Carcinoma ovary

Malignant lesions of the ovaries include primary lesions arising from normal structures within the ovary and secondary lesions from cancers arising elsewhere in the body. Primary lesions include epithelial ovarian carcinoma (70% of all ovarian malignancies), germ-cell tumors, sex-cord stromal tumors, and other more rare types. Metastases to the ovaries are relatively frequent, with the most common being from the endometrium, breast, colon, stomach, and cervix.

Although many histologic types of ovarian tumors have been described, more than 90% of ovarian malignancies are epithelial tumors. Many of these actually originate in the fallopian tubes.

The precise cause of ovarian cancer is unknown. However, several risk and contributing factors (including both reproductive and genetic factors) have been identified.

Ovarian cancer is the most common cause of cancer death from gynecologic tumors in the advanced countries. Around the world, more than 200,000 women are estimated to develop ovarian cancer every year and about 100,000 die from the disease. The lifetime risk of a woman developing epithelial ovarian cancer is 1 in 70.

Early disease causes minimal, nonspecific, or no symptoms. Therefore, most cases are diagnosed in an advanced stage. Prognosis in ovarian cancer is closely related to the stage at diagnosis; thus, overall, prognosis for these patients remains poor.

Standard treatment involves aggressive debulking surgery followed by chemotherapy. The incorporation of neoadjuvant chemotherapy has recently increased, with multiple studies indicating that in some situations it offers an improvement in morbidity and possibly survival.

Aetiology

The precise cause of ovarian cancer is unknown, but several risk and contributing factors have been identified.

Reproductive factors

Parity is an important risk factor. The risk of epithelial ovarian cancer is increased in women who have not had children and possibly those with early menarche or late menopause. Women who have been pregnant have a 50% decreased risk for developing ovarian cancer compared with nulliparous women. Multiple pregnancies offer an increasingly protective effect. Oral contraceptive use decreases the risk of ovarian cancer significantly.

These factors support the idea that risk for ovarian cancer is related to ovulation. The probability of ovarian cancer may be related to the number of ovulatory cycles, and conditions that suppress the ovulatory cycle may play a protective role. Ovulation suppression has been shown to decrease cancer incidence. Although treatment with agents that induce ovulation in women with infertility has been suggested to increase the incidence of epithelial ovarian cancer, this is unproven.

Genetic factors

Family history plays an important role in the risk of developing ovarian cancer. The lifetime risk for developing ovarian cancer is 1.6% in the general population. This compares with a 4-5% risk when 1 first-degree family member is affected, rising to 7% when 2 relatives are affected. From 5-10% of cases of ovarian cancer occur in an individual with a family history of the disease. Only a small percentage of these patients have an inherited genetic abnormality, and the risk of this occurrence increases with the strength of the family history. Hereditary epithelial ovarian cancer occurs at a younger age (approximately 10 years younger) than nonhereditary epithelial ovarian cancer, but the prognosis may be somewhat better.

Integrated genomic analyses by the Cancer Genome Atlas Research Network have revealed high-grade serous ovarian cancer is characterized by *TP53* mutations in almost all tumors. The findings also include the low prevalence but statistically recurrent somatic mutations in 9 further genes.

Evidence from the Cancer Genome Atlas Network showed that serous ovarian tumors and breast basal-like tumors shared a number of molecular characteristics, such as the types and frequencies of genomic mutations, suggesting that ovarian and breast cancer may have a related etiology and potentially similar responsiveness to some of the same therapies.

At least two syndromes of hereditary ovarian cancer are clearly identified, involving either (1) disorders of the genes associated with breast cancer, *BRCA1* and*BRCA2*, or (2) more rarely, genes within the Lynch II syndrome complex. Breast/ovarian cancer syndrome is associated with early onset of breast or ovarian cancer. Inheritance follows an autosomal dominant transmission. It can be inherited from either parent.

Approximately 1 person in 4000 in the general population carries a mutation of*BRCA1*. Some populations have a much higher rate of *BRCA1* and *BRCA2*mutations, especially Ashkenazi Jews. In families with 2 first-degree relatives (mother, sister, or daughter) with premenopausal epithelial ovarian cancer, the likelihood of a female relative having an

affected *BRCA1* or *BRCA2* gene is as high as 40%. The probability is much lower when the disease occurs in relatives postmenopausally.

Individuals with a *BRCA1* gene mutation have a 50-85% lifetime risk of developing breast cancer and a 15-45% risk of developing epithelial ovarian cancer. Those with a *BRCA2* gene mutation have a 50-85% lifetime risk of developing breast cancer and a 10-20% risk of developing epithelial ovarian cancer. Families with *BRCA2*mutations are at risk for developing cancer of the prostate, larynx, pancreas, and male breast.

Families with Lynch II syndrome or hereditary nonpolyposis colorectal cancer are characterized by a high risk for developing colorectal, endometrial, stomach, small bowel, breast, pancreas, and ovarian cancers. This syndrome is caused by mutations in the mismatch repair genes. Mutations have been demonstrated in mismatch repair genes *MSH2, MLH1, PMS1,* and *PMS2*.

Women with a history of breast cancer have an increased risk of epithelial ovarian cancer.

Previous hormone therapy

The risk for ovarian cancer is increased with hormone therapy, regardless of duration of use, formulation, estrogen dose, regimen, progestin type, and administration route.Nearly 1 million women without hormone-sensitive cancer or bilateral oophorectomy were followed. In an average of 8 years of follow-up, 3068 ovarian cancers were detected, of which 2681 were epithelial cancers.

Current users of hormones had incidence rate ratios for all ovarian cancers of 1.38 (95% confidence interval [CI], 11.26-1.51) compared with women who never took hormone therapy. Risk declined as years since last hormone use increased. Incidence rates in current and never users of hormones were 0.52 and 0.40 per 1000 years, respectively. This translates to approximately one extra ovarian cancer for approximately 8300 women taking hormone therapy each year.

Pathology

The World Health Organization Histological Classification for ovarian tumors separates ovarian neoplasms according to the most probable tissue of origin: surface epithelial (65%), germ cell (15%), sex cord-stromal (10%), metastases (5%), miscellaneous

- Surface epithelial tumors are further classified by cell type (serous, mucinous, endometrioid, etc) and atypia (benign, borderline [atypical proliferation, low malignant potential] or malignant; malignant may be invasive or non-invasive)
- Most malignant tumors are surface epithelial (90%)

- **Surface epithelial - stromal tumors**
  - **Serous tumors:**
    - Benign (cystadenoma)
    - Borderline tumors (serous borderline tumor)
    - Malignant (serous adenocarcinoma)

  - **Mucinous tumors, endocervical-like and intestinal type:**
    - Benign (cystadenoma)
    - Borderline tumors (mucinous borderline tumor)
    - Malignant (mucinous adenocarcinoma)

  - **Endometrioid tumors:**
    - Benign (cystadenoma)
    - Borderline tumors (endometrioid borderline tumor)
    - Malignant (endometrioid adenocarcinoma)

  - **Clear cell tumors:**
    - Benign
    - Borderline tumors
    - Malignant (clear cell adenocarcinoma)

  - **Transitional cell tumors:**
    - Brenner tumor
    - Brenner tumor of borderline malignancy
    - Malignant Brenner tumor
    - Transitional cell carcinoma (non-Brenner type)

  - **Epithelial-stromal:**
    - Adenosarcoma
    - Carcinosarcoma (formerly mixed Muellerian tumors)

- **Sex cord - stromal tumors**
  - **Granulosa tumors:**
    - Fibromas
    - Fibrothecomas
    - Thecomas

  - **Sertoli cell tumors:**

        - Leydig cell tumors

    - Sex cord tumor with annular tubules
    - Gynandroblastoma
    - Steroid (lipid) cell tumors

- **Germ cell tumors**
    - **Teratoma:**
        - Immature
        - Mature
        - Solid
        - Cystic (dermoid cyst)

    - Monodermal (e.g., strumaovarii, carcinoid)
    - Dysgerminoma
    - Yolk sac tumor (endodermal sinus tumor)
    - Mixed germ cell tumors

- **Malignant, not otherwise specified**
    - **Metastatic cancer from nonovarian primary:**
        - Colonic, appendiceal
        - Gastric
        - Breast

Signs and symptoms

Early ovarian cancer causes minimal, nonspecific, or no symptoms. The patient may feel an abdominal mass. Most cases are diagnosed in an advanced stage.

Epithelial ovarian cancer presents with a wide variety of vague and nonspecific symptoms, including the following:

- Bloating; abdominal distention or discomfort
- Pressure effects on the bladder and rectum
- Constipation
- Vaginal bleeding
- Indigestion and acid reflux
- Shortness of breath
- Tiredness
- Weight loss
- Early satiety

Symptoms independently associated with the presence of ovarian cancer include pelvic and abdominal pain, increased abdominal size and bloating, and difficulty eating or feeling full.Symptoms associated with later-stage disease include gastrointestinal symptoms such as nausea and vomiting, constipation, and diarrhea. Presentation with swelling of a leg due to venous thrombosis is not uncommon. Paraneoplastic syndromes due to tumor-mediated factors lead to various presentations.

Diagnosis

Physical findings are uncommon in patients with early disease. Patients with more advanced disease may present with ovarian or pelvic mass, ascites, pleural effusion, or abdominal mass or bowel obstruction.

The presence of advanced ovarian cancer is often suspected on clinical grounds, but it can be confirmed only pathologically by removal of the ovaries or, when the disease is advanced, by sampling tissue or ascitic fluid.

Laboratory testing

No tumor marker (eg, CA125, beta-human chorionic gonadotropin, alpha-fetoprotein, lactate dehydrogenase) is completely specific; therefore, use diagnostic immunohistochemistry testing in conjunction with morphologic and clinical findings. Also, obtain a urinalysis to exclude other possible causes of abdominal/pelvic pain, such as urinary tract infections or kidney stones.

Imaging studies

Routine imaging is not required in all patients in whom ovarian cancer is highly suggested. In cases in which the diagnosis is uncertain, consider the following imaging studies:

- Pelvic ultrasonography : Warranted
- Pelvic and abdominal computed tomography (CT) scanning : Warranted
- Pelvic and abdominal magnetic resonance imaging: Increases specificity of imaging when sonography findings are indeterminate
- Chest radiography: Routine imaging to exclude lung metastases
- Mammography: Part of preoperative workup for women older than 40 years who have not had one in the preceding 6-12 months; estrogen-producing tumors may increase the risk of breast malignancies, and breast cancers can metastasize to the ovaries and are often bilateral

In patients with diffuse carcinomatosis and GI symptoms, a GI tract workup may be indicated, including one of the following imaging studies:

- Upper and/or lower endoscopy
- Barium enema
- Upper GI series

Procedures

Fine-needle aspiration (FNA) or percutaneous biopsy of an adnexal mass is not routinely recommended, as it may delay diagnosis and treatment of ovarian cancer. Instead, if a clinical suggestion of ovarian cancer is present, the patient should undergo laparoscopic evaluation or laparotomy, based on the presentation, for diagnosis and staging. An FNA or diagnostic paracentesis should be performed in patients with diffuse carcinomatosis or ascites.

Management

Standard treatment for women with ovarian cancer involves aggressive debulking surgery and chemotherapy. The aim of cytoreductive surgery is to confirm the diagnosis, define the extent of disease, and resect all visible tumor. Neoadjuvant chemotherapy is increasingly used.

Surgery

The type of procedure depends on whether or not disease is visible outside the ovaries. When no disease is visible outside the ovaries, or no lesion greater than 2 cm is present outside of the pelvis, the patient requires formal surgical staging, including peritoneal cytology, multiple peritoneal biopsies, omentectomy, pelvic and para-aortic lymph node sampling, and biopsies of the diaphragmatic peritoneum.

If disease greater than 2 cm is noted then aggressive surgical debulking, with the intent to remove all visible diseaes should be undertaken. If the surgeon determines that optimal debulking is not possible, then neoadjuvant chemotherapy should be considered. For patients with stage IV disease, surgery should be individualized on the basis of presentation.

Surgical procedures that may be performed in women with ovarian cancer are as follows:

- Surgical staging
- Cytoreductive surgery
- Interval debulking
- Laparoscopic surgery
- Secondary surgery

Surgical Staging

The standard care for ovarian cancer includes surgical exploration for primary staging and for cytoreduction or debulking. If the disease appears to be confined to the pelvis, comprehensive surgical staging is indicated.

The incision for surgery should be midline abdominal. In young women with early-stage disease, a transverse incision may be considered. Careful inspection and/or palpation of the abdominal contents should be performed, including all peritoneal surfaces, the liver, large and small bowel and mesentery, stomach, appendix, kidneys, spleen, retroperitoneal spaces, and all pelvic structures.

The staging procedure should include the following:

- Peritoneal cytology
- Multiple peritoneal biopsies
- Omentectomy
- Pelvic and para-aortic lymph node sampling.

Cytoreductive Surgery

Cytoreductive surgery should be performed by a gynecologic oncologist at the time of initial laparotomy. The volume of residual disease at the completion of surgery represents one of the most powerful prognostic factors.

According to the 2016 National Comprehensive Cancer Network (NCCN) ovarian cancer guidelines, in newly diagnosed invasive epithelial ovarian cancer that involves the pelvis and upper abdomen, residual disease of less than 1 cm is evidence of optimal cytoreduction, although the greatest possible effort should be made to remove all obvious disease.The NCCN notes that one or more of the following procedures may be considered for optimal surgical cytoreduction:

- Bowel resection and/or appendectomy
- Stripping of the diaphragm or other peritoneal surfaces
- Splenectomy
- Partial cystectomy and/or ureteroneocystotomy
- Partial hepatectomy
- Partial gastrectomy
- Cholecystectomy
- Distal pancreatectomy

Patients with advanced ovarian cancer are classified in three groups as follows, based on the postoperative residual tumor:

- Good risk - Microscopic disease outside the pelvis (stage IIIa) or macroscopic disease less than 2 cm outside the pelvis (stage IIIb)
- Intermediate risk - Macroscopic disease less than 2 cm outside the pelvis only after surgery
- Poor risk - Macroscopic disease more than 2 cm after surgery or disease outside the peritoneal cavity

Interval De-bulking

Interval debulking can be performed in patients whose cancer was not adequately debulked at the time of initial surgery. It should also be considered in those patients in whom an initial debulking surgery was not attempted.

Patients receive three cycles of postoperative chemotherapy. Approximately 60% of patients are then able to undergo optimal resection. Surgical treatment is followed by three more cycles of chemotherapy.

Laparoscopic Surgery

According to guidelines developed by the American College of Obstetricians and Gynecologists, laparoscopy may be used for diagnostic purposes in a patient at low risk for ovarian cancer and to remove cystic masses, provided that all the following criteria are met :

- The mass is 10 cm or smaller as viewed by a sonogram
- The mass has a distinct border and no solid parts
- No associated ascites is present
- The serum CA125 level is normal (<35 U/mL)
- The patient has no family history of ovarian cancer

If a chance exists that ovarian cancer may be present, surgery is best arranged in conjunction with a specialist in gynecologic cancer surgery. The patient can then undergo all necessary surgery for her cancer during a single anesthetic session, without delay.

As part of initial treatment of epithelial ovarian cancer, laparoscopic surgery may be performed for early-stage disease when no disease is visible outside of the ovaries. Its use in more advanced disease, when spread is visible outside the ovaries, is more limited due to the scope of cytoreductive surgery necessary and the risk of port-site recurrence. Laparoscopy also has a role in second-look inspection and in the staging of apparently early-stage disease found by chance during another surgery.

The 2015 NCCN ovarian cancer guidelines state that minimally invasive surgery may be used by an experienced surgeon in selected patients to achieve surgical staging and debulking. In addition, the NCCN considers that minimally invasive surgery may be useful when evaluating whether maximum

cytoreduction can be achieved in patients with newly diagnosed or recurrent ovarian cancer

Secondary Surgery

An assessment by Park et al found that secondary cytoreductive surgery is safe and effective in patients with platinum-sensitive recurrent ovarian cancer. The surgery was most beneficial in patients who had remained disease free for more than 24 months after primary treatment and in those who achieved optimal cytoreduction.

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Chemotherapy Regimens

Only a small percentage of women with epithelial ovarian cancer can be treated with surgery alone. These include patients with stage IA grade 1 and stage IB grade 1 serous, mucinous, endometrioid, and Brenner tumors. Clear-cell carcinomas are associated with a significantly worse prognosis in stage I, and patients with this histologic subtype should be considered for chemotherapy at all stages.

Patients not treated with chemotherapy should be monitored closely at regular intervals with clinical examination, serum CA125 estimation, and ultrasonography if an ovary is still present. Surgery to remove the uterus and residual ovary should be considered when the patient no longer desires to remain fertile.

Higher-risk early-stage disease includes all histologic subtypes with stage IA and stage IB grade 2 and all stage I grade 3. These patients should be treated with front-line chemotherapy with a taxane/platinum combination for a minimum of three courses. They should consider participating in clinical trials. All patients with stage II cancer and greater should receive front-line chemotherapy and should strongly consider participation in clinical trials.

The NCCN recommends three to six cycles of intravenous taxane/carboplatin adjuvant chemotherapy for high-risk stage IA, IB, or IC epithelial ovarian cancer.For stage II-IV disease, the recommended options include intraperitoneal chemotherapy, in patients with <1 cm optimally debulked stage II and III disease; or intravenous taxane/carboplatin for six cycles. In addition, completion surgery, as indicated by tumor response and potential resectability, may be used in selected patients.

Paclitaxel and docetaxel are usually dosed at 175 mg/m^2 and 60-75 mg/m^2respectively. Cisplatin at 50-75 mg/m^2 can be substituted for carboplatin.

Increasing the dose intensity of cisplatin did not improve progression-free survival or overall survival compared with standard chemotherapy.Docetaxel in combination with carboplatin has been shown to provide equivalent survival rates with less neurotoxicity but greater neutropenia.

Either cisplatin or carboplatin may be combined with paclitaxel. Randomized studies have proven that both regimens result in equivalent survival rates. However, because of a more tolerable toxicity profile, the combination of carboplatin and paclitaxel is preferred. If patients are treated with cisplatin, paclitaxel should be administered as a 24-hour infusion to decrease the risk of neurotoxicity. Another alternative is to combine carboplatin with docetaxel.

The combination of paclitaxel and carboplatin is customarily given every 3 weeks (day 1 of a 21-d cycle). Because adding other drugs to this regimen has proved disappointing, investigators have studied the use of a dose-dense regimen, in which paclitaxel is given on days 1, 8, and 15 and carboplatin on day 1.The dose-dense regimen has resulted in longer median progression-free survival and higher overall survival. Early discontinuance may be more common with the dose-dense regimen, and increased toxicity has been reported.

Monitoring during chemotherapy

The NCCN recommends the following for monitoring during primary chemotherapy :

- Pelvic exams at least every two to three cycles
- Interim complete blood cell count as indicated
- Chemistry profiles if indicated
- CA125 or other tumor markers as clinically indicated, before each cycle
- Radiographic imaging if indicated

Ovarian function and future pregnancy

Many women experience symptoms of ovarian dysfunction (ie, amenorrhea and hot flashes) during treatment with chemotherapy. The younger the woman at the time of treatment, the more likely the return of normal ovarian function and the more tolerant the ovaries are to higher doses of alkylating agents.

An increase in congenital anomalies in babies conceived following treatment with chemotherapy does not seem to occur. The necessity for chemotherapy during a preexisting pregnancy fortunately is rare, but antifolate drugs such as methotrexate probably should be avoided during the first trimester.

Pazopanib

Adding pazopanib, a kinase inhibitor, to the standard postsurgical chemotherapy regimen has shown promise for progression-free survival in

advanced ovarian cancer. In a study of 940 women with advanced ovarian cancer (epithelial ovarian, fallopian tube, or primary peritoneal cancers) who had not shown evidence of postsurgical progression after five or more cycles of platinum-taxane chemotherapy, progression-free survival in these patients was increased with the addition of pazopanib to standard treatment.

Most of the women in the study had stage III/IV disease (91%) at initial diagnosis and no residual disease after surgery (58%). At a median follow-up of 24 months, patients treated with 800 mg of pazopanib once daily had a prolonged progression-free survival, as compared with those receiving placebo. However, the pazopanib group also had a higher incidence of adverse events and serious adverse events, of which the most common were hypertension, diarrhea, nausea, headache, fatigue, and neutropenia.There were four cases of fatal serious adverse events: three in the pazopanib group and one in the placebo group.

Intraperitoneal chemotherapy

Use of chemotherapy agents instilled into the peritoneal cavity has the theoretical advantage that much higher concentrations can be obtained locally without the risk of adverse systemic effects; however, the agents are unable to penetrate more than a few millimeters. At least three randomized studies comparing chemotherapy regimens, including the intraperitoneal route with the intravenous route, have shown a survival advantage for the arms receiving intraperitoneal chemotherapy.

A retrospective analysis of Gynecologic Oncology Group protocols 114 and 172 found that in patients with advanced ovarian cancer, median survival with intraperitoneal therapy was 61.8 months, compared with 51.4 months for intravenous therapy. Intraperitoneal therapy was associated with a 23% decreased risk of death, and with improved the survival of patients with gross residual (≤1 cm) disease. Risk of death decreased by 12% for each cycle of intraperitoneal chemotherapy completed.Thus, intraperitoneal chemotherapy should be strongly considered for the treatment of front-line disease following surgery where 5 mm or less-residual disease exists and perhaps, for more advanced cancers.

This route of chemotherapy may cause more side effects for the patient and administration requires the placement of a subcutaneous tube into the peritoneal cavity (an intraperitoneal port); this is associated with a number of complications including infection, blockage, retraction out of the peritoneal cavity, and discomfort. Nevertheless, randomized studies show a survival benefit and disease-free survival benefit and the National Cancer Institute has

suggested that all women with optimally cytoreduced disease should at least be offered intraperitoneal treatment.

Results from randomized clinical trials suggest that in patients with optimally debulked disease, intraperitoneal administration of chemotherapy (cisplatin) is superior to intravenous administration.Recent meta-analyses confirm that intraperitoneal administration of chemotherapy is associated with an improvement in survival.However, this approach is also associated with more toxicity. The National Cancer Institute released a clinical announcement supporting the use of intraperitoneal chemotherapy in optimally debulked ovarian cancer.

Jaaback et al found that intraperitoneal chemotherapy increases overall survival and progression-free survival in advanced ovarian cancer; however, catheter-related complications and toxicity must be considered in the treatment decision.Patients receiving adjuvant intraperitoneal chemotherapy are more likely to have recurrences outside the abdominal cavity, according to a study by Tanner et al.

Neoadjuvant chemotherapy

This is given to patients with disease that is initially considered inoperable or if the patient is unfit for surgery at the time of diagnosis. If the patient has a good response to three or more cycles of chemotherapy, interval debulking surgery may be performed followed by further chemotherapy. Overall, patients treated with this approach likely have an inferior outcome to patients undergoing initial maximal cytoreductive surgery followed by chemotherapy.

Patients with advanced ovarian cancer who are not candidates for surgical cytoreduction may be treated initially with two to three cycles of conventional chemotherapy and can then be reevaluated for surgical cytoreduction. However, optimal initial cytoreduction remains the standard of care for most patients.

A study by Joly et al found that pegylated liposomal doxorubicin with carboplatin instead of paclitaxel was associated with a low rate of hypersensitivity reaction among patients with relapsed ovarian cancer.In a separate study by Pignata et al, pegylated liposomal doxorubicin with carboplatin produced a similar response rate to carboplatin with paclitaxel; the authors conclude that it could be an alternative to standard therapy.

Neoadjuvant chemotherapy followed by interval surgery provided equivalent outcomes to standard primary surgery followed by chemotherapy in women with stage III and IV ovarian cancer.

The NCCN ovarian cancer guidelines note that upfront debulking surgery remains the treatment of choice in the United States. Neoadjuvant chemotherapy remains controversial, but may be considered for patients with bulky stage III-IV disease who are not candidates for surgery; however, the NCCN recommends that the assessment of such patients be performed by a gynecologic oncologist.

Maintenance chemotherapy

Most patients with ovarian cancer achieve a complete clinical response after debulking surgery and platinum-based chemotherapy. However, 50% experience relapse and ultimately die of the disease. Therefore, strategies to decrease the risk of recurrence have been investigated. A phase III randomized trial exploring the impact of 12 monthly cycles of paclitaxel as maintenance chemotherapy was discontinued by the Data Safety and Monitoring Committee when a prospectively defined interim analysis revealed a highly statistically significant improvement in progression-free survival; an ongoing phase III trial is addressing the question of whether this maintenance strategy has a significant effect on overall survival.

A meta-analysis indicated that continuing chemotherapy improved progression-free survival and overall survival, especially if complete response was reached after primary therapy.

Consolidation chemotherapy

Ovarian cancer has a very high response rate when treated front-line; despite this, most patients develop recurrent cancer. Many groups have shown interest in research into treatments to prevent or prolong the interval of recurrence (such as consolidation therapy).

A Gynecologic Oncology Group protocol was discontinued when a statistical improvement in disease-free survival was demonstrated in patients receiving 12 months versus 3 months of additional monthly paclitaxel after initial therapy. However, questions remain about this study, which was not completed as designed. Since no consensus on management in this situation exists, patients should be encouraged to participate in clinical trials of consolidation therapy.

Hyperthermicintraperitoneal chemotherapy

The instillation into the peritoneal cavity of chemotherapeutic agents in a solution heated to between 40° C and 43° C was first introduced in an attempt to induce longer survival in patients with gastric carcinomas that had spread to the peritoneal cavity. Considerable experimental evidence shows that not only is heat alone tumoricidal, but it also increases the activity of many different chemotherapeutic agents, several of which have activity in ovarian cancer.

Ovarian cancer is a good theoretical target for surgical debulking combined with hyperthermic chemotherapy because it combines three separately useful modalities: surgical debulking, intraperitoneal chemotherapy, and heat. See the videos below.

Radiation Therapy

Radiation has not been widely accepted as a routine treatment modality in the initial treatment of patients with epithelial ovarian cancer, despite reports of efficacy for higher-risk stage I and II disease and in stage III disease where small-volume residual disease is present after surgery. In selected cases, pelvic diseases may respond to palliative dosing regimens with minimal toxicity.

Estrogen Replacement Therapy

The safety of estrogen replacement therapy (ERT) after treatment for epithelial ovarian cancer has not been tested in a randomized trial, but current evidence suggests that the benefits of ERT outweigh the risks.

Younger women with endometrioid subtypes are of concern because these tumors theoretically are estrogen-sensitive. If estrogen is used in such patients, a progestogen probably should be given with it.

Prognosis

Although the 5-year survival rate for ovarian cancer has improved significantly in the past 30 years, the prognosis for ovarian cancer remains poor overall, with a 46% 5-year survival rate. The prognosis of ovarian cancer is closely related to the stage at diagnosis,[23, 24] as determined according to the staging system developed by the International Federation of Gynecology and Obstetrics (FIGO). (See Staging.) Approximately 20%, 5%, 58%, and 17% of women present with stage I, II, III, and IV, respectively.

The 5-year survival rates (rounded to the nearest whole number) for epithelial ovarian carcinoma by FIGO stage are as follows:

- Stage IA - 87%
- Stage IB - 71%
- Stage IC - 79%
- Stage IIA - 67%
- Stage IIB - 55%
- Stage IIC - 57%
- Stage IIIA - 41%

- Stage IIIB - 25%
- Stage IIIC - 23%
- Stage IV - 11%
- Overall survival rate – 46%