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Ovarian cancer update: management challenges and advances

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■ **BACKGROUND** Although less common than cervical or uterine cancer, ovarian cancer accounts for more deaths than the other two gynecologic malignancies combined.

■ **SUMMARY** Ovarian cancer produces few symptoms while confined to the ovary. A palpable ovary in a postmenopausal woman should arouse the clinician's suspicion. Most tumors have already spread at the time of the initial laparotomy and require chemotherapy. The standard regimen contains cisplatin or carboplatin plus cyclophosphamide; paclitaxel (Taxol) shows promise and will probably be incorporated into the standard regimen, as well. Estrogen replacement therapy is not contraindicated. The rate of relapse is high, even in women who have achieved a complete clinical response. If persistent disease is found at a second laparotomy, intraperitoneal chemotherapy may be appropriate in some patients.

■ **CONCLUSIONS** Because the patient's chance of survival is much better if the disease is discovered when it is still confined to the ovary, physicians should be alert to the possibility of ovarian cancer, particularly in postmenopausal women with vague abdominal complaints or with a palpable ovary.

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ALTHOUGH LESS common than cancer of either the cervix or uterus, epithelial ovarian cancer results in more deaths each year in the United States than the other two gynecologic malignancies combined. There are approximately 18 000 new cases of epithelial ovarian cancer in this country each year. It is uncommon in women younger than age 20, and the average age at diagnosis is approximately 52 to 55 years.

The risk factors for epithelial ovarian cancer include nulligravid status or low parity and a history of breast or colon cancer. It is more common in industrialized countries, and available epidemiologic data suggest that environmental factors may contribute to its development. Of interest, use of oral contraceptives may result in a lower lifetime risk of ovarian cancer.

Family studies have demonstrated a genetic influence: women who have two first-degree relatives with epithelial ovarian cancer have approximately a 50% risk of developing it during their lifetime. Fortunately, such a strong family history is very uncommon, but one

can appropriately consider a prophylactic bilateral oophorectomy for a woman with this genetic background who is finished having children.

SYMPTOMS

Epithelial ovarian cancer is rarely diagnosed at an early stage because it causes few symptoms when it is confined to the ovary. When it spreads into the pelvis and upper abdomen, patients experience pelvic or abdominal pain or pressure, abdominal swelling, dyspepsia, and early satiety. As the disease progresses, patients note weight loss and increasing pain, and they can develop bowel or ureteral obstruction.

Afterwards, many patients recall vague abdominal discomfort going back several months before diagnosis; the general internist, family physician, or gynecologist may not initially recognize this nonspecific symptom as representing serious underlying disease. Thus, it is not surprising that more than 70% of patients with ovarian cancer have tumors outside the ovary at diagnosis.

DIAGNOSIS

There is no established method to detect ovarian cancer while it is still localized to the ovary. Early-stage disease can occasionally be discovered on pelvic examination (which should include a rectovaginal examination) performed either at the time of a routine physical examination or as part of an evaluation of nonspecific abdominal or pelvic discomfort. Unfortunately, even when the disease appears to be localized on initial physical examination, exploratory surgery usually reveals it to have already spread.

The Papanicolaou smear, so useful in diagnosing cervical cancer, detects epithelial ovarian cancer in fewer than 10% of patients confirmed to have it. In postmenopausal women, the ovaries atrophy and are not normally palpable on pelvic examination. Thus, palpable ovaries in a postmenopausal woman should be considered cancerous until proven otherwise, although experience has shown that only 10% of them actually are.

Carbohydrate antigen 125 (CA-125) levels are elevated in approximately 80% of women with advanced ovarian cancer, and CA-125 testing has been advocated to detect early ovarian cancer. Unfortunately, CA-125 is not specific for ovarian cancer, or even for malignant disease. In addition, 50% of patients with known ovarian cancer whose CA-125 levels return to normal following cytotoxic chemotherapy are found to still have disease on exploratory laparotomy. Thus, a normal CA-125 value in a woman with a palpable ovary or another reason to suspect the presence of ovarian cancer should not dissuade the physician from performing a laparotomy to assess the ovaries.

Finally, pelvic ultrasonography has been examined as a screening method to evaluate the ovaries in either normal patient populations or in women at risk of developing ovarian cancer (ie, with a family history of ovarian cancer). While ultrasonography shows some promise when performed by skilled operators, it cannot be recommended at the present time as a routine test for all women. However, for women with a strong family history of ovarian cancer, and especially those who wish to retain their ovarian function, it is not unreasonable to monitor changes in ovarian size and shape by ultrasonography on a regular basis.

In the majority of women with ovarian cancer, the diagnosis is made during an exploratory laparotomy. However, patients should first undergo a barium enema to exclude the possibility of colon cancer that has spread to the ovaries.

In a woman with ascites and a pelvic mass, diagnostic paracentesis is generally not recommended, for several reasons. First, a negative cytologic study would not preclude the diagnosis of ovarian cancer, and surgery would still be indicated. Second, the finding of adenocarcinoma on cytologic examination, while quite characteristic of ovarian cancer, is generally not diagnostic, and surgery would be indicated to make the definitive diagnosis. Third, although uncommon, what appears to be free ascites may actually be a large malignant cyst. If paracentesis is performed the cyst may rupture, spilling its contents throughout the peritoneal cavity. Finally, the removal of ascitic fluid for cytologic analysis in such a patient may lead to "seeding" of the paracentesis tract and subsequent tumor growth in this area.

INITIAL SURGERY

The standard surgical procedure for a patient suspected to have ovarian cancer requires that the entire abdominal cavity be adequately visualized, as the cancer can easily spread throughout the cavity once it leaves the confines of the ovary, largely due to the constant peristaltic action of the bowel throughout the abdomen and pelvis.

TABLE 1
RELATIONSHIP BETWEEN SIZE OF TUMOR REMAINING AT INITIATION OF CHEMOTHERAPY AND SURVIVAL IN EPITHELIAL OVARIAN CANCER

Size of largest residual mass (cm)	Median survival (months)
0	40
0–0.5	30
0.6–1.5	18
> 1.5	11

TABLE 2
RELATIONSHIP BETWEEN STAGE OF DISEASE AND SURVIVAL IN EPITHELIAL OVARIAN CANCER

Stage	5-year survival rate (%)
Stage I (confined to the ovary)	70–95
Stage II (confined to the pelvis)	40–60
Stage III (disseminated in abdominal cavity)	15–30
Stage IV (outside the abdominal cavity)	5

If ovarian cancer is confirmed on frozen-section pathologic examination, the operation should include, in most cases, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, complete omentectomy, retroperitoneal lymph node sampling, careful inspection under the diaphragm, and random biopsies and peritoneal-cavity washes (in patients without gross disease evident outside the ovary or pelvis). In addition, if the patient has intra-abdominal tumors, the surgeon should attempt to maximally "debulk" them then and there. Thus, the initial surgical approach is quite aggressive, both in patients who appear to have disease localized to the ovary and in patients with extensive intra-abdominal tumors.

What is the justification for this strategy? There are two very different answers, based on whether the patient appears to have disease limited to the ovary or, far more commonly, advanced cancer in the peritoneal cavity.

Women with epithelial ovarian cancer confined to the ovaries may have an overall long-term disease-free survival rate as high as 95%. Thus, these individuals can reasonably be considered cured with surgery alone. However, patients can only be considered to fall into this very favorable category if they have undergone appropriate staging as described above.

If this complete operation has not been performed, it is inappropriate to consider the woman to have the excellent prognosis noted above, as she may have unrecognized cancer in the lymph nodes or upper abdomen. Thus, in this setting, failure to perform the appropriate staging procedures would lead either to another laparotomy to assess the status of disease, or to adjuvant treatment, generally systemic chemotherapy. This difficult clinical situation can be avoided if surgeons perform the necessary staging evaluation at the time of the initial surgery.

In contrast, surgery *cannot* cure advanced epithelial ovarian cancer or other disseminated cancers of the breast, lung, or colon. However, numerous trials involving thousands of women with epithelial ovarian cancer have confirmed that one of the *major* prognostic factors influencing both the overall response rate to cytotoxic chemotherapy and the survival rate is the *bulk of tumor* present at the *initiation of the chemotherapy* (*Table 1*).

Several hypotheses have been offered to explain this finding. First, removing a large amount of tumor will likely increase blood flow and enhance delivery of cytotoxic agents to the remaining tumor. Second, the improved blood flow will decrease the percentage of tumor cells that are viable but hypoxic. In general, hypoxic cells have a very low proliferation potential and are poorly responsive to cytotoxic drugs. Improvement in tissue oxygenation generally increases the sensitivity of the tumor cells to antineoplastic agents. Finally, a lower tumor volume may also decrease the likelihood of cells being present that are inherently resistant to the cytotoxic drugs or that may develop secondary drug resistance.

While the benefits of debulking surgery in epithelial ovarian cancer have never been demonstrated in a randomized controlled clinical trial, the available nonrandomized studies certainly support this strategy. Thus, standard management of patients with epithelial ovarian cancer should include an attempt at maximal tumor debulking before starting cytotoxic chemotherapy.

PROGNOSTIC FACTORS

In addition to the bulk of the tumor remaining when chemotherapy is started, the stage of the tumor at diagnosis strongly influences the patient's survival (*Table 2*). At any stage, a patient's prognosis

TABLE 3
RESPONSE RATES TO SELECTED ANTINEOPLASTIC AGENTS IN EPITHELIAL OVARIAN CANCER

Agent	Response rate (%)
Alkylating agents (melphalan, cyclophosphamide, chlorambucil, thiotepa)	40–50
Cisplatin or carboplatin	50
5-fluorouracil	30
Hexamethylmelamine	30
Doxorubicin	40
Mitomycin C	25
Methotrexate	15
Paclitaxel	≥ 40–50

is influenced by several additional factors, including the tumor grade (degree of differentiation, ranging from well differentiated to poorly differentiated or anaplastic) and the patient's performance status.

Patients with high-grade (poorly differentiated) tumors have a worse prognosis for any given stage and amount of residual disease than do patients with well-differentiated tumors. In addition, even if patients with poorly differentiated tumors experience an excellent response to cytotoxic chemotherapy (including a surgically documented complete remission), they are much more likely to develop recurrent disease than are individuals with low-grade tumors.

The performance status, which measures the patient's ability to carry on with normal daily activities, has been shown to be an important prognostic factor in many malignant diseases. For the same relative amount of tumor bulk, a patient with an excellent performance status (ie, minimal or no interference with normal activities) can expect to live longer than an individual with a poor performance status (ie, confined to bed, limited daily activities).

Epithelial ovarian cancer is almost always an adenocarcinoma (gland-forming cancer), of which there are a number of morphologic subtypes. However, with the possible exception of clear-cell carcinomas, these subtypes have not been demonstrated to have prognostic significance independent of the tumor grade or stage. In general, clear-cell carcinomas of the ovary impart a particularly poor prognosis, even if discovered at an early stage (ie, I or II).

CHEMOTHERAPY

As most patients with epithelial ovarian cancer have disease that has spread beyond the ovary at the time of diagnosis, additional treatment is necessary following surgical removal of as much of the tumor as possible. While radiation therapy has been employed in such patients in the past, the indications for it are very limited at the present time. Radiation kills ovarian cancer cells, but the amount of radiation required to sterilize an irradiated area, particularly a macroscopic tumor, can lead to serious local complications (eg, bowel obstruction, severe diarrhea).

Thus, systemic chemotherapy has become the major treatment after surgery. A number of cytotoxic agents have antineoplastic activity in epithelial ovarian cancer (*Table 3*).

Cisplatin and carboplatin, two closely related drugs, are the most active single agents in this disease and are essentially identical in their effectiveness. However, carboplatin, the newer of the two, is somewhat less toxic than cisplatin and is being used increasingly as the front-line agent in clinical practice. In addition to causing considerable emesis, cisplatin can damage the kidneys and peripheral nerves. Carboplatin causes somewhat less emesis than cisplatin and is generally not thought to cause either renal or neurological damage; however, it can severely suppress bone marrow growth and can cause thrombocytopenia.

Unfortunately, single agents generally produce only partial responses. Thus, it has become standard practice to administer several agents in combination. Currently, the preferred regimen for patients with advanced epithelial ovarian cancer consists of either cisplatin or carboplatin along with the alkylating agent cyclophosphamide.

When this or similar regimens are used, 70% to 80% of women with advanced epithelial ovarian cancer demonstrate an objective response to treatment, and approximately 50% have no clinical evidence of disease on physical examination, routine blood work, and computed tomographic scanning of the abdomen and pelvis at the completion of a 5- or 6-month treatment program. Unfortunately, when patients who achieve a clinically defined complete response undergo a second laparotomy to document whether they have achieved a pathologic (surgically defined) complete response, 50% are found to have residual disease.

Patients with residual disease following initial cisplatin- or carboplatin-based therapy or who do not respond to their primary chemotherapeutic program have several secondary treatment options. For individuals with very small-volume residual intraperitoneal disease, direct intraperitoneal drug administration with a number of chemotherapeutic regimens (most cisplatin-based) has been demonstrated to produce objective responses, including surgically documented complete responses. For patients with larger-volume residual disease, alternative intravenous chemotherapeutic programs can be tried, although the overall response rate to second-line intravenous therapy in patients with epithelial ovarian cancer previously treated with cisplatin- or carboplatin-based therapy is generally poor (< 10% to 15%).

An exception to the relatively poor outlook for second-line intravenous therapy in epithelial ovarian cancer is the reported activity of a new antineoplastic agent, paclitaxel (Taxol). Patients with epithelial ovarian cancer previously treated with cisplatin have been shown to have a 25% to 50% objective response rate to this agent. Until recently, the availability of paclitaxel, a unique cytotoxic drug obtained from the bark of the Pacific yew, was a major concern. However, over the last year the supply problem of the agent has essentially disappeared, and all patients who may benefit from paclitaxel will be able to receive it.

A preliminary report of a large randomized trial of cisplatin plus paclitaxel compared with cisplatin plus cyclophosphamide in women with advanced ovarian cancer has suggested that the paclitaxel-containing regimen is associated with a higher response rate and improved survival. On the basis of this and other data, paclitaxel will likely soon become an important standard component of the initial chemotherapeutic management plan for women with ovarian cancer.

Because many ovarian tumors have estrogen receptors, investigators have examined a possible role for hormonal therapy. Unfortunately, the overall response rate is < 15% to 20%. However, this treatment causes very few side effects, and it is reasonable to try hormonal therapy in selected patients when chemotherapy would have a limited chance of success and a high likelihood of toxicity.

The presence of estrogen receptors on some ovarian tumors does *not* suggest that estrogen replacement therapy can cause the growth of ovarian cancers. In fact, there is now a general consensus that it is acceptable to give estrogen to women with ovarian cancer, if necessary to control serious menopausal symptoms.

'SECOND-LOOK' LAPAROTOMY

As noted above, when second laparotomies are performed in patients with ovarian cancer who have achieved a complete clinical response, persistent disease is frequently found. However, even in patients who have no evidence of disease at the time of surgery there is a relatively high chance of a relapse. In several series, approximately 50% of patients with high-grade (poorly differentiated) tumors who achieved a surgically documented complete response ultimately relapsed. Thus, the role of the "second-look" laparotomy in ovarian cancer management has been questioned. If the procedure cannot tell a patient that she has a high chance of being cured, why should this major surgery be performed?

This question remains fairly controversial. However, patients found to have small-volume residual ovarian cancer at the time of a second-look surgical procedure can undertake a second-line intraperitoneal chemotherapeutic program. This has been demonstrated to result in a rate of complete response of approximately 40% as documented surgically in patients whose largest residual tumor mass was < 0.5 cm in diameter.

If a second-look laparotomy were not performed and one waited until the patient had clinical evidence of recurrent disease, the bulk of tumor present in the abdominal cavity would be far in excess of what intraperitoneal chemotherapy would be able to successfully treat. Thus, one major justification for a second-look laparotomy is to determine if the patient might benefit from additional chemotherapy directed to small-volume residual disease in the abdominal cavity.

Alternative approaches that could appropriately be considered in patients who still have small-volume disease at the time of a second-look laparotomy include high-dose chemotherapy with bone marrow or peripheral stem cell rescue, or other drugs administered at more conventional dosage levels. Unfortunately, it is still uncertain if any second-line ("salvage") treatment program has a significant impact on survival, despite the high objective response rates observed with several treatment strategies.

PALLIATION

Unfortunately, most women with advanced epithelial ovarian cancer will develop progressive disease, despite an initial response to combination chemotherapy. Thus, the need to palliate symptoms of terminal cancer is common.

One of the most frequent events in patients with progressive epithelial ovarian cancer is small- or large-bowel obstruction. Even a patient with very advanced disease may benefit from surgery to bypass an obstruction caused by a tumor. This may allow a patient to go home and to eat normally when she would otherwise have to be in the hospital with a nasogastric tube to drain secretions. A colostomy may be performed for a large-bowel obstruction, or a small-bowel bypass may be performed for a small-bowel obstruction. In addition, if an obstruction cannot be surgically bypassed, a percutaneous gastrostomy tube may facilitate drainage of gastric secretions and make the patient more comfortable.

Patients with localized pain may undergo a short course of radiation, which is often quite successful in relieving pain and eliminating the need for increasing dosages of narcotic analgesics. Patients who have excessive discomfort from malignant reaccumulation of ascitic fluid may experience short-term relief following paracentesis. Unfortunately, such benefit is generally of limited duration, and frequent procedures are often required. In addition, ascitic fluid is very rich in protein, and frequent fluid removal results in considerable protein loss. An alternative approach to controlling malignant ascites that may help in selected cases is a systemic (eg, "Denver") shunt.

GRANULOSA-THECA CELL TUMORS

A number of rare tumors arise from the ovary. The most common of these is the granulosa-theca cell tumor, which, like the more common adenocarcinoma of the ovary, usually occurs after menopause. Granulosa-theca cell tumors may secrete estrogens, resulting in abnormal vaginal bleeding. This may be the presenting symptom, and patients may be found to have this tumor at the time of a laparotomy performed for presumed endometrial disease.

While pure theca-cell tumors are benign, granulosa-theca cell tumors are most often relatively low-grade cancers. Approximately 80% to 90% of these cancers are confined to the ovary at the time of diagnosis, and the prognosis in these patients is very good. However, high-grade granulosa-theca cell tumors are observed, and in such cases the prognosis is far worse.

In general, a total abdominal hysterectomy and bilateral salpingo-oophorectomy are recommended in patients with granulosa-theca cell tumors. In a younger woman with a low-grade granulosa-theca cell tumor who wishes to retain her childbearing potential, it may be appropriate to perform a unilateral salpingo-oophorectomy. However, when childbearing has been completed it is important that the remaining ovary and the uterus be removed, as this cancer is frequently known to recur in the uterus and residual ovary.

Overall, approximately 80% of patients with granulosa-theca cell tumors can be cured. The remaining 20% eventually experience recurrence, characteristically many years after the initial diagnosis (mean time to recurrence: 5 to 7 years). For patients with late recurrences, which usually involve the pelvis or upper abdomen, or both, a second surgical resection may be appropriate. This is a reasonable consideration for many patients as, in general, chemotherapy has been found relatively ineffective in this cancer. However, a recent report has suggested that a cisplatin-based combination chemotherapeutic regimen may produce a high objective response rate and prolong survival.

METASTATIC TUMORS TO THE OVARY

It has been known for many years that the ovary is a relatively common site of metastatic disease. This condition is known as a *Krukenberg tumor*. To be technically correct, Krukenberg tumors are signet-ring-cell cancers that metastasize from the gastrointestinal tract to the ovary, but in common practice physicians often use the term for all metastatic tumors to the ovary. Other primary cancer sites responsible for metastatic disease to the ovary include the colon, breasts, and endometrium.

In selected patients, surgical resection of metastases to the ovary may be an appropriate consideration, specifically to palliate symptoms of pain or bowel obstruction. Chemotherapy is selected based on the sensitivity of the primary site of the tumor.

OVARIAN GERM-CELL TUMORS

Ovarian germ-cell tumors are uncommon, com-

prising < 5% of all ovarian neoplasms. They are most commonly observed in women under age 30. Ovarian germ-cell neoplasms are divided into two pathologic categories: dysgerminoma and nondysgerminomatous germ-cell tumors. Approximately 50% of patients with germ-cell tumors have each of the two pathologic subtypes.

The most common symptom of germ-cell tumors is mild to moderate abdominal discomfort caused by an enlarging pelvic mass. Rarely, the patient may present with severe abdominal pain caused by torsion or rupture of the tumor. The treatment varies with the stage of the disease and the pathologic subtype. However, in general, the prognosis for this disease, even in its advanced stages, is very good, and survival far exceeds that observed for patients with epithelial ovarian cancer.

Dysgerminoma

Dysgerminoma affects young women, with a median age at diagnosis of approximately 16 to 18 years. Of interest, dysgerminoma is one of the more common neoplasms diagnosed during pregnancy. Dysgerminoma is similar in its clinical behavior to seminoma, its counterpart in the male. The overall long-term survival rate for patients with dysgerminoma exceeds 85%.

In approximately 70% of patients with dysgerminoma, the disease is confined to one ovary. Conservative surgery (unilateral salpingo-oophorectomy) is considered adequate in this clinical setting, but the pelvic and periaortic lymph nodes must be sampled, as this is the major route of spread of this cancer within the abdomen.

Traditionally, standard therapy for patients with metastatic dysgerminoma has included surgical resection of all tumor masses followed by radiation therapy. Dysgerminoma is extremely sensitive to radiation, and the doses of radiation necessary to cure it generally result in limited organ toxicity. However, radiation, even in low doses, can cause sterility. This is a serious concern, considering the overall survival rate in this disease and the young age of the women who are found to have it.

Both advanced dysgerminomas and seminomas respond quite well to cisplatin-based chemotherapy. Thus, many investigators have suggested that all patients with metastatic dysgerminoma or seminoma receive chemotherapy rather than radiation, as limited data suggest that this approach may more successfully preserve fertility. This issue remains somewhat controversial; only short follow-up is available in patients treated with chemotherapy for limited metastatic disease, and the long-term results of radiation, except for producing sterility, have been excellent.

Nondysgerminomatous germ-cell tumors

These neoplasms, which also occur in a young patient population, are potentially far more serious than dysgerminomas. For example, until recently, endodermal sinus tumor, the second most common germ-cell tumor after dysgerminoma, had a dismal prognosis; most patients die < 2 years after diagnosis. Even patients with disease that has appeared to be confined to the ovary have rarely been cured following surgical removal of the primary cancer.

Fortunately, since the introduction of cisplatin-based chemotherapy, the prognosis has significantly improved. In one recent series in young women with metastatic nondysgerminomatous germ-cell tumors who received cisplatin-based chemotherapy following the surgical removal of all gross disease, follow-up to several years revealed no relapses. Other less common nondysgerminomatous germ-cell tumors of the ovary, including embryonal carcinoma, immature teratoma, and choriocarcinoma, should be treated in a similar manner. Standard therapy now calls for the complete removal of as much tumor as possible, followed by a cisplatin-etoposide-bleomycin chemotherapeutic regimen.

Of note, patients with malignant germ-cell tumors may present with more than one type of germ-cell element. Patients should always be treated for the tumor type with the worst prognosis. For example, if a young woman is found to have a localized (confined to the ovary) germ-cell tumor that is 98% dysgerminoma and 2% endodermal sinus tumor, she should be treated with surgical removal of the tumor, followed by cisplatin-based combination chemotherapy.

SUMMARY

Despite advances in its treatment, epithelial ovarian cancer remains deadly. Metastasis usually occurs before the disease is recognized, and although the rate of response to chemotherapy is high, so is the rate of recurrence; few women are cured. A screening test that could detect ovarian cancer before it spreads beyond the ovary would save many lives, as would better chemotherapeutic agents and

protocols. Primary care physicians should be alert to the possibility of ovarian cancer in their postmenopausal patients, especially those with a palpable ovary, vague abdominal complaints, or a family history of this disease.

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