

# OVARIAN CANCER



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Ovarian cancer is a nonspecific term for a variety of cancers that originate in the ovary. There are about 20 microscopically distinct types. They can be classified into three large groups, epithelial cancers, germ cell tumors, and specialized stromal cell cancers. There are three groups because the ovary contains collections of cells with three distinct origins and functions.

## ORIGIN OF OVARIAN CANCERS

During embryonic development when the fetus is at about eight weeks post conception the organ systems are being formed. There is on each side of the fetal abdominal cavity an area that is destined to become the ovary. Into this area special cells migrate from the yolk sac which are destined to become the ova or eggs. These cells are also called germ cells or sex cells. Also in these two areas are cells that are specialized for the manufacture of steroid hormones. Covering all of this is the mesothelium which in the adult is recognized as the peritoneum, the lining of the abdominal cavity. The abdominal cavity is a large space lined with peritoneum in which are contained all of the intestines, the liver and in women, the uterus, tubes and ovaries. Thus, the future ovary is covered with mesothelium and contains germ cells and steroid producing cells. At birth and through adult life the ovary will function as a producer of ova and the steroid hormones, estrogen and progesterone .

During each menstrual cycle a germ cell will mature into an egg contained in a follicle, or cyst. While maturing the egg, the ovary produces estrogen. The follicle cyst is covered with the epithelium that once was the mesothelium. At ovulation, the follicle breaks and out comes the egg. The remnant of the follicle cyst produces progesterone, and is called the corpus luteum. The epithelial covering gives rise to the epithelial ovarian cancers; the germ cells to the germ cell tumors and the steroid producing cells to the specialized stromal cell cancers. About 80% of ovarian cancers are epithelial. About 20% are of germ cell origin and what little is left are of specialized stromal cell origin.

## CLASSIFICATION OF OVARIAN CANCERS

Epithelial	serous mucinous endometrioid clear cell papillary serous Brenner cell undifferentiated adenocarcinomas and sarcomas
Germ cell	teratomas mature teratomas immature teratomas struma ovarii carcinoid dysgerminoma embryonal cell carcinoma endodermal sinus tumor primary choriocarcinoma gonadoblastoma
Specialized	stromal cell cancers granulosa cell tumor theca cell tumor Sertoli-Leydig cell tumor hilar cell tumor

In addition, there are others that are very rare. The ovary is also a site for metastasis from other cancers, especially the intestinal cancers and breast cancer. Cancers metastatic to the ovary are referred to as Krukenberg tumors.

The germ cell tumors are of note because they commonly occur in young women; 50% are in women younger than 21 years of age. They are also of note because these can be very aggressive and virulent cancers, which however, with chemotherapy can be prevented from recurring. They are also noteworthy because the teratomas have the potential to form complete adult type tissues. The common name of a mature teratoma is "dermoid." It can contain hair, teeth, bone and brain tissue. Often they are full of skin. They are not malignant but very rarely can have a secondary malignancy such as a melanoma or a squamous cell cancer of skin. Some contain thyroid tissue and can cause hyperthyroidism. Teratoma means monster which is an apt name for these ovarian tumors full of teeth and hair. If the tissue is immature or fetal in appearance then they are malignant.

The specialized stromal cell tumors are rare but of interest because they can produce hormones. Granulosa and theca cell tumors are often mixed and can produce estrogen. If it occurs in a young girl it can produce premature sexual development which will also stop the bones from growing and thus cause short stature. Sertoli-Leydig cell tumors produce male hormones and will cause defeminization then masculinization with male pattern baldness, deep voice, excessive hair growth and enlargement of the clitoris. The specialized stromal cell cancers are usually not aggressive cancers and usually involve only one ovary.

The majority of ovarian cancers are the epithelial adenocarcinomas and are what most people mean when they say ovarian cancer. Like adenocarcinomas elsewhere they are graded and include a spectrum of disease from benign cysts to low grade borderline cancers to grade I, II, and III cancers. These cancers are often cystic and spread easily throughout the abdomen on all the peritoneal surfaces. This is not surprising since their origin is the same as that of the peritoneum. The peritoneum itself can give rise to an identical cancer long after the ovaries have been removed.

The remainder of this article is primarily concerned with epithelial ovarian cancers.

## SCREENING FOR OVARIAN CANCER

There have been many attempts to screen for ovarian cancers. None have been shown to be worthwhile. Screening means looking for a cancer in a person who has no symptoms and who has no physical findings suggestive of a cancer. That means those who are well and normal. The two methods used to try to screen for ovarian cancers are the Ca-125 blood test and ultrasound examinations. The reason that screening is not advised is because:

1. The incidence of ovarian cancer is low. Of the approximately 40,000,000 women in this country who are of an age to be at risk there are only about 20,000 cancers diagnosed each year. This is only about 1 in 2,000. Since two thirds of the cancers are at an advanced stage at diagnosis that leaves only about 1 woman in 10,000 who would be both asymptomatic and have no physical findings. So, the incidence of finding an unsuspected ovarian cancer is very low on an annual basis.
2. There is no recognized progression from an early premalignant change to an early cancer to an advanced cancer. Screening will only be helpful if you can find a change before it turns into a cancer or find a very early cancer before it progresses to an advanced cancer. Unlike premalignant changes on the cervix that can be found with the Pap test, there is no such progression to cancer in the ovary that is known at this time.
3. The positive and negative predictive values of both the Ca-125 test and ultrasound techniques are too low. There are too many reasons for a positive test other than cancer. If the Ca-125 is elevated in a screened population where there is expected to be only 1 cancer in every 2,000-10,000 women, then it will be elevated for some other reason about 99 to 1 times. The positive predictive value is less than 1%. This means that for every 100 positive tests only one will be due to cancer. Likewise, a negative test is wrong half of the time in women with ovarian cancer and is therefore essentially meaningless. The Ca-125 is a good test to follow the results of treatment in a person already diagnosed with ovarian cancer but is of no value to use to go looking for cancers.
4. There is no easy way to evaluate an abnormal test. All you can do is say that your cancer test is positive but that it is probably wrong by a factor of 99 to 1, and maybe you should just forget about it. Or, you could repeat it in several months and pick the best two out of three results. Or, if you wish to pursue it, you will eventually have to remove the ovaries to prove that there is no cancer. Unlike the abnormal Pap test that can easily be evaluated as many times as you wish there is no easy way to evaluate an abnormal Ca-125 or ultrasound test.
5. There is no recognized professional organization that has evaluated this problem that recommends screening. It may be possible someday but not now.

Those with a documented familial ovarian cancer syndrome where the lifetime risk of developing ovarian cancer is about 50% are advised to have annual physical examinations and consider an annual pelvic sonogram. Those who have set up ovarian cancer screening programs for women with a family history of ovarian cancer have not reported any substantial benefit. Even if you decided to undergo regular Ca-125 and pelvic sonogram testing, how often should it be done? Every year seems not very adequate for ovarian cancer. How long should it be done? For the next 30 years?

## FAMILIAL OVARIAN CANCER

It has been reported that from 1% to 5-10% of ovarian cancers are thought to be due to an inheritable syndrome. For those that are, the other female members of the family have a lifetime risk of about 50% of developing ovarian cancer. If there are several members in several generations with ovarian cancer then this may represent a familial syndrome. In general the lifetime risk of developing ovarian cancer is about 1.7%. If there is one first degree relative with ovarian cancer then the risk is about 3-5%. If there are two or more relatives with ovarian cancer then the risk is about 7%. Familial ovarian cancers tend to occur at an early age, before 50 years, and tend to be advanced serous epithelial cancers.

Those with a familial syndrome are advised to have their ovaries removed by age 35. There are no recommendations for women who have one or more relatives with ovarian cancer but no documented familial syndrome. They should also consider surgery since there is no good way to follow them and they may be at the beginning of a gene mutation. The gene responsible for familial ovarian cancer is thought to be the same as the one for some breast cancers. There is a commercially available test for this gene, but its usefulness is undetermined. There are several familial ovarian cancer registries and, if you are concerned about a familial syndrome, you should consult one of these.

M. Steven Piver, M.D.  
Director, Gilda Radner Familial Ovarian Cancer Registry.  
Roswell Park Cancer Institute.  
Buffalo, New York 14263.

Beth Y. Karlan, M.D.  
Director Ovarian Screening Program.  
Department of Obstetrics and Gynecology.  
Cedars-Sinai Medical Center.  
University of California Los Angeles School of Medicine.  
8700 Beverly Blvd ,Los Angeles, Ca 90048.

Henry T. Lynch, M.D.  
Department of Preventive Medicine.  
Creighton University School of Medicine.  
2500 California Plaza.  
Omaha, Nebr. 68178.

## RISK FACTORS FOR OVARIAN CANCER

Epithelial ovarian cancers tend to be a cancer of affluent societies where expected life spans are long. An increased risk factor, other than age, is nulliparity or delayed childbearing. A decreased risk is seen with multiparity and with prolonged use of birth control pills. The mechanism for this protective effect is thought to be that the number of ovulations is reduced. Each ovulation requires the breakage of the ovarian follicle and the repair to the ovarian surface. Reparative processes means increased cell divisions, or mitoses. Each mitotic event is a time of risk for a mutation to occur. There have been some unsubstantiated claims that the use of talcum powders contaminated with asbestos can cause ovarian cancers. Dietary factors are difficult to determine but if present are very weak in their association. One study has even associated yogurt with an increased risk. More recently there has been a purported increased risk with the use of fertility drugs. The cause of ovarian cancer is unknown.

## SYMPTOMS

There are no symptoms of early ovarian cancer. Occasionally an ovarian cyst will be detected on a routine gynecologic examination. A cyst can break and bleed and that will also cause enough symptoms to cause the woman to seek help. Otherwise, the cancer is usually far advanced before it is diagnosed. The symptoms will be due to a build up of fluid in the abdomen called ascites. Some women will present with several gallons of ascitic fluid.

Ovarian cancer spreads on the surfaces of the intestines and can cause obstruction. Sometimes it will spread into the lining of the lung cavity causing fluid to accumulate which can cause shortness of breath. Often there will be a several month history of digestive problems that are not specific. X-rays of the abdomen, upper GI studies and barium enemas will fail to find the cancer because these tests evaluate the inside of the intestines and the insides are always normal. The problem is on the outside of the intestines. Only when the fluid is detected by an ultrasound test or a CT scan or a mass is felt will the diagnosis be considered. The diagnosis is made at exploratory surgery.

## SURGERY FOR OVARIAN CANCER

The goals of surgery are to establish a diagnosis, determine the stage and remove as much cancer as possible.

SURGICAL STAGES OF OVARIAN CANCER		
Stage	I	Limited to the ovaries
	IA	One ovary involved
	IB	Both ovaries involved
	IC	One or both ovaries involved, but with cancer on the surface of an ovary, rupture of an ovarian cyst malignant ascites or positive abdominal washings
Stage	II	Spread to adjacent pelvic structures
	IIA	Spread to uterus or fallopian tubes
	IIB	Spread to pelvic peritoneum
	IIC	Confined to the pelvis, but with malignant ascites or positive abdominal washings
Stage	III	Spread to the upper abdomen
	IIIA	Microscopic spread to the upper abdomen
	IIIB	Cancer nodules less than 2 cm in the abdomen
	IIIC	Nodules more than 2 cm, or positive pelvic or aortic lymph nodes
Stage	IV	Distant spread beyond the abdomen, liver, lung etc.

The stage is determined at surgery. If there are cancer nodules throughout the abdomen then it is obviously a stage III cancer. If only one ovary is apparently involved then there has to be an extensive search for microscopic cancer on the other abdominal structures and in the lymph nodes. An early stage is assigned only after a more advanced stage has been excluded.

In all but the earliest cancers there is often some cancer remaining after surgery. This is because it spreads throughout the abdomen in little nodules, some are only barely visible and others are too small to see. The surgical goal is not to leave any nodule larger than 1cm which is about a quarter of an inch. If the residual is this small or smaller then the debulking or cytoreduction is considered to have been optimal. Sometimes this is not possible but a maximum effort should be done to try to achieve this optimal situation. This may require removal of a piece of intestine

and even a colostomy in some instances.

In addition to stage, the grade is also important. There is a grade designated grade 0. This refers to an epithelial adenocarcinoma of low malignant potential, also called a borderline cancer. These cancers tend to be indolent and although they may be stage III, not recur for many years even without treatment. Grade I adenocarcinomas are easily identified as being from a glandular origin. Grade III cancers are difficult to identify as glandular; they are also called poorly differentiated. Grade II cancers are intermediate in appearance. Grade I cancers are expected to behave the best, grade III the worst.

## **MANAGEMENT OF OVARIAN CYSTS**

Any woman with an enlarged ovary is considered to have an ovarian cancer and is operated, except those women who are found to have a simple cyst less than 10 cm in size and who are ovulatory or early pregnant. These women can be followed conservatively and reexamined in four weeks. If the cyst is gone or getting smaller, then it can be followed until it is gone. They had a functional cyst. Every ovulating woman gets a cyst every cycle. This follicle cyst is usually about 2 cm when it breaks and releases the egg. Sometimes the follicle cyst does not break and persists and gets larger. It will eventually break on its own, but if detected during this time a cancer will also have to be considered. It should be allowed to go away on its own. Or, the follicle cyst ruptures and becomes a corpus luteum cyst. This will also go away by itself. Persistent ovarian cysts will have to be operated to exclude or diagnose a cancer. An ultrasound test can often distinguish between a simple cyst and a complex cyst. A simple cyst is just a fluid filled structure. A complex cyst has internal structures or solid areas within it. A simple cyst can be followed. A complex cyst or solid tumor should be operated.

## **TREATMENT OF BORDERLINE OVARIAN CANCER**

There is a special category of epithelial ovarian cancers called borderline or cancers of low malignant potential based on the microscopic appearance of the cancer. They are expected to behave as very low grade cancers, that is, to be very slow growing. Signs of recurrence may not develop for fifteen or twenty years. Most will never recur. Most are stage I, but can be stage III when diagnosed. They are usually not treated after surgery. If they recur then they are reoperated. The treatment of advanced stage disease with residual is controversial. The inclination is for chemotherapy; the dilemma is that it cannot be demonstrated to work.

## **TREATMENT OF EPITHELIAL OVARIAN CANCER**

The initial treatment is surgery which will consist of removal of the uterus, tubes and ovaries as well as any large nodules of cancer. There are exceptions when only one ovary is removed. This conservative surgery is indicated in the following situation.

1. The patient has a strong desire for further childbearing and is otherwise fertile.
2. The cancer is stage IA. Grade 0, I, or sometimes II epithelial cancer.
3. The cancer is a stage I germ cell cancer or a specialized stromal cancer.

In this situation a unilateral oophorectomy is indicated. The low grade epithelial cancers require no further treatment, although these women are advised to have the remaining ovary removed when childbearing is completed. The germ cell cancers are usually on only one side. All will receive aggressive chemotherapy and most will do well. The specialized stromal cell cancers are usually unilateral and not aggressive cancers, so the other ovary can be retained until no longer needed.

Otherwise, all ovarian cancer patients receive a maximal surgical effort so that the residual is small. This will give them a better chance for a complete response to chemotherapy. If a segment of intestine has to be removed, then that is done. Sometimes this will result in a colostomy. If all the large pieces of cancer can be removed then a maximum effort is indicated. All the cancer can seldom be removed, but if no piece larger than 1-2 cm remains after surgery then that is considered to be an optimal cytoreduction surgery. After surgery almost all patients will require additional treatment.

The whole abdomen needs to be treated. Sometimes this can be accomplished by radiation. This is not a popular treatment in this country because of the possible major side effects and because chemotherapy seems to work as well. Another way to radiate the abdomen is to instill a radioactive substance into the abdomen. The radioactive isotope of phosphorus, called P-32, is used. This is a one time instillation and the entire abdominal contents receive a dose of several thousand RADs to a depth of several millimeters. It is used only when good distribution is assured and only microscopic amounts of cancer are present.

Chemotherapy consists of receiving the drugs soon after surgery and it is repeated every 3 or 4 weeks if all is going well. There are usually six courses of treatment. How do you know if it is working? If there is any measurable cancer, then you can tell if it is getting bigger or smaller. If there was ascites initially which has not recurred then that is good evidence of success. If the Ca-125 was elevated and reverts to normal then that is evidence of a good response. If the Ca-125 rises or the ascites returns or a new cancer is detected then that indicates failure of the chemotherapy.

Stage IA and IB, grade I cancers usually require no further treatment. The 5 year survival is about 95%.

All stage IC and all grade III cancers receive treatment, either with chemotherapy or P-32. The prognosis for these early stage cancers is usually good, with cure rates of 65-80%.

Stage II and stage III cancers with minimal or microscopic residual receive chemotherapy. The most popular regimen at this time is a platinum and Taxol combination. The 5 year survival rates are 30-50%.

For those with Stage III and IV cancers with bulky residual, the near term response is good, but the long term outlook is poor.

#### RESPONSE TO CHEMOTHERAPY FOR ADVANCED OVARIAN CANCER

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|-------|--|
| 100   | patients with advanced cancer treated with a platinum combination chemotherapy   |
| 80    | patients will have an initial complete clinical response, i.e., the cancer will be undetectable and the Ca-125 normal, but |
| 40    | patients will have persistent cancer if they are reoperated, and   |
| 40    | will have no cancer detected at reoperation, but of these  |
| 20    | will recur within the next 5 years. This leaves  |
| 20    | patients free of cancer, but some will still recur, so   |
| 10-15 | patients will remain cancer free and apparently cured.   |

Those who recur or have progressive disease on chemotherapy will be treated with a variety of methods, but the outlook is not good.

## **SECOND LOOK SURGERY**

A second look procedure is a complete surgical exploration and restaging procedure to determine the status of the cancer upon completion of chemotherapy. In many cases, after an ovarian cancer has been diagnosed and treated, there is no detectable cancer. X-rays, CT scans, Ca-125 and physical examination are all normal. The question is then asked "What to do now?". If there is no more cancer then nothing more needs to be done. If there is still cancer remaining in the abdomen, more treatment needs to be given. At this point the only way to determine the status of the cancer is by another major surgery because even though all the tests are negative there can still be cancer present. This is called a second look.

The dilemma of second look surgery is that if it is positive, that is, persistent cancer is discovered, what can be done about it? The best known treatment has already been given. The odds are poor that any other treatment will be effective. If the second look is negative, the odds of cancer recurring are about 50%. It used to be that if the second look was negative no further treatment was given. But since the odds of recurrence after a negative second look are so high, most oncologists still want to give more treatment. The problem is what that treatment should be. There have been many studies to try to answer this question, but there is no definite answer.

If the second look is positive then there is an opportunity to continue treatment. But with what? Again, there is no demonstrated effective treatment, although many things have been tried.

When contemplating a second look procedure both the patient and oncologist must have a clear idea of why they are going to do it and what they are going to do with the results. Second look procedures can be difficult. If the intestines are stuck together with adhesions from the previous surgery, it can be very difficult to even do the procedure, and the risk of a bowel injury is increased. The surgical procedure can be long and difficult especially if there is no cancer detected. You have to look and biopsy everything that can be biopsied, because when it is all done you have to be convinced that there was nowhere else to look and that the negative results are as accurate as they can be. Of course, if a piece of cancer is detected right away then the procedure is terminated; nothing more needs to be done surgically.

You can predict what the results of a second look will be. If there was large residual at completion of the original surgery the odds of a positive second look are about 80%. If there was no residual after the initial surgery the odds of a negative second look are 80%. If there was no residual after the initial surgery and the second look is negative the odds of recurrence are less than about 10%. If there was large residual initially and a negative second look the odds of recurrence are about 75%.

## **WHAT TO DO WHEN NOTHING IS WORKING**

Most patients with advanced ovarian cancer will do well initially, but most will not be cured. For these women and their families there will be a prolonged course of alternating hope and fear as results of treatment are awaited and new treatments tried. Some of these treatments will result in a complete remission of the cancer. Few remissions will be lasting. Some patients will receive investigational drugs administered through nationwide studies. Some will try investigational techniques such as high dose chemotherapy with bone marrow or stem cell replacement. And, some will opt for unconventional treatments, of which there are many, all with testimonials as to their efficacy.

When ovarian cancer persists, in spite of several different treatment regimens, a decision should be made as to what the overall goals will be. Cure is seldom a realistic goal, but if that is what

is decided then you should probably seek an entirely different approach such as a highly investigational method. These would be available only at major cancer treatment centers. Miracles can be sought through unconventional treatment regimens.

If cure is not a realistic goal, then neither may be longevity. If longevity is not a goal, then you can stop worrying about the cancer and devote your emotional energy and resources to the more important problems of daily living. You are going to live with this cancer. You may die as a consequence of this cancer. BUT, YOU ARE NOT DEAD YET. There are still things for you to do. There are still things that your doctor needs to do for you. There are still things your family and friends need to do for you. And, there are still things you need to do for yourself.

Each day will require provision for comfort and function. Each day will be an opportunity to say good-bye to those you need to say good-bye to. Each day will be an opportunity to resolve past conflicts and reconcile yourself with your religious beliefs. Each day will be a free day. You can do with it as you wish.

How do you decide when to stop treatment? Ovarian cancer is different from other cancers. It is usually diagnosed in an advanced stage, but responds well to initial treatment. About 15% will even be cured. Most other cancers that are diagnosed at advanced stages are essentially untreatable. By contrast, breast cancer is usually diagnosed at an early stage, but is unpredictable and can recur several times over many years. For the ovarian cancer patient both the initial fear and the initial hope are both justified. Most will do well initially, but most will do poorly in the long run.

Since the initial treatment has such a high response rate it is justified to think that treating the recurrences will do as well. The dilemma is that as new active drugs are developed they are rapidly used as initial treatment, leaving few choices for the recurrences. The odds of achieving a complete response for a recurrence following first line treatment are only about 5%. The duration of this complete response is usually less than 6 months. The possibility of cure is unknown, but is probably only a percentage point at most. The odds of cure if the second line treatment does not work are too low to calculate.

How do you decide when to stop treatment? It depends on how you ask the question. If the question asked is:

"Is there any possibility that this cancer can be cured?"

Then the answer is "Probably not, but if there is any possibility that it can be cured then it will require more surgery and chemotherapy or some other treatment. Whatever the possibility, it is potentially more than zero, which is the outcome if nothing is done."

With this approach the decision is usually to agree to more treatment. If the question asked is:

"Is there any known treatment that will cure this cancer?"

Then the answer is "No and any more treatment is futile."

At this point the decisions are based more on personality and philosophy than medicine.

The decision not to try more treatment does not mean being abandoned by your doctors. You may need even more medical care in an attempt to solve or palliate some of the effects of the cancer. Now is also the time to make contact with a Hospice organization if there is one

available. Hospice can help you stay at home and coordinate care with your doctors.

The decision to not take more cancer treatment does not mean to choose death but rather to choose life, for however long it is to be, free of the burden of chemotherapy etc.

## **TREATMENT OF OTHER TYPES OF OVARIAN CANCER**

As a group the Germ cell cancers are usually diagnosed at an early stage and treated surgically, often with removing only the involved ovary. Almost all patients are then given chemotherapy with a combination of drugs selected specifically for this type of cancer. There are some variations in treatment between the specific types of germ cell cancers so each case must be considered individually. In general, the outlook is good.

The Specialized Stromal cell cancers are usually considered low grade malignancies and are usually diagnosed at an early stage. They are diagnosed and treated surgically without postoperative chemotherapy. Since most are diagnosed at an early stage, the outlook is good.

## **FALLOPIAN TUBE CANCER**

Fallopian tube cancers are rare. If they involve the ovary, they are often called ovarian cancers. They arise from the lining of the tube. They have the same microscopic appearance as the serous epithelial ovarian cancers. This is as expected since the lining of the fallopian tube is derived from the same embryologic tissue as is the surface of the ovary. The diagnosis of a fallopian tube cancer requires the determination that the major portion of the cancer is within the tube rather than on the ovary.

Since there are no large series of fallopian tube cancers that have been reported, they are, by default, treated the same as are epithelial ovarian cancers. They seem to have the same behavior and have the same prognosis.

## **INTRAPERITONEAL ADENOCARCINOMA**

Occasionally a cancer that is identical to that of a papillary serous ovarian cancer will occur throughout the abdomen. These cancers are thought to arise directly from the peritoneum and are sometimes referred to as mesothelial adenocarcinomas or as extraovarian papillary serous cystadenocarcinomas. The mesothelium was the lining of the abdominal cavity of the fetus prior to birth. It is the same structure that covers the ovaries; so it is not surprising that the same sort of cancer can occur from the lining of the abdomen as occurs from the surface of the ovary. It is often difficult to determine if the cancer arose from the ovaries or if it arose from the peritoneum. The lining of the uterus is also sometimes involved with the same cancer so the primary site is further confounded. These cancers have been known to occur years after the ovaries were surgically removed. In general, they are treated and behave the same as an ovarian cancer of similar stage and grade.

[William M. Rich, M.D.](#)

Clinical Professor of Obstetrics and Gynecology  
University of California, San Francisco  
Director of Gynecologic Oncology  
University Medical Center  
Fresno, California