2016 **State of the State** of Gynecologic Cancers

Report to the Women of America

Thirteenth Edition

Foundation for Women's Cancer

Table of Contents

A Letter to the Women of America

This year marks the 25th anniversary of the Foundation for Women's Cancer (FWC). During the past two and one-half decades, there has been steady progress in the prevention, early detection and optimal treatment of gynecologic cancers. Working in tandem with the Society of Gynecologic Oncology (SGO), the FWC is dedicated to funding research, and providing educational materials that better inform women and the public about risks, prevention strategies and treatment options. Equally important is the message that women treated first by a gynecologic oncologist experience improved outcomes.

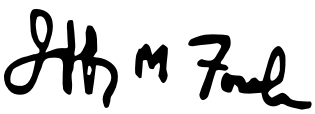
As we learn more about new ways to treat cancer, especially immunotherapy, it is clear that harnessing the power of one's own body can play an important role in both preventing cancer and improving outcomes. We know that a healthy diet resulting in proper weight management plays a key role in reducing the rate of cancers fueled by estrogen, as is the case in uterine cancer, the most common gynecologic cancer. We continue to learn more about endorphins, and the role they play in pain management, stress reduction and an enhanced immune system. Endorphin triggers include exercise, acupuncture, massage therapy and sex, among others. Just as it is important for women at risk for a gynecologic cancer and those who are diagnosed to commit to a healthy lifestyle, it is equally important that their health care team do the same. For this reason, a major focus of the Society of Gynecology is to encourage its members to adopt a healthy work-life balance to better serve their patients.

We also urge women to LEARN, LISTEN, ACT. LEARN the symptoms and risks of each gynecologic cancer as described in this report. Take note of your family history and seek genetic testing if appropriate. LISTEN to your body for symptoms associated with these cancers. ACT to seek care and if a gynecologic cancer is suspected or diagnosed, seek care first from a gynecologic oncologist.

This year's report is published jointly by the SGO and FWC. This is a tangible example of the closer working relationship achieved during the past year that has resulted in increased shared leadership and staff. It also enables gynecologic oncologists and other members of the cancer care team to serve both the Foundation and the Society. All of the authors of this year's report are practicing gynecologic oncologists, leaders in their academic institutions, and have volunteered their time to produce this report. We thank them.

And finally, we thank you for your interest in cancers that are unique to women. This report chronicles the advances made during the preceding year, and we hope to deliver even more encouraging news in the years to come. In order to accomplish this, an increased investment in gynecologic cancer research, including clinical trials, is critical. You will read more about the current research environment and funding challenges in this report, and we ask for your support in addressing them.

Sincerely,



Jeffrey M. Fowler, MD
President, Society of Gynecologic Oncology

David G. Mutch, MD
Chairman, Foundation for Women's Cancer

25 Years of Progress in the Subspecialty of Gynecologic Oncology

By Jeffrey M. Fowler, MD
President, Society of Gynecologic Oncology

The Society of Gynecologic Oncology (SGO) is the nation's only professional organization whose mission it is to promote the highest quality of comprehensive clinical care through education and research in the prevention and treatment of gynecologic cancers. Its foundation, the Foundation for Women's Cancer, supports this mission by raising funds for research, educating the public about these cancers unique to women, and supporting women and their families who are surviving a gynecologic cancer.

Gynecologic oncologists are board-certified obstetrician/gynecologists sub-specialists who train an additional three to four years in the specialized treatment of gynecologic cancers in 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 all modalities of treatment, including surgery, radiation, chemotherapy and experimental treatments.

The treatment of gynecologic cancers and the subspecialty itself have undergone transformative changes during the past 25 years. These include changes in the demographics of the Society and the attendant attention to work-life balance, its membership composition, clinical practice, funding for research, and the legislative and regulatory environment, to name a few.

Like most of medicine, 25 years ago the majority of gynecologic oncologists were men. Now more than 40 percent are women, a percentage that is likely to increase since nearly 85 percent of OB/GYN residents are women. This demographic shift, coupled with the entry into the workforce of millennials with a different approach to work-life balance, has fostered an interest in addressing this topic among SGO members.

If you are one of almost 106,000 women diagnosed with a gynecologic cancer this year, you have seen firsthand that the practice of gynecologic oncology is demanding. Additionally, the health care environment has become more complex while access to resources is more difficult, leading to increasing demands on a gynecologic oncologist's time. The SGO leadership has recognized this challenge and created the SGO Wellness Initiative that provides resources to clinicians to enable them to improve this balance, and thus provide even better patient care.

The composition of the membership itself has changed over time for two primary reasons. First, the Society endorses a patient-centered medical home model of comprehensive care for women diagnosed with a gynecologic cancer. The includes the entire health care team—medical oncologists, radiation oncologists, pain and palliative care specialists, physician assistants, nurse practitioners, oncology nurses, genetic counselors, social workers, etc. Rather than restricting membership in the Society to gynecologic oncologists, as was the case prior to 2010, the membership categories now are inclusive of the entire health care team.

Second, the Society embraces the globalization of medicine and recognizes the value of global best practices. International members are welcome and play a vital role in the Annual Meeting on Women's Cancer through participation in the Global Program. This year's focus will be global gynecologic cancer epidemiology, the burden of disease in low- and medium-resource countries, public health reporting, and the development and implementation of reliable and accurate cancer registries. The more than 2,000 members of the Society practice in 43 countries around the world.

Clinical practice also has changed with a greater emphasis on outcome measurements. To this end, the Society has made an investment in its Clinical Outcomes Registry. Data shows that registries of this type result in improved patient care by clinicians, and better decision-making by patient and payors. Initiated in 2014, the registry is expected to enroll more than 5,000 cervical, ovarian and uterine cancer patients during the next two years. This will allow for the tracking of outcomes over time, leading not only to improved measures of quality, but also improved quality of care. Challenges in the current research and legislative/regulatory environments are the subjects of the two other special articles in the *2016 State of the State of Gynecologic Cancers: Report to the Women of America*.

In conclusion, each member of the Society of Gynecologic Oncology joins me in expressing our appreciation for the privilege of caring for women diagnosed with a gynecologic cancer. Just as we focus on work-life balance for ourselves, we urge our patients and readers to do the same. Eat well, exercise your body and your mind, take time to enjoy family and friends, and try to always see the glass half full.

25 Years of Progress in Gynecologic Cancer Research

By Anil K. Sood, MD
Chair, Research and Awards Committee, Foundation for Women's Cancer

Funding for gynecologic cancer research has been a cornerstone of the mission of the Foundation for Women's Cancer since its founding 25 years ago by the Society of Gynecologic Oncology.

In 1995 the Foundation awarded its first two research grants, and since then 151 grants have been awarded totaling more than $7.5 million. These include research and training grants, prizes and recognition of outstanding papers. In most instances, a family touched by a gynecologic cancer has made this funding possible.

Most of the research funding has been awarded to young investigators—individuals just beginning the long path to becoming physician-scientists. Of those receiving their first research award from the Foundation, more than 94 percent have pursued a career in research. In fact, many of today's leading gynecologic cancer scientists received their research grant from the Foundation, leveraging their first award to a 24-fold return on the initial grant award.

In recent years, the Foundation has expanded its research portfolio to include multi-year grants, more career development grants and funding for established investigators, often in a mentorship role. This year, eleven research awards, four prizes and three career development awards—two of which are multi-year—are available in a very competitive funding environment.

During the past 25 years, we also have witnessed significant scientific advances in the prevention, early detection and optimal treatment of gynecologic cancers. The impact of the completion of the mapping of the human genome in 2003 is far reaching and a major scientific advance impacting both the prevention and treatment of gynecologic cancers. Genes are the building block of all cells that carry instructions for the body's functions.

Cancers arise due to accumulation of damage to genes involved in controlling cell growth and DNA repair. Hereditary cancers affect individuals who have inherited a mutation in a cancer-causing gene. There are two hereditary syndromes associated with gynecologic cancers: hereditary breast-ovarian cancer syndrome and Lynch syndrome.

Inherited mutations in the *BRCA1* and *BRCA2* genes substantially increase the risk of breast, ovarian, fallopian tube and peritoneal cancers. The lifetime risk of having one of the gynecologic cancers is 39-46 percent in *BRCA1* carriers and 12-20 percent in *BRCA2* carriers.

This knowledge has led to the recommendation that women with known risk factors for these cancers undergo genetic counseling and testing that might result in the decision to undergo prophylactic ovary and fallopian tube removal to reduce the risk of ovarian cancer. The Society of Gynecologic Oncology recommends that all women diagnosed with ovarian cancer undergo genetic counseling and testing, even in the absence of family history.

Important for women with recurrent ovarian cancer (80 percent of all women diagnosed with ovarian cancer) with *BRCA1* or *BRCA2* mutation is the 2014 FDA approval of the first PARP inhibitor for a specific gynecologic cancer, olaparib. A PARP inhibitor is a substance that blocks an enzyme in cells called PARP. The PARP helps repair DNA when it causes damage. As part of the approval of olaparib, the FDA also approved a companion diagnostic test to detect a mutation in the *BRCA* genes. The clinical trial that supported this approval demonstrated a 34 percent positive response rate in *BRCA*-positive women treated with olaparib.

About 3 percent of endometrial cancers are linked to Lynch syndrome. It is due to inherited mutations in DNA mismatch repair genes, most often *MSH2* and *MLH1*. The average age of diagnosis is in the early 40s compared to the early 60s for other cases. These cancers are usually confined to the uterus and are rarely fatal. The risk of ovarian cancer is also significantly increased to about 10 percent, but this accounts for only about 1 percent of ovarian cancers. Women with Lynch syndrome should be carefully monitored; current recommendations advise women to consider having the CA125 blood test and transvaginal ultrasound annually to evaluate the ovaries, and a biopsy of the lining of the uterus beginning at age 25 to 35 years.

The discovery of the link between the human papillomavirus (HPV) and cervical, vaginal and vulvar cancers represents another groundbreaking advance in the prevention of gynecologic cancers. While there are other causes of vaginal and vulvar cancers, virtually every cervical cancer is due to an infection with HPV. While there are diagnostic tests to determine the presence of cancer-causing types of HPV, even more exciting is the availability of a vaccine to prevent the infection altogether. The vaccine is recommended for both boys and girls beginning at age 9. It is the most effective before exposure to the virus, which is sexually transmitted. The Foundation for Women's Cancer and the Society of Gynecologic Oncology urge women to be screened for cervical cancer as recommended and that all young people receive the vaccine.

The FDA approved bevacizumab for patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancers in 2014 and approved it for those with platinum-sensitive recurrence in 2016. Bevacizumab is an angiogenesis inhibitor, meaning it slows the growth of blood vessels. When given in combination with a chemotherapy regimen, it offers a significant clinical improvement, increasing the progression-free interval in these cancers.

Moving forward, researchers are actively working to harness the potential of immune therapies for women diagnosed with gynecologic cancers, especially ovarian cancer. These immunotherapy strategies can be bifunctional in that they work by targeting a biochemical pathway in cancer cells and then help stimulate the patient's own immune system to fight the cancer. For example, sample cells from an ovarian cancer tumor removed during surgery can be taken to develop an immunotherapy treatment specific to an individual patient.

While much has been accomplished in the last 25 years, much more research is required to lessen the burden of these cancers unique to women. Some of the funding challenges impeding research opportunities are described in the article, 25 Years of Patient Advocacy.

25 Years of Patient Advocacy

By Carol L. Brown, MD
Chair, Health Policy and Socio Economic Committee, Society of Gynecologic Oncology

Advocating for gynecologic cancer research and patient access to high quality cancer care has been and continues to be a focus of the Society of Gynecologic Oncology's patient advocacy program. In 1999, working with its foundation, the Foundation for Women's Cancer, the Society was successful in having September declared Gynecologic Cancer Awareness Month (GCAM), resulting in almost every state issuing proclamations and engaging in awareness activities in the intervening years.

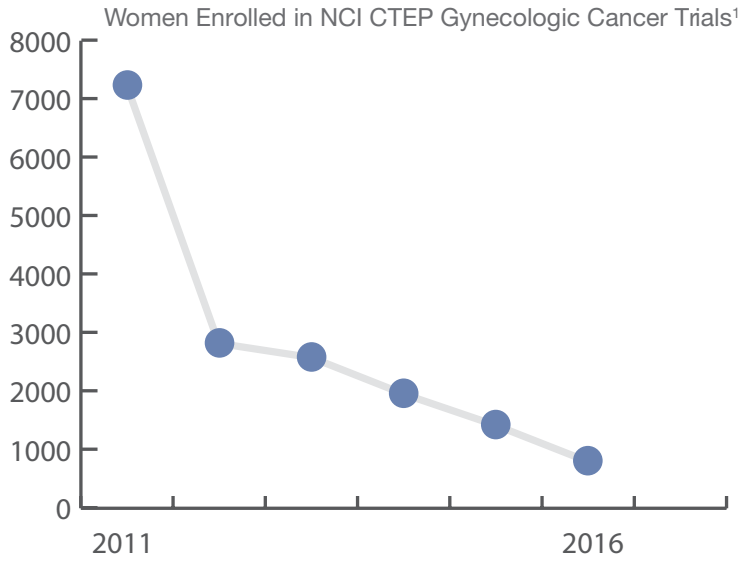
The Society works diligently at the federal level on legislation and other policy activities to increase awareness about gynecologic cancers, to maintain and increase funding for gynecologic cancer research, to insist that clinical trials for gynecologic cancer continue and expand, and to ensure patient access to high quality, cost effective cancer care.

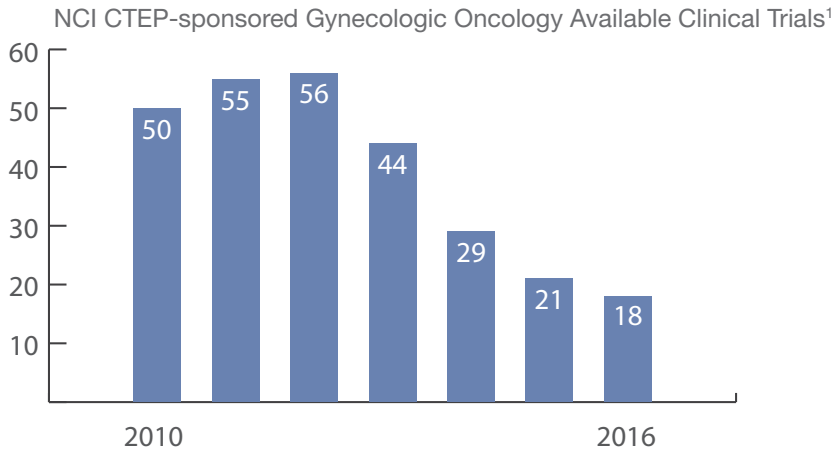
In 2002, two years following death of her sister Johanna from ovarian cancer at age 58, Sheryl Silver asked the FWC and the SGO to join her determined effort to pass federal legislation to educate women about gynecologic cancers. In 2005, the Gynecologic Cancer Education and Awareness Act, also known as Johanna's Law, was introduced by Senators Arlen Specter and Tom Harken, and it was signed into law by President George W. Bush in January 2007. Monies were appropriated by Congress to fund the Centers for Disease Control and Prevention (CDC) to implement the Law. The CDC produced its first "Inside Knowledge" public service announcement (PSA) in 2010. This program continues today and has garnered more than 5 billion impressions through a combination of TV, radio and print PSAs; digital ads; and Out of Home Display ads.

The Society also has worked diligently and collaboratively to maintain and increase federal funding for the Department of Defense (DoD) Ovarian Cancer Research Program, initially passed in 1997 as part of the DoD's Congressionally Directed Research Programs. In addition to its goal to increase the pool of ovarian cancer scientists, the program funds high impact research that meets unmet needs in accordance with set priorities, including an emphasis on our active and retired military members and their families. Since the program began, it has awarded over $276.5 million in ovarian cancer grants. However, as Congress realigns and reduces budgets, maintaining this important source of ovarian cancer research funding becomes more challenging every year.

The same holds true for funding for gynecologic cancer research supported by the National Cancer Institute (NCI), part of the National Institutes of Health. Since 2003, the budget for cancer research has been relatively flat, with the exception of FY 2016, while the incidence of cancer increases in our aging population. Moreover, the cost of cancer research has increased. While this budget reality has impacted all cancer research, basic and translational gynecologic cancer research has been disproportionately impacted.

This trend also has negatively impacted the availability of gynecologic cancer clinical trials, critical to bringing new treatment options to the bedside. Prior to the reorganization of the NCI's clinical trials network in 2014, there was a clinical trial organization focused solely on gynecologic cancer. The consolidation has dramatically limited the number of trials open for enrollment: 33 percent overall and a disproportionate reduction of 82 percent for gynecologic cancer trials. The Society is extremely concerned about the impact on our patients, and is starting a campaign to work with the Administration and Members of Congress to rectify this deeply troubling situation.





Also of concern are several areas affecting patient access to care. First, the Society is actively working with Food and Drug Administration (FDA) to aid in the approval of breakthrough gynecologic cancer drugs. We also are engaged in efforts to address the cost of cancer drugs, once approved. And finally, the Society is carefully monitoring physician payment reform to ensure that gynecologic oncologists can continue to offer high quality cancer care to all patients.

We are fortunate to live in a democracy founded on the principle of participatory government. Participating in government on behalf of our patients continues to be priority for the Society of Gynecologic Oncology. We meet with policymakers, and Members of Congress and their staff in Washington, and we invite them into our cancer centers when they are home. We thank you for your support and involvement as we advocate for you, our patients.

[1]Gynecologic Oncology Group, www.gog.org

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 Human papillomavirus, or HPV.

Who is at risk?

Every woman is at risk for developing a gynecologic cancer. It is estimated that there will be about 105,890 new cases diagnosed and approximately 38,890 deaths from gynecologic cancers in the United States during 2016.[1]

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.

Can gynecologic cancers be prevented?

Screening and self-examinations conducted regularly can aid 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. In particular, obesity is a major risk factor for uterine (endometrial) cancer, the most common gynecologic cancer.

Heredity also plays a role in the development of certain gynecologic cancers due to accumulation of damage to genes involving cell growth and DNA repair. The two primary hereditary cancer syndromes that cause gynecologic cancers are hereditary breast-ovarian cancer syndrome (HBOC) and Lynch syndrome.

Inherited mutations in *BRCA1* and *BRCA2* genes dramatically increase the risks of breast, ovarian, fallopian tube and peritoneal cancers. The inherited risk in having one of the gynecologic cancers is 39 to 46 percent in *BRCA1* carriers and 12 to 20 percent in *BRCA2* carriers.

Approximately 1 of out of every 500 individuals in the general population has a mutation in one of the *BRCA* genes. In certain ethnic populations, the mutation frequency is much greater. For example, 1 out of every 40 Ashkenazi Jewish individuals carries mutations. Both men and women can carry a mutation and have a 50 percent chance of passing the mutation to each of their children.

Lynch syndrome is due to inherited mutations in DNA mismatch repair genes, and is associated with higher risk for several cancers, predominately colorectal cancer. This syndrome also places women at higher risk for endometrial cancer. The risk for endometrial cancer associated with Lynch syndrome is 30 to 40 percent, and about 3 percent of all endometrial cancers are attributable to Lynch syndrome.

It is important that women with a family history of breast, ovarian, fallopian tube, peritoneal, and/or endometrial cancer talk with their doctor, a genetic counselor or other health care professional about genetic testing. Based on these results, specific risk reduction options can be offered.

Additionally, now there is a vaccine that can prevent cervical cancer, and in some instances, vaginal and vulvar cancers. This vaccine is recommended for both girls and boys between 11 and 13 years of age, but can be given to children as young as 9 years of age. Widespread vaccination plus regular screening holds the promise of preventing virtually all cervical cancer.

[1]American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016.

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, young girls, and boys before they become sexually active and exposed is the greatest prevention strategy against pre-cancer and cancer.

Early vaccination routinely recommended between 11 and 13 years of age or in children as young as 9 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. However, the precancerous cells that are asymptomatic and easily treatable, often occurs in women who are younger than age 30.

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 cervical cancer screening tests that often include a Pap test and HPV test.

Risk Factors: Infection with high-risk HPV has been shown to cause virtually all cervical cancers. However, HPV is very common and most women with HPV will never develop any cervical disease that would require treatment. Other risk factors include smoking; weakened immunity due to HIV infection or taking immune-weakening 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 percent. A Pap test is a standard way health care 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.

Due to a better understanding of the risks of screening and natural history of cervical cancer, guidelines for cervical cancer screening have changed to include increased intervals between screening, meaning fewer Pap tests for women. Also, the American College of Obstetricians and Gynecologists and others 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. These updates include recommendations for conservative management of equivocal abnormalities in young women. Some abnormal Pap tests will be followed by colposcopy (examination using a magnifying device to see the abnormalities of the cervix 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.

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.

In January 2015, 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 can be used to detect 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.

In European trials, when compared to Pap alone, more women who have invasive cervical cancer are found earlier through a primary HPV screening strategy. This strategy is estimated to provide as much as 60 percent more protection against being diagnosed with an invasive cervical cancer than with a Pap alone because it is often identified earlier.

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 and boys. Recently, the next generation vaccine has been FDA approved. This vaccine can protect an individual from 9 different HPV types. 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 12,990 new cases of invasive cervical cancer diagnosed and approximately 4,120 deaths in the United States during 2016.[2]

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 2013, the Gynecologic Oncology Group (GOG) reported the results of a clinical trial that showed a biologic agent called bevacizumab, that blocks new blood vessel growth in cancer, was effective in shrinking tumors when combined with other agents in some women with recurrent cervical cancer. In this trial, in those women who received bevacizumab had about a 30 percent 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 treatment is using novel technologies to retrain one's own immune system to target cancer. In a process developed by investigators at the National Cancer Institute (NCI), immune cells were reprogrammed to recognize and target HPV inside cervical cancer tumors. In early trials in women with advanced cervical cancer, many had a much better than expected response to this therapy. This novel treatment is now being explored in larger trials.

Recently a new generation HPV prevention vaccine that protects against 9 HPV types has been available in the US. 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 percent of all cervical cancers and HPV 18 cause an additional 10 to 20 percent. HPV types 16 and 18 are the most important HPV types to include in a vaccine designed to prevent the development of cervical cancer. Both FDA approved HPV vaccines protect against infection with HPV types 16 and 18.

This new vaccine that protects against 5 more types than the prior generation vaccine has the potential to prevent up to 90 percent 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 percent. These high vaccination rates have already been achieved in some developed countries, but the rates are disappointingly low in the United States. Recent reports of vaccine registries show that while vaccine use in the United States is increasing, only a limited number of young girls and boys had 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 Oncology, recommend routine vaccination of girls and boys ages 11 and 12 years (ideally before first intercourse), and young women and men.

The American Cancer Society has spearheaded the National HPV Vaccination Roundtable, consisting of 65 national organizations, whose purpose is to increase vaccination rates, especially among the routinely recommended group, 11 and 12 year olds.

Expanded 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 that are 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.

[2]American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016.

Ovarian Cancer: Epithelial

State of Epithelial Ovarian Cancer

Ovarian cancer is the ninth most common cancer among women in the United States. About 85 to 90 percent of ovarian cancers are classified as epithelial type, which means the cancer is thought to come from the cells that cover the outside if the ovary. These cells are similar to those covering the end of the fallopian tube and the lining of the abdomen that is called the peritoneum. So, the diagnosis, treatment, and prevention of epithelial ovarian, primary peritoneal, and fallopian tube cancers are the same.

Symptoms: Bloating, pelvic or abdominal pain, difficulty eating or feeling full early after meals, and/or needing to urinate suddenly or often.

Women with ovarian cancer report that symptoms develop either gradually or suddenly, do not subside, and are a noticeable change 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 ovarian cancer has a better prognosis than late-stage cancer, in general. Unfortunately, however, in most cases the cancer grows quickly and does not lead to symptoms until it is in a later stage, meaning it has spread to several locations within the abdomen. Therefore, diagnosis at a later stage does not necessarily mean that an early cancer was missed. In contrast, cancers found at an earlier stage are usually more slow-growing and, thus, more likely to be detected early. In other words, sometimes the amount of cancer present has more to do with how fast the tumor grows than with how fast it gets diagnosed.

Several other symptoms have been commonly reported by women with ovarian cancer. These 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 women in the general population who do not have ovarian cancer.

Risk Factors: The risk of 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. A personal history of premenopausal breast cancer or a family history of epithelial ovarian, fallopian tube, primary peritoneal cancers or premenopausal breast cancer are also important risk factors that may indicate an inherited susceptibility to cancer due to mutations in *BRCA1*, *BRCA2* or other genes.

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. Women who have given birth to three children or use the pill for five years decrease their risk by about 50 percent compared to those who have not had children or used the pill. Endometriosis can also increase the risk of some types of epithelial ovarian cancers, particularly clear cell and endometrioid types. Lesser risks have been associated with menopausal hormone use, obesity and pelvic inflammatory disease.

Some studies that ask women to recall their exposure to various risk factors have suggested that long-term genital talcum powder use may increase ovarian cancer risk. However, larger studies that followed women over the course of many decades have not confirmed this finding. Although a link between genital talc use and ovarian cancer is still being debated in the scientific community, there are ongoing lawsuits against a talcum powder manufacturer for failure to warn the public about this risk.

Incidence: Ovarian cancer causes more deaths than any other gynecologic cancer. It is estimated that there will be about 22,280 new cases and approximately 14,240 deaths from ovarian cancer in the United States during 2016.[3] The death rate from ovarian cancer has declined by 16 percent from 2002 to 2012. This may be due to preventative measures such as oral contraceptive use, and preventative screening and surgeries in women who have familial ovarian cancer caused by Lynch syndrome or *BRCA1*, *BRCA2*, and other mutation carriers.

Advances in Ovarian Cancer

Differences in Causes and Behavior of Different Ovarian Cancer Subtypes

Remarkable advances in the understanding of how ovarian cancer starts, grows and spreads have been made over the last few years. This understanding has led us to know that there are different subtypes of ovarian cancer, giving us a basis for a more targeted approach to prevention, screening and treatment of ovarian cancer, and continues to be the foundation for future discoveries.

Recent evidence suggests that epithelial ovarian cancer should be classified into two distinct categories. Type I ovarian cancers include endometrioid, clear cell, mucinous and transitional carcinomas, and low- grade serous cancers. Endometrioid and clear cell cancers frequently arise from sites of endometriosis in the pelvis or on the ovary. They are more often diagnosed at an early stage and frequently have specific mutations in the tumor (*ARID1A*, *KRAS*, *PTEN* and *PIK3CA*). Because low-grade serous tumors grow more slowly, they are less responsive to chemotherapy than high grade cancers. They frequently have mutations in genes called *KRAS*, *BRAF*, and *MEK*, which can be paired with new targeted treatments that are different from traditional chemotherapy.

Type II ovarian cancers include high-grade serous and undifferentiated cancers. It is becoming increasingly accepted that they often arise from the fallopian tube, not the ovary. Importantly, a precancerous growth, serous tubal carcinoma in situ, has been identified in the lining of the end of the fallopian tube that is close to the ovary. This was serendipitously discovered by removing the tubes and ovaries for cancer prevention in women with *BRCA1* or *BRCA2* mutations.

This may offer an opportunity for early detection and prevention. Type II ovarian cancers usually present in advanced stages and are more responsive to chemotherapy than their Type I counterparts. However, they do account for most ovarian cancer deaths. *p53* and *BRCA1* and *BRCA2* mutations are common in this group of tumors.

DNA changes linked to rarer types of ovarian cancer have also been recently discovered. For example, in ovarian stromal tumors, mutations in genes called *FOXL2* and *DICER1* are present in almost all granulosa cell and Sertoli Leydig tumors, respectively, and their presence can aid in confirming their diagnosis. Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare type of ovarian cancer that has been shown to uniformly carry mutations in the *SMARCA4* gene, a key protein in handling how chromosomes are folded. The mutations are inherited in some cases and may cause familial predisposition, while in other cases the mutations are not inherited, or sporadic. Targeting this protein experimentally 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 (salpingectomy) in all women undergoing tubal ligations or hysterectomy. 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 salpingectomy 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.

A recent Scandinavian study found that salpingectomy alone reduced the risk of ovarian cancer. However risk was reduced even more by removal of both fallopian tubes and ovaries, suggesting that some ovarian cancers do develop from the ovary. However, the primary ovarian tumors may develop from fallopian tube cells that have been trapped in the ovary due to inflammation and healing associated with ovulation. 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

Ovarian cancer screening programs have tried CA 125 blood tests, ultrasound, and biomarkers other than CA 125, but these have not been successful. One, the CA 125 test can be normal when cancer is present and elevated when cancer is not present. Two, because the ovaries grow inside the body and are not accessible without surgery. And three, and ovarian cancer can spread quickly (between screening tests). So, in general, more harm than good can be caused with screening.

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. Using symptoms alone is not likely to lead to early detection, but incorporating them with other tests, such as CA 125 and ultrasound might improve the effectiveness of these approaches. Patients with symptoms could be referred for additional testing, or patients with positive tests could conceivably undergo surgery only if they are having symptoms consistent with cancer.

One distinct screening program is still being studied in the United Kingdom clinical trial of ovarian cancer screening, or UKCTOCS. In this trial, over 200,000 postmenopausal women, were randomly assigned to either have no screening, have screening with annual pelvic ultrasound or annual multimodal screening (MMS). MMS involves a risk of ovarian cancer algorithm (ROCA) score based on changes in an individual woman's CA 125 levels over time, along with other known risk factors. If the ROCA is concerning, additional CA125 testing and/or ultrasound is performed to determine the need for surgery. In the UKCTOCS study, a mortality reduction of 15 percent was seen in the MMS group compared to the non-screened group over 14 years, but this difference did not meet the statistical criteria needed to call it a significant result.

In addition, the reduction in mortality appeared only after seven years of screening. MMS led to far fewer unnecessary surgeries per cancer detected than ultrasound (4 vs. 17), and there were more cases diagnosed at an early stage with MMS compared to unscreened women (40 percent vs. 26 percent).

UKCTOCS will be re-analyzed in 2018 to see if the results reach the statistical benchmarks if given more time. In the meantime, the US Food and Drug Administration (FDA) has recommended against using the ROCA screening test because its ability to lower death rates from ovarian cancer remains unproven. In addition, they expressed concern that women who have normal ROCA results may be falsely reassured that they are not at risk for ovarian cancer.

Efforts are also being directed to promising techniques that may allow early detection of ovarian cancer through blood tests or other noninvasive approaches. Though Pap smears are not able to detect ovarian cancer, finding ovarian cancer DNA changes in vaginal secretions has shown promise. 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 tested 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 cancer development, 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 common DNA and protein abnormalities that might be useful as treatment targets. This resource has also made possible searches for correlations between expression of various genes and patient survival that would have taken years.

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 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 therapeutic is still under debate. A review of one of largest (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 highly recommended 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 prior to surgery. This is typically followed by surgical removal of remaining disease and then additional chemotherapy. 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 when 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 other significant medical problems. 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 (EORTC 55971) and found that there was similar survival between the two groups. In 2015 the CHORUS (Chemotherapy OR Upfront Surgery) trial was published and showed similar overall survival. As expected, in both trials surgical complications were reduced.

However, both of the EORTC 55971 and CHORUS European trials had lower rates of ovarian cancer survival compared to primary cytoreductive surgery trials conducted in the United States. 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. Patients whose disease is not likely to be completely or almost completely resected may not benefit much from primary debulking with its attendant increased risks. And they may be best served by neoadjuvant chemotherapy with interval debulking after the cancer has been reduced with chemotherapy. The Society of Gynecologic Oncology and American Society of Clinical Oncology in August 2016 released a helpful joint clinical practice guideline, "Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer."

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 side effect (toxicity) concerns, the platinum agent is the more important one to receive. The most commonly used platinum agent is carboplatin (preferred over cisplatin because of a more moderate side effect profile). Paclitaxel (Taxol) is the most common taxane and is given in combination with carboplatin. These agents can be delivered through an IV either once every three weeks, or as a dose dense weekly regimen (as detailed below). Docetaxel is sometimes substituted for paclitaxel, because it causes less numbness in the fingers and toes (peripheral neuropathy), although this is at the expense of increased risk of low blood counts and other symptoms.

Intraperitoneal chemotherapy: Intraperitoneal (IP) chemotherapy delivers some of the platinum/taxane combination directly into the abdominal cavity where ovarian cancer predominantly grows. This approach also allows more total chemotherapy to be delivered. Several trials have demonstrated its superiority to IV therapy alone, though the most appropriate combination and schedule is still under investigation. The GOG-172 trial evaluated IP chemotherapy (IP cisplatin and IV paclitaxel the first week, IP paclitaxel in week two) in women with optimally cytoreduced advanced ovarian cancer compared to standard, every three weeks, 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 five-year overall survival rate. However, delivery of IP chemotherapy can be challenging, with increased side effects and discomfort, and many gynecologic and medical oncologists are still not comfortable with the approach.

In 2016, results of the GOG-252 study were reported at the annual meeting of the Society of Gynecologic Oncology and did not confirm better survival in optimally debulked patients treated with IP compared to IV chemotherapy. The reasons for this were not clear, but one possible explanation is that the dose of cisplatin was reduced and the duration of paclitaxel administration shortened from that used in GOG-172. This was done in an attempt to reduce cisplatin toxicity, and to reduce the duration of treatments. The results of GOG-252 were disappointing because they did not support the use of IP chemotherapy. Some have concluded based on this study that if IP chemotherapy is to be used in practice, it should be given according to the GOG-172 protocol. Most experts still believe that IP chemotherapy should be discussed as an option for patients who have had optimal primary surgical resection.

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, or 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 surgical resection. Results from GOG-262 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 in addition to dose-dense therapy confers no advantage. Since bevacizumab is not approved in the U.S. for newly diagnosed ovarian cancer, dose-dense therapy is increasingly being adopted, especially for patients with suboptimal surgical resection, as these patients 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 *BRCA1/2* mutations, either inherited (germline) or for patients in which the tumor develops a *BRCA* mutation locally (somatic). On the basis of multiple trials, the FDA gave approval to the PARP inhibitor, olaparib, for use in women with germline *BRCA1/2* mutations who have received at least 3 lines of prior therapy. The response rate to olaparib in these patients is approximately 35 percent. This represents the first therapy approved for a specific population of ovarian cancer patients, officially welcoming the era of precision therapy. The second PARP inhibitor to be approved is called rucaparib and is for women with at least 2 lines of prior therapy who carry a somatic and/or germline mutation in *BRCA 1* or *2*. Both drugs were granted accelerated approval, meaning the FDA will require the drug company to provide more information to get final approval. Many ovarian cancer patients without germline *BRCA* mutations have defects in homologous recombination local to the tumor (approximately an additional 30 percent of patients) that make them potential candidates for this therapy. Assays are under development to predict which patients tumors have HR defects and are most likely to respond to PARP inhibitors. An examination of various methods to profile tumors is included in current PARP inhibitor trials. PARP inhibitors are relatively well tolerated, with the most prominent side effects being fatigue and nausea.

Several other PARP inhibitors including niraparib, and veliparib are under development for treatment of ovarian cancers with HR defects. Another PARP inhibitor, talazoparib, will be evaluated in women with prior exposure to PARP inhibitors, to determine if there is a benefit to re-initiation of PARP inhibitors beyond progression. The NOVA study of niraparib was reported in 2016 and was particularly promising, showing improved progression free survival of recurrent *BRCA1/2* mutated ovarian cancers from 5.5 to 21 months. The FDA will be evaluating niraparib for consideration in the treatment of women with advanced ovarian cancer.

Antiangiogenic Agents

Tumor growth requires the development of small blood vessels to supply needed oxygen and nutrients. Antiangiogenic drugs prevent the development of small blood vessels in tumors, and have been shown to inhibit the growth of many types of cancers in clinical trials.

Several studies have shown that the antiangiogenic drug bevacizumab increases the time to relapse after primary chemotherapy by 3-4 months when used as a maintenance therapy, but no differences had been seen in overall survival. In the US, bevacizumab is approved by the FDA for use with chemotherapy for platinum-resistant relapsed ovarian cancer based on improvements in PFS. More recently, in 2015 the large ICON7 trial in Europe found that although the addition of bevacizumab to primary chemotherapy did not improve survival in all patients, overall survival of those with suboptimally debulked disease was improved from 34.5 to 39.3 months.

This suggests that this expensive drug and other antiangiogenics may be best used in patients with the most advanced cancers that are not amenable to optimal surgical resection. Further studies are needed to confirm this approach.

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 reported in 2014 and demonstrated that when used in combination in recurrent disease, both drugs produced an 84 percent response rate compared to 56 percent 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 development of Phase III trials that incorporate these agents alone or in combination with cytotoxic chemotherapy in primary and recurrent ovarian cancer.

Immunotherapy Agents

The field of immuno-oncology harnesses the individual's immune system response to combat cancer. These types of treatments have generated significant progress in various solid tumors leading to FDA-approved immunotherapies for several different types of cancers. The treatments have ranged from adoptive immune cell therapies, to cancer vaccines and immune checkpoint inhibitors. Immune checkpoint inhibitors are monoclonal antibodies that inhibit pathways that block T-cell response to antigens. There are several immune checkpoint antibodies directed against *PD-1*, *PD-L1*, and *CTLA-4* that are being tested in ovarian cancer and across studies the overall response rate has been approximately 10 to 15 percent. The response rate may be higher in patients with cancers characterized by microsatellite instability which may represent a selected population more likely to benefit from these agents. Studies are ongoing evaluating the combination of immune checkpoint inhibitors with standard cytotoxics in ovarian cancer as well as in combination with anti-angiogenic agents and/or PARP inhibitors.

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. Biological 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 under development. There is a trend towards reduced ovarian cancer incidence and mortality over the past few decades and hopefully this will continue with the focus on all areas of research described in this report.

[3]American Cancer Society. Cancer Facts & Figures, 2016. Atlanta: American Cancer Society; 2016

Uterine Cancer: Endometrial Adenocarcinoma and Uterine Sarcomas

State of Uterine Cancer

Endometrial cancer arises from the inner lining of the uterus (the endometrium), which can grow in an uncontrolled fashion. 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 "low-grade" endometrioid subtype and these carry a very favorable prognosis. However, other cancers are "high-grade" endometrioid, or other more aggressive types of cancer (serous and clear cell carcinomas and uterine carcinosarcomas), which carry a high risk for recurrence.

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 percent of all uterine cancers, uterine sarcomas are much less common than endometrial cancer, but have a much more aggressive clinical behavior.

Signs and Symptoms: The most common warning sign for uterine cancer is abnormal vaginal bleeding, and recognition of this sign often affords an opportunity for early diagnosis and treatment. Any bleeding after menopause may be a sign of uterine cancer and the amount of bleeding does not correlate with the risk of cancer. Younger women (before menopause) may experience irregular or heavy vaginal bleeding as a sign 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 external sources (prescribed estrogen or tamoxifen/raloxifene) or internal sources (due to changes that occur with obesity), without adequate opposition from the hormone progesterone. 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, as well as diabetes and hypertension (due to a link with these diseases and obesity). 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. Less commonly, these cancers are diagnosed with advanced stage disease or are part of the more aggressive types of cancer. For unclear reasons, these high-risk cancers may occur more commonly in black women. Though uterine sarcomas are rare, having a history or pelvic radiation and use of tamoxifen increase the risk of developing this type of uterine cancer.

Screening: Women with any bleeding after menopause or heavy, prolonged or unexpected bleeding prior to menopause (after the age of 45 or younger if risk factors for cancer exist, such as obesity) should have a biopsy of the endometrium to exclude uterine cancer. In the absence of signs of abnormal bleeding, there are no routine screening tests for uterine cancer. Importantly, a Pap test is designed to detect cervical and not uterine cancer.

Prevention: Women can decrease their risk of endometrial cancer by exercising regularly, eating a balanced plant-based diet and maintaining a healthy weight. Progesterone use, either alone or in combination with estrogen (as is found in most birth control pills), lowers the risk of endometrial cancer and thus can be used to prevent endometrial cancer from developing in those women at risk. Progesterone can also be administered through an IUD that secretes this hormone, and this has been shown to reduce the risk of endometrial cancer in women at risk. There are no known methods to prevent uterine sarcoma. Women should be aware of her family history, since there is a risk of endometrial cancer due to an inherited (genetic) condition, Lynch syndrome. Families with multiple generations of family members with colon, endometrial, ovarian, and other cancers should be evaluated by a genetic counselor and should consider testing for Lynch syndrome. In patients with Lynch syndrome, prevention strategies (such as hysterectomy and oophorectomy to prevent uterine and ovarian cancer) can be considered. Additionally, some groups recommend screening with endometrial biopsy and pelvic ultrasound to detect cancers early.

Incidence: Cancer of the uterus is the most common reproductive cancer. It is estimated that there will be about 60,050 new cases diagnosed in the United States during 2016, and more than 95 percent of these will be endometrial adenocarcinomas. Approximately 10,470 women will die from uterine cancer in the United States during 2016.[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.

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. Evidence supports that minimally invasive approaches (robotic and laparoscopic surgery) should be the standard surgical approach in women with endometrial cancer due to a lower rate of complications compared with traditional surgery.

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).

Given that the benefit of complete lymph node dissection in endometrial cancer is uncertain, investigators have attempted to refine "surgical staging" to maximize patient outcomes and minimize side effects. Recent efforts have been focused on identifying women with endometrial cancer in whom the risk for spread to the lymph nodes is highest, and avoiding removal of the lymph nodes in women at low risk for spread (to avoid resulting leg swelling, known as lymphedema, which can occur following lymph node removal).

Recently, the technique of sentinel lymph node mapping, currently the standard of care in breast cancer and melanoma, has become increasingly utilized in endometrial cancer. This technique focuses on identifying and removing just the lymph nodes that most likely are draining the cancer. In this procedure, a fluorescent and/or blue dye is injected into the cervix prior to hysterectomy once the patient is under anesthesia. Using a special camera (to detect the fluorescent dye) or visualize the blue dye, those lymph nodes that are highlighted are removed and examined closely to see if they contain any cancer cells. This technique is still being evaluated for use in certain endometrial cancer tissue types and stages. In further efforts to individualize surgical approaches, recent data suggests that ovary conservation in young patients with endometrial cancer is reasonable.

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. The majority of women diagnosed with endometrial cancer do not require any adjuvant therapy after hysterectomy. However, in women at higher risk for recurrence, radiation or chemotherapy may be recommended. Radiation reduces vaginal or pelvic recurrence but has not improved overall survival (cure).

Based on the results of important clinical trials (and in an effort to reduce potential radiation related risks), 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, in what order chemotherapy or radiation should be administered. Uterine sarcomas, which carry a high risk for recurrence, often are treated with chemotherapy with or without radiation after hysterectomy.

Adjuvant chemotherapy is now the mainstay of treatment for women with Stage III and IV endometrial cancer. Clinicians frequently use therapy that combines the systemic (or whole body) effects of chemotherapy with the improved local control provided by radiation. Two chemotherapy agents, paclitaxel and carboplatin, have been shown to be effective for treatment of advanced endometrial cancer and have fewer side effects than other treatments. Many treatment options under current clinical evaluation are using these biologic or targeted agents alone, or in combination with chemotherapy. NRG Oncology has clinical trials specifically investigating these targeted therapies.

Recently, exciting results have been reported regarding the use of a new class of drugs known as "immune checkpoint inhibitors" (which block the programmed cell death protein (PD-1) or its binding partner (a ligand called PD-L1). While preliminary, the use of a PD-1 inhibitor in a subset of women whose endometrial cancers recurred despite standard therapy was shown to lead to disease stabilization and reduction for far longer than typically seen with targeted therapies. Given these promising preliminary results, these agents continue to be investigated in a large number of clinical trials.

Clinical Trials

The use of targeted therapy is under active investigation in uterine cancers. The targeting of blood vessels (angiogenesis pathways) has been successful in Phase II trials with bevacizumab showing 36 percent of patients to be progression free at 6 months. This finding resulted in this agent being added to GOG-86P, a randomized Phase II trial. Preliminary results from this study suggest that the addition of bevacizumab to standard chemotherapy may improve overall survival relative to previous drug combinations and updated results are expected soon. The other chemotherapy combinations (including inhibitors of the mTOR pathway and the use of an agent with a similar mechanism to paclitaxel with bevacizumab) did not show any improved survival.

Carcinosarcomas are being studied using ifosfamide and paclitaxel versus carboplatin and paclitaxel in GOG-261. Results will be forthcoming. Uterine leiomyosarcoma is currently treated with gemcitabine and docetaxel, and despite this, most women experience recurrent disease. A current clinical trial (GOG-277) is evaluating combination chemotherapy versus observation after hysterectomy in patients with disease confined to the uterus to see whether the current chemotherapy strategy improves survival.

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 health care 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.

Another area of survivorship is looks at other medical illnesses in women with uterine cancer. Given that women with endometrial cancer are overall more likely to die of cardiovascular disease than endometrial cancer, addressing risk factors such as obesity is critical to improving the overall health and outcome of survivors.

Gynecologic oncologists have taken an active role in referring women to weight reduction programs, including bariatric surgery, dietician, exercise programs, and in turn, are emphasizing diabetes and cardiovascular risk-reduction strategies.

In support of this effort, NRG Oncology is leading a prospective trial to evaluate an exercise intervention as a means to improve survival in women with endometrial cancer. The Foundation for Women's Cancer is exploring funding for additional programs to aid in addressing this barrier to good gynecologic health.

[4]American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016.

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 may be prevented by the same vaccinations that are advocated for the prevention of cervical cancer. The Center for Disease Control and Prevention (CDC) recommends HPV vaccination routinely for all 11-and 12-year-old boys and girls. The current vaccine can be given as young as age 9 and up to age 26. The vaccine protects against 9 types of HPV.

Incidence: Primary vaginal cancer is one of the rarest gynecologic cancers. It is estimated that there will be about 4,620 new cases diagnosed and 960 deaths from vaginal cancer in the United States during 2016.[5] Vaginal cancer accounts for about 3 percent of reproductive cancers. About 1 in 1,100 women develop vaginal cancer in her lifetime.

Advances in Vaginal Cancer

Because of its rarity, vaginal cancer is not amendable 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.

Most women with vaginal carcinoma are past child-bearing years. Advances in the surgical therapy for vaginal cancer include 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.

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. Imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are often used to guide therapy. One study evaluated magnetic resonance imaging (MRI) of vaginal cancer and showed that MRI correctly identified over 95 percent of the tumors, and correctly demonstrated disease that involved tissues beyond the vagina in 88 percent of patients. MRI staging correlated very well with survival. Thus, for patients with advanced disease, staging may allow a treatment plan to be enacted without need for surgery.

PET imaging has become a standard diagnostic tool in the initial staging of cervical cancer and for post-treatment surveillance, and has similar applicability for vaginal cancer. Metabolic imaging with positron emission tomography (PET) may be more sensitive than CT and MRI. Positron emission tomography (PET) in combination with MRI (or CT scans) may be an even better method to image vaginal cancer. A recent study evaluated PET prior to a planned radical surgery to remove recurrent cervical or vaginal cancer. PET was found to have a sensitivity of 100 percent and a specificity of 73 percent 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, for more advanced vaginal cancers there is a need for better treatments. For patients with advanced disease, chemotherapy prescribed concurrently with the radiation therapy may improve 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.

Advances in radiation therapy are also being used in patients 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.

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.

[5]American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016.

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. Smoking also increases a woman's risk for developing vulvar cancer.

Screening/Prevention: Because many vulvar cancers are associated with HPV, 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 and boys.

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 5,950 new cases diagnosed and approximately 1,110 deaths from vulvar cancer in the United States during 2016.[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 most significant recent advance is sentinel lymph node biopsy, which can improve detection of node metastases, and can reduce the risk of lymphedema in women with 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.

Two prospective, multicenter clinical trials have demonstrated the feasibility and reproducibility of sentinel lymph node (SLN) biopsy as part of the standard management of early-stage vulvar carcinoma. In a Gynecologic Oncology Group study, 510 women with vulvar cancer were enrolled in the study. From 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 percent of patients, confirming that this technique is feasible and safe in women with vulvar cancer.

In a large 2008 Dutch study that followed 259 women with unifocal vulvar disease, sentinel lymph node biopsy was found to be safe in patients with early vulvar cancer (less than 4 cm). On the basis of the results of these trials, many surgeons who treat vulvar cancer have incorporated SLN biopsy into their practice. Studies have further shown that SLN biopsy is associated with better quality of life than full lymphadenectomy, is more cost-effective than full lymphadenectomy, and pathologic evaluation studies further have shown that SLN biopsy is associated with better quality of life than full lymphadenectomy, is more cost-effective than full lymphadenectomy, and has improved pathologic evaluation by incorporating immunohistochemical ultra staging.

A large observational study is currently evaluating the outcomes of patients with early stage vulvar cancer according to the results of their SLN biopsy and the approach to their care; this study may confirm that full inguinofemoral lymphadenectomy is no longer necessary in most patients with this disease.

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.

[6]American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016.

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