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Treatment of ovarian cancers not of epithelial origin

ABSTRACT

The ovary can harbor neoplasms other than epithelial ovarian cancer; these include less-common primary cancers of the ovary and cancers that metastasize to the ovary from other parts of the body. Depending on the specific histology, site of origin of a metastatic lesion, extent to which the cancer has spread, and comorbid medical conditions, women with these less-common neoplasms may be candidates for aggressive surgical intervention, systemic chemotherapy, or therapy focused on symptom management and comfort.

KEY POINTS

Granulosa cell tumors of the ovary can secrete estrogen and therefore, like endometrial cancer, can cause abnormal vaginal bleeding.

Granulosa cell tumors are generally malignant, although in most cases they are histologically low-grade. Fortunately, on exploratory laparotomy, as many as 90% are found to be in stage 1, ie, confined to the ovary.

In contrast to both epithelial ovarian cancer and granulosa cell tumors, germ cell tumors of the ovary most commonly occur in women younger than 30 years.

Therapy of female germ cell tumors is greatly influenced by the pathologic findings and stage of disease; the prognosis for this group of neoplasms is excellent, even in their advanced stages.

As many as 6% to 7% of all ovarian tumors are secondary rather than primary ovarian malignancies.

NOT ALL CANCERS found in the ovary are epithelial ovarian cancer. A number of less-common but no less important cancers can arise in ovarian tissue; in addition, the organ can be involved as a secondary metastatic site.

Some of these nonepithelial ovarian cancers carry a prognosis quite different from that of epithelial ovarian cancer, and call for totally different treatment. Therefore, a basic knowledge of these cancers is important for optimal management of a woman discovered to have a pelvic malignancy.

This article briefly reviews malignant tumors other than epithelial ovarian cancer that may involve the ovary.

EPITHELIAL OVARIAN CANCER RECEIVES MOST ATTENTION

In terms of the number of women it kills, epithelial ovarian cancer is the most serious of the female pelvic malignancies, causing more deaths in the United States each year than cancers of the cervix and endometrium combined.

Over the past decade, the lay and medical presses have paid considerable attention to this disease, chronicling not only the danger but also major advances in its chemotherapy, a rapidly evolving understanding of its molecular genetics, and intensive efforts to develop an effective and cost-effective screening strategy. However, this appropriate focus on epithelial ovarian cancer may lead to the unfortunate conclusion that it is the only malignancy that can affect the ovary.

GRANULOSA CELL TUMORS

The most common of the nonepithelial cancers that arise in the ovary are granulosa cell

tumors.[1,2] Like epithelial ovarian cancer, this malignancy usually occurs in postmenopausal women.

Of interest: granulosa cell tumors may secrete estrogen, which may lead to abnormal vaginal bleeding. Any vaginal bleeding in a postmenopausal woman should be evaluated further: the primary concern is endometrial cancer, but surgery for suspected endometrial cancer may uncover a granulosa cell ovarian tumor instead.

Prognosis and treatment of granulosa cell tumors

Granulosa cell tumors are generally malignant, although in most cases they are histologically low-grade. Fortunately, on exploratory laparotomy, as many as 90% are found to be in stage 1, ie, confined to the ovary.

Low-grade granulosa cell tumors. Patients with low-grade granulosa cell cancers that are contained within the ovary have an excellent prognosis. In such patients the standard treatment is a total abdominal hysterectomy and bilateral oophorectomy. Overall, this surgery cures approximately 80% of patients.

Low-grade granulosa cell tumors carry an excellent prognosis after surgery

Some younger patients may wish to retain the ability to bear children, however. If the tumor is low-grade and in stage 1, a reasonable option is a unilateral salpingo-oophorectomy, which preserves the contralateral ovary and uterus. The patient should be warned that this type of cancer is known to recur in both the uterus and the other ovary. In addition, when childbearing is complete, the uterus and remaining ovary should be removed to minimize the risk of recurrence.

High-grade granulosa cell tumors carry a considerably worse prognosis than do low-grade tumors, and patients with high-grade tumors are far more likely to present with higher-stage disease (ie, with cancer that has spread beyond the confines of the ovary) at diagnosis.

However, after surgery, even high-grade tumors may take many years to recur in the pelvis and upper abdomen—the median time to disease recurrence is 5 to 7 years. Therefore, if the disease recurs more than 2 years after the initial surgery, it is reasonable to consider a second attempt at surgical removal of the tumor to both palliate symptoms and prolong the time to further disease progression.

The role of systemic chemotherapy has not been well defined, since granulosa cell tumors are relatively uncommon and the short-term prognosis is relatively good (even for patients with high-grade cancers that have spread beyond the confines of the ovary). However, data from several trials suggest that this cancer will respond to cisplatin-based chemotherapy.[3,4] The most commonly used regimen is the combination of cisplatin, etoposide, and bleomycin—the standard treatment for germ cell tumors of the ovary (see below). Although it is unknown whether all three agents are necessary in this malignancy, objective responses are observed with this regimen, with an improvement in both symptom-free survival and overall quality of life in patients with advanced granulosa cell tumors.

Should patients with high-grade, high-stage granulosa cell tumors undergo chemotherapy as part of their initial therapy (ie, as "adjuvant" therapy after the initial surgery)? This question is also unresolved. Although the risk of relapse is great, the time to recurrences may be measured in years, even for high-grade, high-stage tumors. Therefore, most investigators feel that patients should not receive adjuvant chemotherapy. Rather, chemotherapy should be used only if the disease is known to be progressing despite recent surgical tumor debulking, or if a large volume of residual cancer persists after the initial surgical resection.

MALIGNANT OVARIAN GERM CELL TUMORS

In contrast to both epithelial ovarian cancer and granulosa cell tumors, germ cell tumors of the ovary most commonly occur in women younger than 30 years. Although ovarian germ cell tumors are the most common female pelvic neoplasm in young women, they account for fewer than 5% of all ovarian malignancies.

Like their counterpart in men, ovarian germ cell tumors are divided approximately equally into two pathologic categories: dysgerminomas (comparable to seminomas in men)

and nondysgerminomatous germ cell tumors (comparable to nonseminomatous germ cell tumors in men).

As with epithelial ovarian cancer, the symptoms of ovarian germ cell tumors are quite nonspecific. Most commonly a young woman will present with mild to moderate abdominal pain that persists over time and that in most cases is found to be due to an enlarging pelvic mass.

Occasionally, a patient may present with the sudden onset of severe abdominal or pelvic pain, due either to rupture or torsion of a rapidly expanding tumor mass. In this situation the diagnosis may be made during an exploratory laparotomy for a presumed ruptured benign ovarian cyst or appendix.

Therapy of female germ cell tumors is greatly influenced by the pathologic findings and stage of disease. Of importance: the prognosis for this group of neoplasms is excellent, even in their advanced stages, and far exceeds that currently achieved in epithelial ovarian cancer.

Dysgerminoma

In more than 70% of cases of dysgerminoma, the initial surgery reveals that the disease is confined to a single ovary. If the frozen-section pathologic diagnosis is that of a dysgerminoma and the disease appears to be confined to the ovary, it is reasonable to perform only a unilateral salpingo-oophorectomy as the definitive surgical procedure for this condition. This is particularly relevant, as most women with this malignancy are quite young (median age 16–18), and childbearing potential is a major issue.

However, even if limited surgery is performed in this situation, it is important that both the pelvic and the periaortic lymph nodes be sampled at the time of surgery, as this is the most common route by which this malignancy spreads.

In patients confirmed to have stage 1 disease (eg, confined to the ovary), no adjuvant treatment is indicated. If disease has spread beyond the ovary, additional treatment will be required. Although dysgerminomas (like seminomas in male patients) are exquisitely sensitive to radiation, there is legitimate concern about the risk of sterility, even with the low doses of radiation used in this situation. Therefore, many investigators advocate using cisplatin-based combination chemotherapy rather than radiation for more advanced disease, as the limited clinical data available suggest this approach poses a lower risk of inducing permanent sterility and controls the disease equally well in the long term.

On the other hand, the long-term results of radiation therapy in locally advanced dysgerminoma have been excellent, other than the concern about sterility. Therefore, if sterility is not an issue for an individual patient (eg, if the patient is older and has completed childbearing), then radiation therapy for locally advanced dysgerminoma should be considered a reasonable option.

In patients with more advanced disease, combination chemotherapy with cisplatin, etoposide, and bleomycin is the treatment of choice.[5] Of note, the overall long-term disease-free survival for women with a dysgerminoma, including all stages of the disease, is more than 85% to 90%.

Nondysgerminomatous ovarian germ cell tumors

Nondysgerminomatous germ cell tumors of the ovary are a far more ominous group of diseases than dysgerminomas. For example, before cisplatin chemotherapy was introduced, the large majority of women with endodermal sinus tumors (yolk sac tumor—the second most common germ cell tumor after dysgerminomas) died of their disease, even if the cancer was apparently confined to a single ovary at the time of diagnosis.

The therapy for advanced germ cell tumors is cisplatin, etoposide, and bleomycin

Fortunately, over the past 2 decades, the prognosis for patients with these malignancies has improved radically.[6,7]

Results of a large trial from the Gynecologic Oncology Group dramatically emphasize this point.[7] In this multi-institutional experience, women with nondysgerminomatous ovarian germ cell tumors underwent surgery to remove all macroscopically visible disease and then received cisplatin-based combination chemotherapy. The relapse rate was extremely low, with more than 90% of patients cured of their disease. Of note, this study included women with documented metastatic disease in the pelvis and

upper abdomen at the time of the initial surgical evaluation.

The standard treatment for nondysgerminomatous ovarian germ cell tumors is surgery to remove all gross evidence of disease if technically feasible, followed by combination chemotherapy with cisplatin, etoposide, and bleomycin.[6]

In addition to endodermal sinus tumors, other cancers that should be treated with this chemotherapy program, even if apparently confined to the ovary, include embryonal carcinoma, immature teratoma (grades 2 and 3), and choriocarcinoma. The only patients with nondysgerminomatous ovarian germ cell tumors who do not require chemotherapy at initial diagnosis are those with a stage 1, grade 1, immature teratoma.

Mixed ovarian germ cell tumors, in which the pathologic evaluation reveals more than one element (eg, dysgerminoma plus a small focus of endodermal sinus tumor) are not uncommon. In this clinical setting it is critical that treatment be based on the morphologic element with the worst prognosis, even if this constitutes only a small percentage of the tumor. Thus, a patient with a stage 1 ovarian germ cell cancer comprising 99% dysgerminoma and 1% endodermal sinus tumor must be given cisplatin-based chemotherapy following surgical tumor resection.

From 6% to 7% of ovarian tumors are metastatic rather than primary

CANCER METASTATIC TO THE OVARY

The ovary is a relatively common site of metastasis. As many as 6% to 7% of all ovarian tumors are secondary rather than primary ovarian malignancies.

The finding of metastatic cancer in the ovary has been referred to as a Krukenberg tumor. To be technically accurate, a Krukenberg tumor refers specifically to metastatic signet ring cell cancers that have spread to the ovary from the gastrointestinal tract. However, physicians often refer to all metastatic tumors to the ovary as Krukenberg tumors. Other primary cancers that are well known to metastasize to the ovary include cancers of the endometrium, colon, and breast.

Surgical resection of metastatic disease to the ovary may be considered in appropriately selected patients to palliate symptoms (eg, pain, bowel obstruction). Depending on the site of origin, chemotherapy may be an effective therapeutic strategy to improve symptoms and prolong survival.

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