KRAS BRAF, and MEK mutations, offering an opportunity for directed therapies. Ongoing trials evaluating the use of MEK inhibitors in low-grade serous ovarian cancer appear promising. Although Type I cancers are often described as more slow growing, this generally applies to only the low-grade cancers — endometrioid and clear cell cancers are highly aggressive. These subtypes may frequently arise from sites of endometriosis in the pelvis or on the ovary. They also are more often diagnosed at an early stage, but are as aggressive as serous cancers that more often originate in the fallopian tube, and are treated similarly. Biologically, they frequently harbor ERBB2, PTEN and PIK3CA mutations.

Type II ovarian cancers include high-grade serous carcinomas and undifferentiated carcinomas. It is becoming increasingly accepted that they often (50–70% of cases) arise from the fallopian tube. Importantly, precursor lesions have been identified in the lining of the fallopian tube prior to the development of invasive carcinoma, which may offer an opportunity for early detection. The pathway to tubal ovarian cancer is thought to include secretory cell outgrowths (SCOUTS) that have low expression of PTEN, Ki67, PAX2 and typically no p53 expression. Serous tubal intraepithelial lesions (STILs) subsequently follow and are characterized by p53 overexpression (p53 signature) that lead to serous tubal intraepithelial neoplasia, or STIC's, prior to the development of invasive ovarian cancer. Type II ovarian cancers usually present in advanced stages and are more responsive to chemotherapy than their low-grade counterparts. However, they do account for more ovarian cancer deaths overall. P53 and BRCA mutations are common in this group of tumors.

³ American Cancer Society. *Cancer Facts & Figures, 2014*. Atlanta: American Cancer Society; 2014.

One exciting discovery was recently made regarding an aggressive subtype of ovarian cancer, the small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). Unlike the extensive molecular variability of most ovarian cancers, this subset was found to uniformly carry mutations in the SMARCA4 gene, a key protein in handling how chromosomes are folded. Targeting this protein led to reductions in tumor growth, leading to hope that effective therapies can be found for these patients.

Prevention

It is with the understanding that many high-grade serous ovarian cancers arise from the fallopian tubes that researchers have begun to study the impact of recommending removal of the tubes (salpingectomies) in all women undergoing tubal ligations or hysterectomies. It is thought that salpingectomy could decrease the number of fallopian tube/ovarian cancer cases. A large US trial is currently underway to evaluate the impact of salpingectomies in women at high risk of developing breast and/or ovarian cancer. This trial is appropriate for women who have completed child bearing, are younger than the current recommended age for removal of the tube and ovaries (risk reducing salpingo-oophorectomy or RRSO) and would like to avoid surgical menopause until this procedure is required.

A recent retrospective Scandinavian study found that salpingectomy alone did indeed reduce risk of ovarian cancer. However risk was reduced even more by removal of both fallopian tubes and ovaries, suggesting that many ovarian cancers do develop from the ovarian proper. In patients for whom ovarian preservation is important, salpingectomy may offer a reduced risk. But if reducing ovarian cancer risk is the priority, removal of both tubes and ovaries is still the most effective option.

Screening and Early Detection

Unfortunately most ovarian cancers are diagnosed at a late stage, and immense efforts have been made to develop programs that might find them at an early and more curable stage. Programs have included evaluating CA 125, ultrasound, other biomarkers and symptomatology. The primary barriers to early detection includes nonspecific symptomatology, growth in a deep cavity where noninvasive tests are not feasible, and the relative rarity of disease, which requires any test to be highly accurate to avoid causing more harm (removal of benign ovaries) than good.

Even early-stage ovarian cancers can cause symptoms, so screening using a symptom index has been shown to be feasible and acceptable at primary care visits. It is undergoing further study in larger clinical trials to see if it is also effective. Using symptoms alone is not likely to lead to early detection, but incorporating them into other tests, such as CA 125 and ultrasound might improve the efficacy of these approaches. Patients with symptoms could be referred for additional testing, or patients with positive tests could conceivably only undergo surgery if they are having symptoms consistent with disease.

The Prostate, Lung, Colorectal and Ovarian Cancer screening trial (PLCO) has demonstrated that examining CA 125 (using an absolute cutoff value for normal versus abnormal) combined with transvaginal ultrasound in all women leads to about 30 unnecessary operations for every cancer detected. Additionally, even when cancers were detected, they were not found at an earlier stage, making it less likely that this approach could improve survival. Therefore routine screening is only recommended for very high-risk patients, such as those with a BRCA mutation or Lynch syndrome. However, modifications to this approach are showing promise for the general population.

The United Kingdom Collaborative Trial of Ovarian Cancer Screening trial (UKCTOCS) modified this approach by performing CA 125 first, with repeats for concerning values prior to performing an ultrasound or taking the patient to surgery. Because many benign conditions are detected by ultrasound, this reduced the rate of unnecessary surgery to only 4–5. Additionally, of the cancers that were found, half were still early stage. Long-term follow-up will be required to determine if this approach is cost effective in increasing survival, but it is promising.

In another modification to this approach, investigators have taken years of prospectively collected CA 125 data and developed mathematical models that look at CA 125 changes over time instead of using an absolute cutoff value. By following CA 125 over time, several cases were identified where the CA 125 was increasing but staying in the “normal” range. By identifying these increases, further evaluation was pursued, and all of the cancers identified were Stage I or borderline tumors. This exciting “Risk of Ovarian Cancer Algorithm” (ROCA) approach is being examined in a larger group of patients that may allow effective screening programs for all women.

Efforts are also being directed to promising technologies that may allow early detection of ovarian cancer through blood tests or other noninvasive approaches. In one novel approach to early detection, it was recently shown that highly sensitive DNA tests can identify mutations in ovarian cancers by collecting secretions making their way into the vagina. Ovarian cancer patients placed a tampon in the vagina the evening before surgery, which was removed the following day. DNA from those tampon specimens was sequenced for P53, and the same mutations in the patient tumor were present in the vaginal secretions. Importantly, these same P53 mutations are often present prior to malignancy developing, and so could possibly be identified in a precancerous state with noninvasive testing.

Molecular Biology

The Cancer Genome Atlas (TCGA) Research Network has profiled and analyzed a large number of tumors, including ovarian, to detect molecular abnormalities that may be used as targets. With the emergence of new agents that target specific pathways, researchers can compare genetic profiles among different tumor types to detect similarities that may be used as targets using the same agent across cancer types. This resource has also made possible immediate searches for expression of novel genes, with associated patient survival information, that ordinarily would have taken months to conduct individually.

Treatment

Surgery

The mainstay of management of ovarian cancer remains a combination of surgery and platinum-based chemotherapy. The goal of surgery should be to remove all visible disease, as patients achieving this status routinely are shown to have improved survival. Whether this improved survival is due to a difference in tumor biology in which a less aggressive tumor is associated with decreased difficulty removing all disease, or the act of removing as much disease as possible is a cause versus an association, is still under debate. A recent extensive review of one of largest Gynecologic Oncology Group (GOG) trials ever conducted, GOG-182, demonstrated that the greatest effect on overall outcome is extent of disease at the time of surgery, but that removing all visible disease had a modest beneficial effect even in those with the greatest disease burden. Until it is more definitively understood, every effort should be made to remove all visible disease. It is preferred that patients be initially managed by a gynecologic oncologist, who can guide patients

in deciding whether surgery or chemotherapy is the appropriate first step. Numerous studies of various large national databases have repeatedly shown that patients have longer survival if they are managed by gynecologic oncologists at larger institutions that have extensive experience treating ovarian cancer.

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is the treatment of ovarian cancer patients with chemotherapy, followed by surgical removal of remaining disease (and then likely additional chemotherapy) instead of surgery first. Neoadjuvant chemotherapy has been shown to reduce the complexity and complications (ICU admissions, length of hospitalization, transfusions required, etc) associated with surgery. It is most often used in patients who may have excessive morbidity with surgery, such as those with widely disseminated disease (especially if in the thoracic cavity) such that removal of all visible disease is not likely feasible. It also may be appropriate for those with other medical problems who might not tolerate extensive surgery, such as the very elderly, or those with significant renal or cardiopulmonary disease. Whether use of neoadjuvant chemotherapy is appropriate for all patients is still under investigation. In 2010 Vergote published the first randomized trial of neoadjuvant chemotherapy versus upfront surgery and found that there was similar survival between the two groups. Unpublished but presented at the 2013 American Society of Clinical Oncology (ASCO) meeting were results of the **CHORUS (CHemotherapy OR Upfront Surgery)** trial, which also showed similar overall survival. As expected, in both trials surgical complications were reduced, and rates of optimal resection were higher after neoadjuvant chemotherapy. However, both of these European trials had less than average rates of resection and survival compared to patients managed by gynecologic oncologists in the United States. The assumption cannot be made that the improved optimal resection rates allowed by chemotherapy automatically allow improved survival. However, it also cannot be ignored that these are the only randomized trials conducted to address the question, and survival was not compromised. The decision to proceed with surgery or chemotherapy first must be individualized to each patient, taking into account the best estimate of disease burden at presentation and the patient's overall health. Some physicians elect to perform laparoscopic surgery to aid in this decision.

Cytotoxic Chemotherapy

All patients with newly diagnosed ovarian cancer should be treated with a combination of platinum and taxane agent. If only one drug is initially used due to toxicity concerns, the platinum agent is the more important. The most commonly used agents are carboplatin (preferred over cisplatin because of a more moderate side effect profile) and paclitaxel, given in a 3-week schedule (except as detailed below). Docetaxel is often substituted for paclitaxel, because it causes less neuropathy, although this is at the expense of increased bone marrow suppression. Increasing evidence continues to accumulate that demonstrate improvements in survival can be achieved with adjustments to the conventional 3-week IV schedule and should be considered.

Intraperitoneal chemotherapy: Intraperitoneal (IP) chemotherapy delivers some of the agent directly into the abdominal cavity where ovarian cancer predominantly grows. This approach also allows more total chemotherapy to be delivered. Several trials have demonstrated superiority to IV therapy alone, though the most appropriate combination and schedule is still under investigation. GOG-172 is the most recent and relevant trial examining how patients are treated today, which evaluated IP chemotherapy (IP cisplatin and IV taxol the first week, IP taxol in week 2) in women with optimally cytoreduced advanced ovarian cancer compared to standard, every 3 week, intravenous (IV) chemotherapy. Long-term follow-up of patients from this trial was recently

presented, and showed a survival benefit of IP over IV therapy that extended beyond 10 years (110 vs 43.2 months). In addition, those who completed more cycles of IP therapy had a higher 5 year overall survival rate. Delivery of IP chemotherapy can be challenging, with increased side effects and discomfort, and many gynecologic or medical oncologists are still not comfortable with the approach. However, use of IP chemotherapy is steadily increasing and should be discussed as an option for patients who have had optimal cytoreduction. Whether this is appropriate for patients with suboptimal cytoreduction is still under investigation.

Dose dense chemotherapy: The Japanese Gynecologic Oncology Group (JGOG) reported on its long-term data of dose dense chemotherapy (carboplatin day 1 AUC-6 and paclitaxel 80 mg day 1, 8, 15 every 21 days). In this trial, dose dense chemotherapy provided a significant benefit in time to relapse (Progression-Free Survival, PFS) and overall survival (OS) compared to standard 3 week chemotherapy (median PFS-28.2 months versus 17.5 months, OS-100.5 versus OS-62.2 months). These results are comparable to the intraperitoneal chemotherapy trials, but importantly are relevant to patients with both suboptimal and optimal cytoreduction. Dose dense chemotherapy trials in Europe and North America are ongoing (GOG-262 and ICON 8.). Preliminary results suggest that dose-dense chemotherapy is superior to conventional 3-week IV chemotherapy, but similar effects can be obtained with addition of bevacizumab, and bevacizumab on top of dose-dense therapy confers no advantage to either alone. However, since bevacizumab is not approved in the up-front setting, dose-dense therapy is increasingly being adopted, especially for patients with suboptimal cytoreduction that may not be eligible for IP chemotherapy.

Biologic Therapies

PARP inhibitors: PARP inhibitors are designed to be toxic to cancer cells with defects in a DNA repair process called homologous recombination (HR). These include patients with BRCA mutations, either inherited or developing spontaneously. On the basis of multiple trials, the FDA gave approval to the PARP inhibitor olaparib for use in women with germline (inheritable) BRCA mutations who have received at least 3 lines of prior therapy. The response rate to olaparib in these patients is approximately 35%. This represents the first therapy approved for a specific population of ovarian cancer patients, officially welcoming the era of personalized therapy. Although many ovarian cancer patients without BRCA mutations have defects in homologous recombination (approximately an additional 30% of patients), it is not yet known the best way to identify these patients, and it is not yet proven that they will indeed have a positive response to PARP inhibitors as predicted. An examination of various methods to profile patients is included in current PARP inhibitor trials, to hopefully expand indications in the future. PARP inhibitors are relatively well tolerated, with the most prominent side effects being fatigue and nausea.

Anti-angiogenic agents: Cediranib is a novel anti-angiogenic agent that inhibits multiple VEGF receptors. It has had modest activity alone, but recently was found to synergize well with PARP inhibitors. A Phase II trial of combined cediranib and olaparib was presented at the American Society of Clinical Oncology (ASCO) 2014 Annual Meeting and demonstrated that when used in combination, both drugs produced an 84% response rate compared to 56% with olaparib alone, with median progression-free survival of 17.7 versus 9.0 months, respectively. About half of the patients in the trial had germline BRCA mutations, and most were platinum sensitive. This exciting result has led to discussion on development of Phase III trials with this combination, with decisions to be made on which populations to study, which comparison groups to include, and which biologic markers should be evaluated during the study.

Pazopanib is an inhibitor of multiple angiogenic and growth factor receptors (VEGFR-1, -2, -3, PDGFR- α and - β and c-Kit). As presented at ASCO in 2014, a Phase II trial was reported including patients resistant to platinum agents, and treated with weekly paclitaxel plus pazopanib versus weekly paclitaxel alone. The combination of drugs led to prolonged PFS (3.5 versus 6.3 months ($p=0.0008$), with nearly as significant an improvement in overall survival as well (14.8 versus 18.7 months, $p=0.07$) in this highly resistant population. Follow-up Phase III studies are being designed.

Summary

These are exciting times as our understanding of the origin of ovarian cancer improves, and our knowledge of the molecular profiles and pathways important to ovarian cancer growth increases exponentially. Targeted therapies are making their way into clinical practice, and multiple promising agents are in the pipeline. Strategies to reduce ovarian cancer risk and increase rates of detection at early stages are also making progress. Improved overall survival rates are slowly being seen, with the hope that advanced programs in all aspects of ovarian cancer research will continue this trend, and with even greater rates of improvement.

Uterine Cancer: Endometrial Adenocarcinoma and Uterine Sarcomas

State of Uterine Cancer

The endometrium forms the inner lining of the uterus or womb, and most uterine cancers begin because of cancerous changes in this 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). The majority of endometrial carcinomas are of grade 1 or 2 endometrioid subtype and these carry a very favorable prognosis. Grade 3 endometrioid, serous and clear cell carcinomas are considered high risk variants of endometrial carcinoma. In addition, recent molecular evidence supports including carcinosarcomas in this classification, and both the epidemiology and clinical behavior of these tumors closely mimic aggressive endometrial carcinoma.

Uterine sarcomas represent a type of uterine cancer in which malignant cells form in the muscular wall of the uterus (leiomyosarcoma) or in the network of support cells in the uterine lining (endometrial stromal sarcomas). Accounting for fewer than 5% 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. Any bleeding after menopause may be a symptom of uterine cancer and the amount of bleeding does not correlate with the risk of cancer. Younger women should note irregular or heavy vaginal bleeding because they may be symptoms of uterine cancer. Sarcomas can also cause abnormal bleeding and may produce pelvic pain or pressure.

Risk Factors: The primary risk factor for most endometrial cancers is prolonged exposure to the hormone estrogen (either from internal or external sources) without adequate opposition from progesterone. This may occur from hormone therapy with estrogen only (without progesterone), tamoxifen therapy or obesity related estrogen imbalance. Irregular menstrual cycles, and infertility due to ovulatory dysfunction or polycystic ovarian syndrome present a risk for similar hormonal reasons. Additional risk factors include an early age at onset of menses, late age at menopause, never giving birth, diabetes and hypertension. A strong family history of endometrial or colon cancer may signal an inherited risk for developing endometrial cancer.

Most women with endometrial cancer are diagnosed at an early stage and have a very good prognosis. The risk factors for higher risk variants are less clear. These high risk cancers may occur more commonly in black women. Though uterine sarcomas are rare, having a history of pelvic radiation and use of tamoxifen increase the risk of developing this cancer.

Screening/Prevention: Women with post-menopausal 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 and maintaining a healthy weight. Progesterone use, either alone or in combination with estrogen as is found in birth control pills, lowers the risk of endometrial cancer. Progestins can prevent cancer from developing in women who have irregular menstrual cycles and infertility. Women who are obese may benefit from a progestin containing IUD which directly distributes a progestin into the endometrium and needs replacement only every 5 years. 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 52,630 new cases diagnosed in the United States during 2014, and more than 95% of these will be endometrial adenocarcinomas. Approximately 8,590 women will die from uterine cancer in the United States during 2014.⁴

Advances in Uterine Cancer

Molecular Biology

The Cancer Genome Atlas (TCGA) Research Network analyzed in-depth genetic data from a large number of endometrial cancers and published their findings in 2013. This landmark study provided novel insights into disease biology and diagnostic classification that could have near term therapeutic applications. Follow up investigations are underway to develop the concept of utilizing this new molecular classification to tailor adjuvant treatment targeting the distinct genomic features. Secondary analyses are providing additional molecular insights into the common as well as the distinct features of uterine cancers and indicate potential additional opportunities for therapeutic selectivity.

Screening

Screening is a population-based strategy or test to detect a disease in individuals before they show signs or symptoms. Unfortunately, there are no good screening tests for endometrial cancer at this time though it is an active area of research. Routine screening for asymptomatic women is not advised. Factors against screening are the relatively low prevalence of disease, typical early stage presentation and early symptoms that allow detection when treatment can stop progression. Because of these factors it is very difficult to demonstrate a survival benefit from mass screening. Another problem is that there is no current test that is sensitive and specific enough (statistical terms that measure false negatives and false positives) that is also acceptable to patients and physicians.

In patients with a hereditary predisposition that places them at very high risk of uterine cancer (40–60% lifetime versus 2%), screening becomes more reasonable. In these patients, routine screening with an endometrial biopsy is suggested by some national organizations and now recommended by the American College of Obstetricians and Gynecologists. Certainly the hope for the future of screening lies in biomarker discovery. Biomarkers are substances that can be detected in patients at an early or even precancerous stage that are not present in healthy individuals. Ideally these substances (or biomarkers) are easily obtained – potentially in urine, blood, or even in the vaginal canal at the time of Pap test, and ongoing research is looking to pursue this potential.

⁴ American Cancer Society. *Cancer Facts & Figures 2014*. Atlanta: American Cancer Society; 2014.

Surgery

The initial management of endometrial cancer should, in most cases, include removal of the uterus, cervix, fallopian tubes, ovaries, and consideration of removing pelvic and para-aortic lymph nodes. Studies also support surgical removal of metastatic implants when encountered at initial surgery. Growing evidence supports that minimally invasive approaches should be embraced as the standard surgical approach in women with endometrial cancer. There is strong evidence supporting laparoscopic techniques and accumulating data that robotic-assisted surgery is also feasible, safe and may allow more women to benefit from a minimally invasive approach.

The need for comprehensive surgical staging, and in particular, the role of lymph node sampling or removal in early endometrial cancer remains controversial. Surgical assessment of lymphatic dissemination may alter or eliminate the need for additional therapy and more accurately guide discussions of prognosis. Potential complications include surgical injury to major vessels or nerves, or postoperative fluid retention and swelling of the lower extremities caused by a compromised lymphatic system (lymphedema).

Sentinel lymph node assessment, which is standard of care in a number of cancers such as breast cancer and melanoma, is now being investigated in endometrial cancer. This technique focuses on the first draining lymph nodes from the uterus and cervix to predict the status of the remaining regional nodes as a potential means to minimize or eliminate the need for a complete lymphadenectomy. Initial data appears promising and this technique, once validated, may offer a more tailored approach to lymph node assessment in presumed early-stage endometrial cancer. Additionally, new molecular analyses of biomarkers that indicate a more aggressive profile may help identify patients that would benefit from more extensive surgical assessment or treatment.

In further efforts to individualize surgical approaches, recent data suggests that ovarian conservation in young patients with very good prognosis disease may be reasonable and worth discussing in the right clinical scenario. Similarly, data continues to accumulate and techniques continue to be refined that make consideration of fertility preservation (again in properly selected patients) a very real option.

Adjuvant Treatment

Adjuvant therapy may include radiation, chemotherapy, hormone therapy, immunotherapy or molecularly targeted treatments. The benefit of adjuvant treatment in Stage I and II endometrial cancer patients with risk factors associated with disease relapse remains unclear. Radiation reduces vaginal or pelvic recurrence but has not improved overall survival. Based on the results of important clinical trials, external radiation continues to decline in favor of vaginal brachytherapy. Several groups are investigating chemotherapy in combination with radiation for higher-risk endometrial cancer. Questions remain as to whether combination or sequential treatment is better than single modality, and if so, what order chemotherapy or radiation should be administered. GOG protocols 249 and 258 should help determine if chemotherapy alone or in combination with vaginal brachytherapy can replace pelvic radiation, and improve survival by reducing both local and distant recurrences.

Adjuvant chemotherapy is now the mainstay of treatment for women with Stage III and IV endometrial cancer. As in the treatment of intermediate-risk disease, clinicians frequently use multimodality therapy to combine the systemic (or whole body) effects of chemotherapy with the improved local control provided by radiation. In 2012, the outcome of the GOG 209 clinical trial confirmed that in women with gross residual disease, paclitaxel and carboplatin chemotherapy was as effective as other regimens reported in the literature with less toxicity. The investigators concluded that this regimen was an acceptable backbone for further trials in combination with

“targeted” therapies. Many treatment options under current clinical evaluation are using these biologic or targeted agents alone, or in combination with chemotherapy and NRG Oncology has a specific cue or line-up of clinical trials specifically investigating these targeted therapies.

Clinical Trials

The use of targeted therapy is under active investigation in uterine cancers. The targeting of angiogenesis pathways has been successful in Phase II trials with bevacizumab showing 36% of patients to be progression free at 6 months, which resulted in this agent being added to GOG-86P, a randomized Phase II trial.

Another exciting pathway being studied in GOG-86P is the PI3 kinase pathway. MTOR inhibitors are being investigated to take advantage of the molecular changes in endometrial cancer with response rates of 26–44%. Temsirolimus and everolimus are FDA approved mTOR inhibitors for other indications and are the most studied.

Carcinosarcomas are being studied using ifosfamide and paclitaxel versus carboplatin and paclitaxel in GOG-261. Uterine leiomyosarcoma is currently treated with gemcitabine and taxotere, and GOG-250 did not find a benefit with adding bevacizumab. The current trial GOG-277 is evaluating chemotherapy versus observation after hysterectomy in patients with disease confined to the uterus.

Survivorship after a Diagnosis of Endometrial Cancer

Cancer survivorship is an emerging area of research which addresses the maintenance of physical, social, spiritual, sexual and economic well-being which may be impacted by short- and long-term cancer and treatment-related side effects. Along with survival, quality of life (QOL) and Patient-Reported Outcomes (PROs) have emerged as important endpoints when evaluating cancer treatments. Patients and their advocates continue to identify vital issues such as fertility preservation and sexuality that need to be addressed by their healthcare team. Additionally, survivors often face significant hurdles from late effects of treatment and other medical conditions that potentially threaten their survival, and almost certainly threaten their quality of life. This field of research is making great strides in identifying and addressing these patient centered outcomes.

It is well known that more women with the diagnosis of endometrial cancer actually die of their other major health problems (36% cardiovascular deaths, 20% other cancers, 25% other causes) rather from their endometrial cancer (19% cause of death). Women are surprised to learn that obesity has caused their cancers, and need to take the cancer diagnosis as an opportunity to change their lifestyle. Gynecologic oncologists have taken an active role in referring women to weight reduction programs, including bariatric surgery, nutritionists, exercise programs, and in turn, are emphasizing diabetes and cardiovascular risk-reduction strategies.

NRG Oncology is committed to a prospective trial to demonstrate a survival benefit in using this cancer diagnosis as an opportunity to encourage and incentivize women to improve their behavioral health risks with healthy diet and exercise choices. Obesity is an epidemic in our country and endometrial cancer is a downstream indicator of this problem in our society. The Foundation for Women’s Cancer is exploring funding for additional programs to aid in addressing this barrier to good gynecologic health.

Vaginal Cancer

State of Vaginal Cancer

Vaginal cancer originates in the vagina, usually in the squamous epithelium (lining). It is typically 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 the vaccinations advocated for the prevention of cervical cancer. 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. Recently, the FDA approved a new vaccine that protects against nine HPV types, five more than the others. This vaccine also is approved and recommended for both boys and girls

Incidence: Primary vaginal cancer is one of the rarest gynecologic cancers. It is estimated that there will be about 3,170 new cases diagnosed and 880 deaths from vaginal cancer in the United States during 2014.⁵ Vaginal cancer accounts for about 3% of reproductive cancers.

Advances and Vaginal Cancer

Because of its rarity, vaginal cancer is not amenable to comparing one form of treatment with another in a large clinical trial. Therefore, much of what is understood in vaginal cancer treatment is borrowed from clinical trials in other related cancers, such as 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 in select patients with localized disease for tumor excision, or to precisely define radiation treatment fields to permit protection of normal organs during radiation treatment.

⁵ American Cancer Society. *Cancer Facts & Figures 2014*. Atlanta: American Cancer Society; 2014.

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.

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% and a specificity of 73% in detecting sites of cancer beyond the pelvis. 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 similar cervical and vulvar cancers, chemotherapy prescribed concurrently with the radiation therapy has improved the response rates and overall survival. A recent study showed that by giving chemotherapy at the same time as radiation to women with vaginal cancer also improved the response and survival with an acceptable level of side effects. Side effects of radiation treatment for vaginal cancer include shortening and closure of the vaginal tube, and remain a significant issue for these patients.

It is hoped that the integration of PET/CT with other new imaging methods may also improve the accuracy of surgery or radiation treatment planning, resulting in improved survival and reduced treatment-related side effects for women with vaginal cancer. Intensity-Modulated Radiation Therapy (IMRT) is a newer advanced type of high-precision radiation that is the next generation of 3-Dimensional Conformal Radiotherapy. IMRT's use in vaginal cancer has improved the ability to modify the radiation and conform to tumor shapes while avoiding treatment of vulnerable structures, such as the bladder and bowel.

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 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. Other risk factors include smoking and a skin condition known as lichen sclerosis. Vulvar cancer in older women is associated with chronic vulvar irritation from any source.

Screening/Prevention: Because many vulvar cancers are associated with HPV types 16 and 18, vulvar cancer can be prevented by the vaccinations advocated for the prevention of cervical cancer and vaginal cancer. 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. Recently, the FDA approved a new vaccine that protects against nine HPV types, five more than the others. This vaccine also is approved and recommended for both boys and girls

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 4,850 new cases diagnosed and approximately 1,030 deaths from vulvar cancer in the United States during 2014.⁶ 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

⁶ American Cancer Society. *Cancer Facts & Figures 2014*. Atlanta: American Cancer Society; 2014.

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 study identified that women undergoing treatment for vulvar cancer are at extremely high risk of developing lymphedema. The GOG is planning future trials to identify more effective methods to diagnose and prevent lymphedema in women having surgery for vulvar cancer.

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 259 women with unifocal vulvar disease and negative sentinel lymph nodes for 3 years and concluded that sentinel lymph node biopsy is safe in many patients with early vulvar cancer (less than 4 cm). However, sentinel lymph node dissection alone is not advocated for larger lesions, multifocal lesions or women who have a positive sentinel node. These patients are best treated with a full lymph node dissection. Based on the encouraging results of the data to date, a woman with vulvar cancer should discuss with her gynecologic oncologist their experience with, and the risks of, a sentinel lymph node assessment given their personal clinical situation.

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 within other risk factors may make node counting itself an unreliable measure of surgical quality or risk for recurrence.

In general, cancers are divided into categories or stages, with the assignment within a stage based on the risk for recurrence. For vulvar cancer, the final stage depends on the pathologic review of the surgical specimens from the vulva and the regional lymph nodes. In 2009 FIGO announced the first major revision in staging for vulvar cancer since 1988. In the revised system, Stage IA lesions do not require a regional lymph node evaluation because of the low risk of metastasis. Patients with Stage IB have tumors with deeper invasion (greater than 1 mm), however the regional lymph nodes are negative. These patients remain in the Stage I category as they have a low risk for

recurrence. Stage II was reconfigured to include those patients with local extension to the urethra, anus or vagina, but still had negative lymph nodes. These patients have a lower risk of recurrence than the node positive Stage III patients with whom they were previously categorized. Stage III now includes those patients with lymph node metastases regardless of the size, location and extension of the primary vulvar tumor. The presence and extent of nodal involvement is the single most important factor in determining the risk for recurrence in vulvar cancer patients. Stage III is now subdivided by the size of the metastatic foci, the number of nodes involved and the presence of extracapsular spread. The new staging system will hopefully identify those patients at greatest risk for recurrence who would clearly benefit from adjuvant treatment.

Another area of progress is the treatment of vulvar cancer by using a combination of therapies 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 otherwise lost rectal, bladder or sexual function from radical surgery 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 and is more commonly being utilized for these patients.

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