

EVERYONE'S GUIDE FOR CANCER THERAPY
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OVARY

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Carcinoma of the ovary is one of the most common gynecologic malignancies. In many cases, it is curable when found early, but because it does not cause any symptoms in its early stages, most women have widespread disease at the time of diagnosis. Partly because of this, the mortality rate from ovarian cancer exceeds that for all other gynecologic malignancies combined. It is the fourth most frequent cause of death in women in the United States. About one in every 70 women will develop cancer of the ovary and one in every 100 women will die from it. The American Cancer Society estimates that there will be 26,000 cases of ovarian cancer diagnosed each year with approximately 15,000 deaths.

Types The most common form of ovarian cancer arises from the cells covering the surface of the ovary and is known as epithelial carcinoma. There are five major types of this carcinoma-serous, mucinous, endometrioid, clear cell and undifferentiated. Epithelial carcinomas are further divided into grades, according to how virulent they appear on microscopic examination.

Tumors of low malignant potential, also known as borderline tumors, are the most well-differentiated malignancy (Grade 0) and account for 15 percent of all epithelial carcinomas of the ovary. The other three grades are well-differentiated (Grade 1), moderately-differentiated (Grade 2) and poorly-differentiated (Grade 3). Well-differentiated tumors have a better prognosis than poorly-differentiated tumors. Clear cell carcinoma and especially undifferentiated carcinoma have a poorer prognosis than the other cell types.

The two other major kinds of ovarian cancer-germ cell tumors, which arise from the eggs, and ovarian stromal tumors, which arise from supportive tissue-are relatively uncommon and account for less than 10 percent of all ovarian malignancies (*see "Ovarian Germ Cell Tumors"*).

How It Spreads Ovarian cancer spreads early by shedding malignant cells into the abdominal cavity. The cells implant on the lining of the abdominal cavity (peritoneum) and can grow on the surface of the liver, the fatty tissue attached to the stomach and large intestine (omentum), the small and large intestines, the bladder, and the diaphragm.

Disease on the diaphragm may at times result in impaired drainage of fluid from the abdominal cavity, resulting, for some women, in a large collection of abdominal fluid known as ascites. The cancer cells spread to the surface of the lungs and chest cavity, resulting in a collection of fluid around the lungs known as a pleural effusion.

Ovarian cancer may also spread to the pelvic, aortic, groin and neck lymph nodes.

What Causes It Unknown.

RISK FACTORS

There is a much higher incidence of ovarian cancer in industrialized countries. Some researchers have implicated talcum powder, which until recently contained asbestos, as a possible cause. Ovarian cancer can occur in any age group, but is most common in postmenopausal women. Not ovulating-by having children, breastfeeding, using birth control pills or having a condition that interferes with ovulation such as polycystic ovaries-has been shown to offer protection against developing cancer. There may also be a genetic predisposition to this cancer. There are rare families in which several members of the same or different generation develop ovarian cancer. This is known as hereditary ovarian cancer syndrome. Women with hereditary ovarian cancer syndrome are also at significant risk for the development of breast cancer, uterine cancer, and colon cancer. These individuals are often positive for the BRCA-1 or BRCA-2 gene, which can be tested for. It generally affects women in their mid-forties. There may be up to a 50 percent risk of developing ovarian cancer in their lifetime. It can also be inherited through the male side of the family. This syndrome occurs in less than 3 percent of all women who have a positive family history of ovarian cancer. Approximately 7 percent of all women with ovarian cancer do not seem to have a genetic disposition but have a positive family history. Ninety percent of these women have only one other family member with ovarian cancer.

Suggested management in women with a family history for ovarian cancer is as follows: Removal of both ovaries and sometimes the uterus after childbearing or very close follow-up with serum CA-125 and pelvic ultrasound for those women who have hereditary ovarian cancer syndrome. If there is a family history of only one relative with ovarian cancer, prophylactic removal of the ovaries is not recommended. In women who are BRCA-1 or BRCA-2 negative and who have 2-3 close relatives with ovarian cancer, prophylactic removal of the ovaries is generally recommended by most gyn oncologists and geneticists.

SCREENING

There are no diagnostic methods accurate enough to be used for routine screening of women without symptoms. Nonetheless, it is recommended that all women have an annual pelvic and rectal examination since an ovarian mass can occasionally be detected. A Pap smear will detect ovarian cancer in only 10 percent of women with the disease. Studies have shown that a serum tumor marker known as CA-125 is elevated in 90 percent of women with advanced epithelial ovarian cancer and only 50% of women with cancer confined to the ovary (Stage I). Unfortunately, this test is not accurate enough for screening all women for ovarian cancer. Approximately 2 percent of normal women will have an elevated CA-125 (normal is less than 35). Approximately 1 percent of normal women will have a CA-125 greater than 65. Because of the small incidence of false-positive tests, screening all women with CA-125 has not been recommended. A great deal of research is taking place exploring the use of CA-125 as well as other tumor markers for screening. Tumor markers are, however, useful for assessing response to therapy.

A pelvic ultrasound (sonogram) examination may become a part of the routine annual gynecologic examination in the future. It is performed using a minimally uncomfortable vaginal probe, as well as through the abdominal wall. It is used to examine the ovaries as well as the uterus. When used in combination with CA-125, it is fairly accurate in detecting ovarian neoplasms.

A small number of women have hereditary ovarian cancer syndrome and have a gene in their chromosomes, known as the BRCA-1 or BRCA-2 gene. It may be possible to test women who are thought to be carriers for this gene. If so, counseling or therapeutic intervention can be instituted (see risk factors).

COMMON SIGNS AND SYMPTOMS

Many women with early stages of ovarian carcinoma have no symptoms. The unfortunate result is that two-thirds of all women with ovarian carcinoma have advanced disease at the time of diagnosis.

Many women have vague, non-specific abdominal symptoms including pain, pelvic pressure, low back discomfort, mild nausea, feeling full early when eating, constipation and gas. Some women have abnormal uterine bleeding. Although some cases are diagnosed during a routine gynecologic examination, many women are diagnosed only when they have developed abdominal distention because of ascites.

Advanced ovarian cancer often results in blockage of the intestines, causing severe nausea, vomiting, pain and weight loss.

DIAGNOSIS

Physical Examination

- A careful pelvic exam is performed with attention to the ovaries, uterus, bladder and rectum.
- The neck, groin and underarms (axilla) are examined for enlarged lymph nodes.
- The lungs are carefully examined for excess fluid.
- The abdomen is examined for the presence of an enlarged liver, a mass or ascites.

Blood and Other Tests

- Complete blood count (CBC).
- Serum liver and kidney function tests.
- Serum CA-125.

Imaging

Abdominal and pelvic CT or MRI scans may be obtained in advanced cases.

- X-rays of the upper gastrointestinal tract (UGI series) may occasionally be done.
- Intravenous pyelogram (occasionally).
- Barium enema (occasionally).

Endoscopy and Biopsy

- A definitive diagnosis requires microscopic examination of part or all of the involved ovary or any other suspicious abdominal mass. Cystic ovarian tumors that are less than 2-1/2 in. (6 cm) in diameter occurring in premenopausal women are usually benign cysts.

Surgical evaluation should be strongly considered for any ovarian mass in a postmenopausal woman, masses that are larger than 2-1/2 in. (6 cm) in diameter, masses persisting longer than one menstrual cycle and masses that are suspicious on imaging of the pelvis.

STAGING

Ovarian carcinoma is staged at surgery. Stages are usually defined according to the classification system devised by FIGO (International Federation of Gynecology and Obstetricians). The TNM system corresponds to the stages accepted by FIGO.

Stage I Cancer is confined to one or both ovaries.

- **Ia** Cancer is limited to one ovary. There is no ascites and no tumor on the surface of the ovary and the surface of the tumor is unruptured.
- **Ib** The cancer is limited to both ovaries. There is no ascites and no tumor on the surface of either ovary and the surfaces of the tumors are unruptured.
- **Ic** The cancer is either Stage Ia or Ib and one or more of the following applies: there is tumor on the surface of one or both ovaries, at least one of the tumors has ruptured, ascites is present or the abdominal washings contain malignant cells.

Five-Year Survival 60 to 100 percent, depending on the histologic type, grade, and sub-stage.

Stage II The tumor involves one or both ovaries with extension to other pelvic structures.

- **IIa** There is extension of the cancer or metastases to the uterus and/or fallopian tubes.
- **IIb** There is extension to the bladder or rectum.
- **IIc** The cancer is either stage IIa or IIb and one or more of the following applies: there is tumor on the surface of one or both ovaries, at least one of the tumors has ruptured, the ascites contains malignant cells or the washings from the abdominal cavity contain malignant cells.

Five-Year Survival About 60-80 percent.

Stage III The tumor involves one or both ovaries with tumor implants confined to the abdominal cavity but outside the pelvis, or there is cancer in the pelvic, para-aortic or groin nodes.

- **IIIa** The tumor is grossly limited to the pelvis and the lymph nodes are negative but there is biopsy-proven microscopic cancer on the intra-abdominal (peritoneal) surfaces.
- **IIIb** The tumor involves one or both ovaries and there are tumor implants on the peritoneal surfaces less than 3/4 in. (2 cm) in diameter. The lymph nodes are negative.
- **IIIc** The tumor involves one or both ovaries, there are tumor implants on the surface of the abdominal cavity greater than 3/4 in. (2 cm) in diameter or there is cancer in the pelvic, para-aortic or groin lymph nodes.

Five-Year Survival About 20-50 percent.

Stage IV Growth involves one or both ovaries. There are distant metastases to the liver or lungs, or there are malignant cells in the excess fluid accumulated around the lungs.

Five-Year Survival 10-25 percent.

TREATMENT OVERVIEW

Surgery In women with early-stage cancer, one or both ovaries are usually removed (with or without removal of the uterus) and meticulous surgical staging is performed. This involves washings from the abdominal cavity to detect malignant cells, removal of the pelvic and aortic lymph nodes, meticulous inspection of the abdominal cavity surfaces with biopsy of any suspicious lesion, removal of the fatty tissue attached to the stomach and large intestines (omentectomy), and multiple random biopsies of the lining of the abdominal cavity including the surfaces of the diaphragms.

In women with advanced cancer, surgical removal of as much tumor as possible, called tumor debulking is standard therapy. If possible, the uterus, the omentum and as much as the grossly visible cancer as possible is removed.

Recent studies have shown that 25 to 35 percent of women with ovarian carcinoma will require intestinal or urologic surgery to obtain optimal tumor debulking (defined as leaving behind no tumor implant greater than 3/4 in. (1 cm) in diameter). An enormous effort is made by most gyn oncologists to leave no cancer at the end of surgery. A permanent colostomy may occasionally be necessary, but is rare in women who have had a preoperative bowel prep-a cleansing of the intestines with enemas and laxatives and administration of antibiotics.

To decide if further treatment is required, second-look abdominal surgery is often performed after six cycles of chemotherapy in women without evidence of persistent cancer (see "*Treatment Follow-Up*").

In women with recurrent cancer, surgery is often required to relieve intestinal obstruction or to remove all visible cancer if possible.

Complications of surgery can include infection, bleeding requiring transfusion and injury to the bladder, rectum or ureter causing a leak. There may be blood clots in the legs, which can occasionally dislodge and travel to the lungs (pulmonary embolism).

Over the past several years, minimally invasive surgery has become possible in women with ovarian cancer. The primary use has been in women who have ovarian tumors thought to be confined to the ovary. Laparoscopic removal of the ovary with a frozen section (intraoperative rapid diagnosis) is performed and if it is cancer, then either a laparoscopic or open traditional staging procedure can be performed with removal of the ovary, peritoneal washings, removal of the pelvic and para-aortic nodes, inspection of the abdominal cavity with multiple random biopsies if no obvious disease is identified. In addition, if required, both ovaries and the uterus can also be removed at the same setting. Laparoscopy, however, is generally limited to non-obese women.

Laparoscopy is actively being studied by the Gynecologic Oncology Group in the management of women who have had removal of one or both ovaries, as well as the uterus for ovarian cancer, but who are incompletely staged. Within ten weeks of initial surgery, laparoscopic surgical staging can be performed. Lastly, in selected women, second-look minimally invasive surgery can be performed in those women who are 1) non-obese, 2) had relatively uncomplicated initial surgery, 3) who are clinically free of disease, and who are thought to be at high risk for either diffuse intra-abdominal small disease or who are thought to have no cancer.

Chemotherapy In most cases, chemotherapy is begun one to four weeks after surgery. The standard regimen includes carboplatin or cisplatin + Taxol given intravenously every three to four weeks as tolerated for at least six cycles. Forty to 80 percent of patients can be expected to respond. The response rate depends to a large degree on the amount of cancer remaining after surgery, with those who have no visible cancer after surgery having the best response rate.

Carboplatin is now being used more often than cisplatin because it can be given on an outpatient basis. It causes less kidney damage, hearing loss, nausea and vomiting and peripheral nerve damage (manifested by muscle weakness and numbness or tingling). Unfortunately, it does have more bone marrow toxicity than cisplatin.

Another technique known as intraperitoneal (intra-abdominal) chemotherapy has been developed to deliver the chemotherapy directly into the abdominal cavity. This procedure requires surgery to place a port and its attached catheter beneath the skin. The catheter is brought through the abdominal wall and placed directly into the abdominal

cavity. The cancer drugs are then given via a needle directly into the subcutaneous port. Complications can include infection, malfunction of the catheter and occasionally intestinal blockage.

Intraperitoneal chemotherapy is generally given monthly for six months. Large trials are now under way to compare the effectiveness of intraperitoneal versus intravenous chemotherapy.

Chemotherapy, depending on the drug, can cause hair loss, nausea and vomiting, infection or bleeding because of bone marrow toxicity, and damage to the heart, kidneys, nerves and liver.

Radiation There is some evidence that external beam radiation therapy is as effective as chemotherapy for patients with early stages of ovarian carcinoma who have no visible cancer remaining after their operation.

Sometimes radiation therapy is used for microscopic persistent ovarian cancer or cancer that has not responded well to chemotherapy. Radiation may be given only to the pelvis or more typically, to the entire abdomen (usually five days each week for four to five weeks), which results in a better survival rate. Complications and side effects can be considerable and include diarrhea, nausea and vomiting, bleeding from the bladder or rectum, vaginal scarring, intestinal obstruction, or leaks (fistulas) in the urinary or intestinal tracts.

Radioactive phosphate inserted directly into the abdominal cavity is sometimes given to women who have no visible cancer or less than 1 mm of residual disease after surgery.

TREATMENT BY STAGE

Stage Ia

Standard Treatment Therapy depends primarily on the age of the patient and the grade of the cancer.

For borderline or well-differentiated tumors (Grade 1) in women who want to preserve their reproductive function, standard therapy includes removal of the cancerous ovary and the adjacent fallopian tube (the other, apparently healthy ovary should be biopsied, however), removal of the omentum and removal of the pelvic and para-aortic lymph nodes.

For postmenopausal women and those who do not want to preserve their reproductive function, standard therapy includes a total hysterectomy, removal of both fallopian tubes and ovaries and careful surgical staging. Women with Stage Ia borderline or Grade 1 carcinoma are usually cured with surgery alone.

Standard therapy for Grade 2 or 3 tumors is total hysterectomy, removal of both tubes and ovaries, meticulous surgical staging and six monthly cycles of combination chemotherapy, usually with cisplatin or carboplatin + Taxol. Other therapies that are

sometimes recommended are total abdominal and pelvic radiation therapy or occasionally intra-abdominal administration of radioactive phosphate (P³²).

Investigational

- Intra-abdominal chemotherapy with agents such as cisplatin or carboplatin or etoposide.
- The Gynecologic Oncology Group is conducting a trial comparing carboplatin + Taxol given three times versus the same regimen six times in selected women with Stage Ic and Iia, Iib, or Iic and selected women with Stage Ia and Ib carcinoma of the ovary.

STAGE Ib

Standard Treatment A total hysterectomy, removal of both tubes and ovaries and meticulous surgical staging is performed. Women with tumors of low malignant potential or Grade 1 carcinomas do not require further treatment.

Women with Grade 2 or 3 cancers usually receive postoperative combination chemotherapy (usually carboplatin or cisplatin + Taxol given every three weeks for a total of six courses), whole abdominal and pelvic radiation therapy, or intra-abdominal radioactive phosphate.

Investigational Same as Stage Ia.

STAGE Ic

Standard Treatment Hysterectomy, removal of fallopian tubes and ovaries, partial omentectomy and removal of the pelvic and para-aortic lymph nodes is done. Careful inspection of the remaining intra-abdominal surfaces is vital. Suspicious lesions should be biopsied, and washings of the abdominal cavity should be taken to check for malignant cells.

Standard therapy after surgery includes six courses of carboplatin or cisplatin + Taxol.

Investigational

- The Gynecologic Oncology Group is conducting a trial comparing carboplatin + Taxol given three times to the same regimen given six times in selected women with Stage Ic and Iia, Iib, or Iic and selected women with Stage Ia and Ib carcinoma of the ovary.
- Intra-abdominal cisplatin or carboplatin or etoposide with or without other anticancer drugs.
- Whole-abdomen and pelvic radiation therapy.

STAGE Iia

Standard Treatment The surgical procedure is the same for the Stage Ic, again with biopsy of any suspicious lesions, pelvic and aortic node dissection, and washings of the

abdominal cavity to check for malignant cells. Standard therapy after surgery includes six courses of carboplatin and Taxol.

Investigational

- Intra-abdominal carboplatin, cisplatin or etoposide with or without other anti-cancer drugs.
- The Gynecologic Oncology Group is conducting a trial comparing carboplatin + Taxol given three times to the same regimen given six times in selected women with Stage Ic and IIa, IIb, or IIc and selected women with Stage Ia and Ib carcinoma of the ovary.

STAGES IIb, IIIa, IIIb, IIIC, IV

Standard Treatment In women with advanced ovarian carcinoma, standard therapy involves removing as much of the tumor as possible as well as the uterus, both fallopian tubes and ovaries and the omentum. Removal of the pelvic and para-aortic nodes is also performed.

If there is optimal residual disease after surgery-no tumor implant greater than 1/2 in. (1 cm) in diameter-combination chemotherapy including carboplatin or cisplatin + Taxol (CT) is given for six cycles (one course every three weeks). Total abdominal and pelvic radiation may be given, but only if the residual disease is less than 1/4 in. (0.5 cm) in diameter. Intra-abdominal radioactive phosphate may be given only if the residual disease is less than 1 mm in diameter.

If there is residual cancer larger than 1/2 in. (1 cm) in diameter or metastases outside the abdominal cavity, intravenous chemotherapy is used exclusively. The commonly used combinations are the same as used for Stage IIa, namely CP, CAP, AP, CHAD and IE.

Investigational Many investigational protocols are being used in the treatment of ovarian cancer:

- High-dosage intravenous carboplatin + etoposide with autologous (self-donated) bone marrow transplant.
- High-dosage Cytosin + cisplatin plus chest and abdominal radiation followed by autologous bone marrow transplant.
- High-dose carboplatin + ifosfamide + Mesna with autologous bone marrow transplant.
- Intravenous Topotecan.
- Intravenous Doxil.
- Different doses and schedule of administration of cisplatin, carboplatin + Taxol.
- Intravenous Gemzar
- Intra-abdominal administration of single agents such as interferon, cisplatin, carboplatin, Ara-C, bleomycin, mitoxantrone, 5-fluorouracil (5-FU) and etoposide.

- Intra-abdominal melphalan + Ara-C, carboplatin + etoposide (VP-16), monoclonal antibodies to ovarian carcinoma cells and cisplatin + etoposide with thiosulfate.
- Intravenous fludarabine, Hexalen or cisplatin + 5-FU + VP-16.
- Intravenous carboplatin + ifosfamide.
- Intravenous Taxol with other drugs.
- Intravenous cisplatin + Cytosan + hyperfractionated (twice daily) abdominal radiation therapy.
- Intravenous Thiotepa with autologous bone marrow transplant.
- Immunotherapy with interleukin-2 or interleukin-2-activated mononuclear cells.
- Leuprolide acetate (Lupron) in women with low malignant potential tumors.
- Tamoxifen.
- Megace.
- Oral Hexalen or Etoposide.

TREATMENT FOLLOW-UP

Follow-up is generally performed every three months for the first two years after treatment.

- The neck, lungs, abdomen and pelvis are carefully examined at each visit.
- The serum CA-125 level is followed closely and is sometimes the first indication of recurrent cancer.
- Abdominal and pelvic CT or MRI scans may be done, but their routine has not been shown to be effective in the absence of symptoms.

Second-Look Surgery If after six cycles of chemotherapy there is no evidence of persistent disease-as determined by physical examination, the serum CA-125 level and pelvic and abdominal CT scans-then second-look surgery may be performed. Although it is sometimes considered the standard of care, there has been no consistently proven survival benefit of this procedure. It is, however, the most reliable way of determining whether any cancer is left after treatment. Any residual cancer can also be removed.

If no cancer is found during the second-look operation, a thorough procedure requires taking peritoneal washings and biopsies from all adhesions or 20 to 30 random biopsies. These include the surfaces of the bladder, pelvis, pelvic sidewalls, diaphragm and the pelvic and aortic lymph nodes if not removed previously. If any of the omentum is still present, it is also removed. An appendectomy is usually done as well. Traditionally, at the second-look operation, if all the biopsies are negative, no further treatment is required.

In the hands of a gynecologic oncologist, approximately 25 to 60 percent of the women who have sub-optimal disease after chemotherapy (any tumor nodule greater than 1/2 - 3/4 in./1-2 cm) will have an optimal surgical debulking. An intra-abdominal catheter for intraperitoneal chemotherapy can also be placed during the operation.

Prognosis The prognosis primarily depends on the stage, grade and type of carcinoma and especially the amount of residual disease after the initial surgery.

Women who have Stage II, III or IV Grade 1 carcinoma and a negative second-look procedure have an excellent prognosis. Women with Grade 2 or 3 cancers and a negative second-look also have a good prognosis, but have a significant risk for developing recurrent disease. It is estimated that 30 to 50 percent of women with Grade 3 cancer will develop a recurrence within five years even after a negative second-look. As a result, many gynecologic oncologists recommend giving additional treatment-intravenous or intraperitoneal chemotherapy, radioactive phosphorus or whole-abdomen radiation therapy-after a negative second-look operation. The Gynecologic Oncology Group is conducting a study of women who have a negative second-look surgery, comparing intra-abdominal radioactive phosphorus to no further therapy.

For women who have microscopic disease at their second-look procedure, the prognosis is not as good and is partially dependent upon the grade of the cancer. These women are treated with more intravenous combination chemotherapy, intra-abdominal chemotherapy or whole-abdomen radiation.

Women with bulky residual cancer (implants greater than 3/4 in./2 cm) after a second-look procedure have a poor prognosis despite aggressive treatment with second-line chemotherapy.

RECURRENT CANCER

Women whose cancer returns are candidates for exploratory surgery for further aggressive tumor debulking. The goal of surgery is to remove all visible disease.

Postoperative therapy varies and may include intravenous chemotherapy, intra-abdominal chemotherapy or whole-abdomen radiation therapy. In many cases treatment is only palliative.

Different regimens of chemotherapy have been used with some benefit, including various combinations and doses of carboplatin, cisplatin + Taxol, Topotecan, Doxil, Cytosan, Gensar, hexamethylmelamine, 5-fluorouracil, ifosfamide and Cytosan, Adriamycin, etoposide and Alkeran (melphalan). (*See "Investigational Treatment"*).

THE MOST IMPORTANT QUESTIONS YOU CAN ASK

- What qualifications do you have for treating cancer? Will a gynecologic oncologist be involved in my care?
- Is there a medical oncologist and radiation oncologist available for consultation?
- What is the cell type, grade and stage of my cancer?
- How much cancer remained after surgery?
- Can my surgery be performed laparoscopically?
- What is the benefit of second-look surgery?
- What is the reason for the type of therapy you recommended after surgery?