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Ovarian carcinoma

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Introduction

Ovarian cancer, one of the most common gynecological cancers, begins as a malignant tumor or as an abnormal growth of cells that surrounds tissue. It may originate in one or both ovaries and eventually travel to other parts of the body. In 1992, approximately 21,000 cases of ovarian cancer were reported, and 13,000 women died. This year the American Cancer Society is predicting that there will be about 23,100 new cases of ovarian cancer, and 14,000 women will succumb to the disease.[12]

Ovarian cancer is the sixth most common cancer, besides skin cancer, in women, and is responsible for more deaths than any other reproductive organ cancer. Ovarian cancers account for 18 percent of all gynecological neoplasms, and most commonly occur in women in their 50s. Over half of all ovarian cancers are found in women over age 65.

One of the reasons that ovarian cancers are so dangerous is that they lie deep within the pelvis and often show no early symptoms. Pap tests do not usually reveal tumors of the ovaries. Only 25 percent of ovarian cancers are found in the early stages. An ovarian neoplasm usually remains occult until it enlarges or extends enough to produce symptoms; thus, early detection is difficult. In 70 percent to 80 percent of patients, the disease has advanced outside the pelvis at the time of diagnosis.[3] On exam, most tumors of the ovaries are greater than 5 cm in diameter.

Before investigating the types and treatments for ovarian cancer, it would be valuable to discuss the anatomy and function of the ovaries. In addition, readers may want to review the September 1999 issue of *The Surgical Technologist* for helpful information regarding the endocrine system.

anatomy of the ovary

The paired ovaries lie in the pelvic cavity, superior and lateral to the fundus of the uterus. These 1½" oval structures are contained by the posterior part of the broad ligament. The medial end of each is attached to the uterus by the ligament of the ovary. The more lateral end is closely associated with the fimbriated end of the fallopian tube.

Essentially, the ovaries are a mass of Graafian vesicles within a well-vascularized soft tissue called stroma. The stroma consists of spindle-shaped cells, very similar to smooth muscle cells. In addition, there is a relatively small number of connective tissue cells. A single layer of columnar epithelial cells surrounds this mass.

Function

The ovaries have two important functions. The first is the production of ova for fertilization. The second is the secretion of the female sex hormones: estrogen and progesterone.

The production of the ova begins before birth. The ova develop in the Graafian vesicles. There are approximately 7 million in a 20-week fetus. At puberty, a girl may have around 400,000 ova, but many eventually degenerate and are reabsorbed. The ova in their primary stages result from mitotic division and, therefore, have the diploid number of human chromosomes. Only the ovum that has developed and is preparing for ovulation will undergo a meiotic division resulting in the haploid number of twenty-three chromosomes and thus be ready for fertilization.

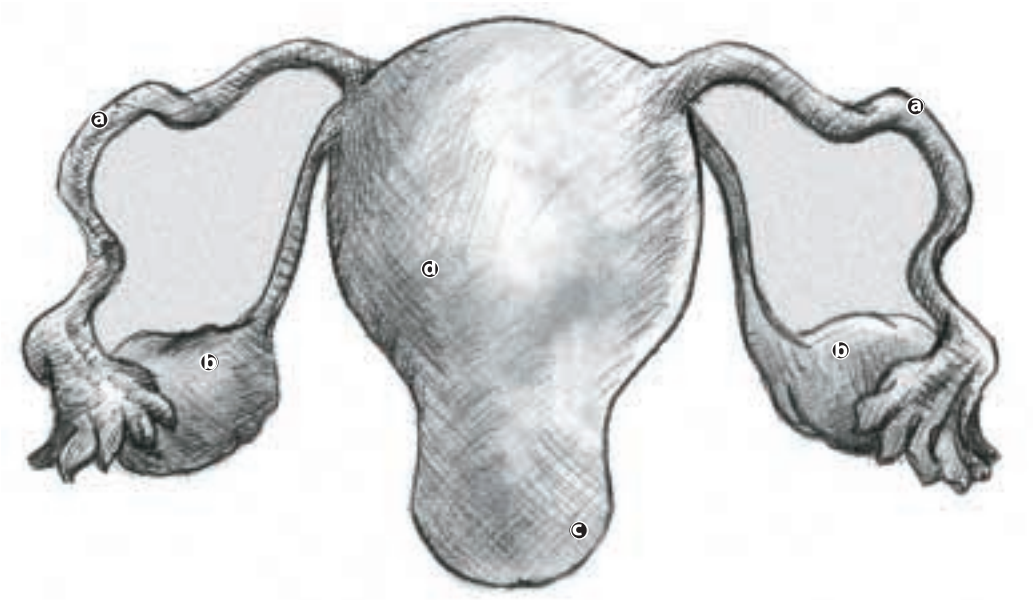
Under the influence of gonadotropic hormones, a vesicle in the cortical area of the ovary will begin to grow and move toward the medullary portion. Several of these follicles are usually found within the ovary at various stages of development. As it matures, the ovum will grow and the surrounding follicular cells will proliferate. As the ovum grows, it will become separated from the follicle cells by a membrane that develops from the follicle. This area is called the zona pellucida. When the ovum reaches full size, a fluid-filled space forms called the antrum. As this antrum swells, the wall of the follicle thins and eventually ruptures. This is the point of ovulation at which the ovum is ejected toward the fallopian tube for possible fertilization and begins its journey toward the uterus for implantation. Once the follicle has ruptured, it becomes the corpus luteum and the primary source for progesterone.

Hormonal functions

There are several hormones (ie estradiol, estrogen, and estriol) that are collectively referred to as estrogen. Primarily, the follicular cells secrete estrogen. The effects of estrogen include: stimulating the growth of the ovaries and follicles;

FIGURE 1

The female reproductive system



a Fallopian tubes
b Ovaries
c Cervix
d Body of uterus

growth of external genitalia and breasts; development of secondary sex characteristics, such as fat distribution and pubic hair patterns; and negative feedback inhibition to the hypothalamus and the anterior pituitary. Estrogen also prepares the uterus for implantation of a fertilized ovum by stimulating growth of the myometrium and the glandular epithelium or endometrium.

Progesterone, produced by the corpus luteum, continues the effects of estrogen on the uterus. It stimulates the secretions of the endometrium (including a sticky secretion by the cervix), inhibits the effects of prolactin on breast tissue, and also provides feedback to the hypothalamus and the anterior pituitary.

Hormonal Controls of the Menstrual Cycle

The menstrual cycle can be divided into a follicular stage and a luteal stage. Based on hormonal feedback, the hypothalamus will secrete FSH Releasing Factor and LH Releasing Factor. The target for these hormones is, of course, the anterior pituitary, which secretes Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). Both FSH and LH will stimulate the development and maturation of a follicle and the production of estrogen by the follicle cells of the ovaries. Between 12 and 24 hours before ovulation, the production of both FSH and LH peaks, with the production of LH being the greater of the two. This, apparently, stimulates ovulation and the formation of the corpus luteum. Upon entry to this luteal phase, estrogen production decreases slightly and progesterone production increases considerably.

If implantation of a fertilized ovum occurs, the uterine lining is thus prepared. If implantation does not occur, hormone production falls off sharply, the thickened uterine lining is sloughed of, and the approximate 28-day cycle begins again.

Types of ovarian tumors

Ovarian tumors are identified by the cells where they originate in the body. They fall into three main classifications: epithelial, germ cell and stromal cell tumors.

Epithelial ovarian tumors

The most common type of ovarian tumor begins in the epithelial cells that cover or line the ovary. Seventy-five percent of all ovarian tumors and 95 percent of malignant tumors belong to this category. Within this classification, several types of tumors are found: serous, endometrioid, mucinous, clear cell carcinoma and borderline.

Nearly 40 percent of the epithelial tumors are serous tumors, which frequently occur in women between the ages of 40 and 60. Endometrioid carcinoma occurs in almost 20 percent of the common epithelial tumors and is usually seen in women ranging in ages between 40 to 60. Approximately 1 percent of epithelial tumors are mucinous and occur in women between the ages of 30 and 50. Clear cell carcinoma, another type of epithelial ovarian tumor commonly seen in women between the ages of 40 and 80, represents about 6 percent of epithelial ovarian tumors. In 10 percent to 15 percent of the frequency of ovarian tumors, a subgroup of the epithelial tumor appears, borderline ovarian tumors. Often originating on the surface of the ovary, this type is accompanied by a better prognosis and cure rate than invasive tumors.

Also in this category is a benign cystic tumor that appears as thin cysts with thin walls on the surface of the epithelium. Often called serous cystadenomas, they are recognized by translucent walls that contain clear fluid. (Figure 2)

A rare member of this classification is the Brenner tumor. This fibroepithelial tumor is seen in later life and only has a slight malignant potential.

Germ cell ovarian tumors

Germ cell ovarian tumors represent 15 percent of ovarian tumors but only 1 percent are malignant. Originating where germ cells form the eggs, this type of ovarian tumor is found in girls or young women. Dysgerminoma, the most common type of germ cell ovarian tumor, is seen

in approximately 50 percent of all occurrences in women between 10 and 30 years. Nearly 80 percent are found in women younger than 30 and often occur in pseudohermaphrodites. Endodermal sinus tumors are found in younger women with the greatest incidence at age 19 and represent nearly 20 percent of germ cell ovarian tumors.

Less common germ cell cancers include embryonal carcinoma, immature teratoma, polyembryoma and mixed germ cell. In this group, choriocarcinoma are very rare tumors of the ovary that elaborate chorionic gonadotropin. Therapy for this type of ovarian tumor has been disappointing.[5] (Figure 3)

FIGURE 2

shows a benign cystic tumor (serous cystadenomas)

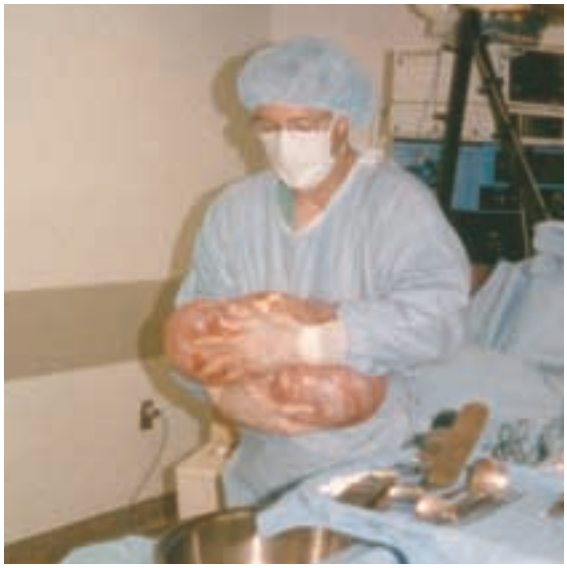
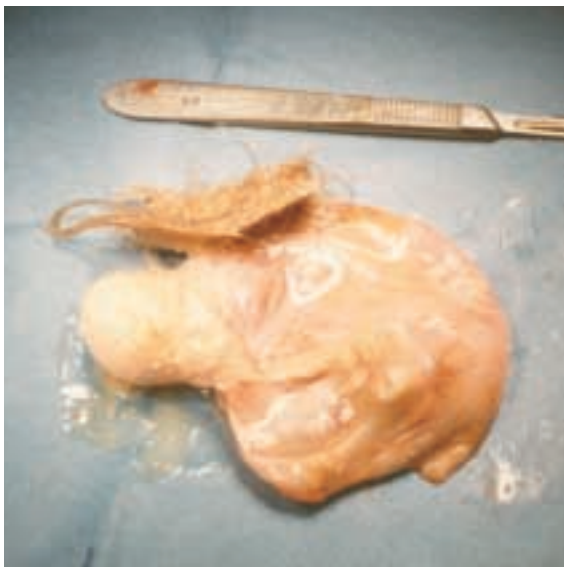


FIGURE 3

is a teratoma (dermoid) that contains human teeth



Stromal cell tumors

Stromal cell tumors, seen in about 5 percent of the incidences of ovarian cancer, begin in the tissue that holds the ovaries together and produces female hormones. Most often found in younger women, this type of ovarian cancer may demonstrate a condition called virilism in one-third of the cases. Characteristics include infrequent menstrual periods, menstrual periods after menopause, appearance of facial hair and a lower voice. Types of stromal cell tumors include: granulosa-theca, Sertoli-Leydig tumors, hilus cell tumors, and struma ovarii.

True theca cell tumors are benign, but those with granulosa cell elements may be malignant.[5] Usually, granulosa cell tumors release estrogen, but sometimes these tumors may not have any hormone production. In cases of young females, they may manifest precocious puberty. In older females the absence of hormone production is sometimes associated with endometrial carcinomata.[5] These types of tumors occur at all ages, from childhood to the postmenopausal period, but are more common in later life, with maximal occurrence between the ages of 40 to 60 years.[5]

Sertoli-Leydig cell tumors (arrhenoblastomas) are rare but potentially malignant tumors, which are seen with the production of androgen and masculinization.[5] In young patients with a single ovary involved, unilateral oophorectomy is adequate therapy, if there is no extension of tumor.[5] As in older patients with bilateral involvement, total hysterectomy and bilateral salpingo-oophorectomy are performed.

Hilus cell tumor, also rare, is characteristically associated with masculinization.[5] These primarily occur in later life, with no reported cases of malignancy.[5]

In struma ovarii tumors, the ovary contains detectable thyroid tissue, usually as the predominant element in dermoid cysts.[5] This tissue occasionally may produce the clinical picture of hyperthyroidism.[5]

Table 1 Staging of Primary Ovarian Cancer[2]

Stage 1
Growth limited to the ovaries.

1a Growth limited to one ovary with an intact capsule and without ascites or tumor on the external surface.

1b Growth limited to both ovaries with intact capsule and without ascites or tumor on the external surface.

1c Growth limited to one or both ovaries with tumor on the ovarian surfaces or with rupture of the capsules or ascites present containing malignant cells or with positive peritoneal washings.

Stage 2
Growth involving one or both ovaries with pelvic extension.

2a Extension and/or metastasis to the uterus or tubes.

2b Extension to other pelvic tissues.

2c Growth involving one or both ovaries with metastasis to uterus, tubes, or pelvis with tumor on the ovarian surface or with rupture of the capsule or ascites present containing malignant cells or with positive peritoneal washing.

Stage 3
Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis indicates stage 3 disease. Tumor is limited to true pelvis.

3a Tumor grossly limited to the true pelvis with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surface.

3b Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative.

3c Abdominal implants greater than 2 cm in diameter or a positive retroperitoneal or inguinal nodes.

Stage 4
Growth involving one or both ovaries with distant metastasis parenchymal liver metastasis.

Incidence and symptoms
The causes of ovarian cancer remain undetermined, but some of the following factors are influential: age, fertility drugs, menstrual history, family history, breast cancer, diet, birth control pills, hysterectomy and pregnancy. Recognized symptoms include: abdominal swelling; problems such as gas, bloating, long-term stomach pain or indigestion; bleeding between periods or after menopause; pelvic pain; feeling of pressure in the pelvis; and leg pain.

Stromal tumors can occur at any age. Juvenile granulosa cell and Sertoli-Leydig tumors are found more frequently in younger females; whereas, the peak incidence of adult granulosa cell tumors are in the perimenopausal period.[2] The more common epithelial ovarian cancers are seldom encountered in women less than 35 years, but incidence sharply increases with advancing age, peaking between 75 and 80.[2] The median age of patients with epithelial ovarian cancer is 60 years. Most epithelial ovarian cancers occur sporadically. Less than 5 percent of ovarian cancer patients belong to families in which ovarian, breast, endometrial and colon cancer are tracked as an autosomal dominant trait.[3] In this type of clinical setting, the risk can be as high as 50 percent. A single first-degree relative with ovarian cancer increases a woman's risk by at least three fold; whereas, personal his-

tory of breast cancer or colon cancer increases the risk of developing ovarian cancer by two fold.[3]

Environmental factors include high fat diet, as does the intake of lactose in subjects with relatively low tissue levels of galactose -1- phosphate uridyl transfers. Early menarche, late menopause and nulliparity are all associated with increased risks.[2]

Factors that decrease the risk of ovarian cancer are pregnancy, lactation, and oral contraceptives. The use of oral contraceptives for as long as five years can reduce the risk of ovarian cancer by 50 percent.[2] Thus factors that favor prolonged and persistent ovulation increase ovarian cancer risk, whereas factors that suppress ovulation decrease risk. Estrogen replacement does not appear to increase the risk of epithelial ovarian cancer in postmenopausal patients.[2]

Tumor size may be the only criterion for surgery, because one in four ovarian tumors removed surgically are malignant. The ratio increases with age.[3] Ovaries in postmenopausal women are very small and normally not palpable.[3] Thus, any enlargement of the ovary in postmenopausal women should signify a malignancy that requires prompt surgical excision. Serous cystadenocarcinoma is the most common type, occurring bilaterally in 30 percent to 50 percent of patients.

Non-neoplastic cysts of the ovary

In addition to carcinoma, other types of masses in the ovaries are often encountered. Some of the most commonly occurring growths include follicle cysts, lutein cysts and endometriomas.

Follicle Cysts

These arise from sample cystic overdistention of follicles during the process of atresia. Every month, a considerable number of follicles are blighted, with death of the oocyte, followed by degeneration of the follicular epithelium.[5] The cavity is greatly overdistended with fluid, producing cysts of clinically important size. Hemorrhage into the cystic cavity may take place causing a follicular hematoma. Symptoms of an enlarged cyst may cause a sensation of heaviness or aching discomfort in the affected side. This may lead to an ovarian cyst torsion of the pedicle and, in rare cases, to a spontaneous rupture with intra-abdominal bleeding, giving the clinical picture of a ruptured tubal pregnancy. Diagnosis is made by palpation of the cysts if cysts are unicellular.

One should avoid prompt operations. Cysts are frequently evanescent and may regress to normal size in a few weeks. By contrast, neoplastic-type cysts not only persist but gradually increase in size. In younger females, therapy in indicated over eight to 10 weeks before deciding on a laparotomy. In middle-age females, however, therapy should not be prolonged, and in postmenopausal females, any adnexal enlargement prompts immediate laparotomy.

Lutein Cysts

Lutein cysts are clinically important if a woman is pregnant, and a possible concern even if she is not pregnant.[5] The origin is from the corpus luteum hematoma. When the bleeding is excessive, a large corpus luteum hematoma is produced, characterized chiefly by a thinned out, bright yellow lutein wall about the blood-filled central cavity.[5] Gradually, however, there is a resorption of the blood elements, leaving a clear or slightly bloody fluid. Symptoms resemble those of early tubal pregnancy. Menstruation is apt to be slightly delayed, with a persistent scant bleeding, often pain in one or the other of the lower quadrants, and with the presence in pelvic examination of a small, tender swelling in the corresponding side of the pelvis.[5] The diagnosis of lutein cysts is difficult and, in the majority of cases, their presence is not suspected before operation. When such a problem arises, pregnancy tests may be of service, for they are often positive in tubal gestation and negative in the corpus lutein cysts.[5] Culdoscopy or laparoscopy is more conclusive. Lutein cysts usually undergo spontaneous disappearance. In cases of hemorrhagic cysts of considerable size or where there is evidence of intraperitoneal bleeding, excision is the proper treatment.

Endometriomas (Endometriosis)

This is a benign disease in which functioning endometrial tissue is present in sites outside the uterine cavity. Common sites are the ovaries (called chocolate cysts). Clinically, women will present with pelvic pain, pelvic mass and infertility. The endometriotic implants on the ovary or adnexal structures can form an endometrioma or adnexal adhesions, giving rise to pelvic mass. Occasionally, rupture or leakage from an endometrioma may be associated with acute abdominal pain. Treatment consists of: medical therapy to suppress ovarian function and arrest the growth and activity of the endometrial implants; conservative surgical resection of as much of the endometriosis as possible; or a combination of the two therapies.

Table 2 Cytotoxic drugs active against ovarian cancer[3]

Alkylating Agents
Cyclophosphamide
Ifosfamide
Melphalan
Chlorambucil
Thiotepa
Cisplatin
Carboplatin

Antimetabolites
5-Fluorouracil
Hydroxyurea

Anthracycline
Doxorubicin

Other
Hexamethylmelamine
Taxol

Screening patients

To determine how far the cancer is spread, the doctor initiates several tests in a process called staging. Treatment and outlook are determined by the stage of the cancer (Table 1). Since stage 1 and 2 can be cured using conventional therapy, early detection of ovarian cancer could improve survival.[3] A pelvic exam is an insensitive technique for the detection of ovarian cancer in the early stages.[3] Transvaginal sonography is more sensitive in detecting ovarian enlargement. Despite high sensitivity, 10 to 15 benign lesions are found at laparotomy for each ovarian cancer detected, but Doppler flow ultrasound may reduce the number of false-positive tests.

Another test performed is the CA-125 serum marker, that have been elevated 10 to 20 months prior to the diagnosis of the tumor.[2] Only 60 percent of patients with early stage ovarian cancer will have elevated antigen levels. In postmenopausal patients, only 2 percent will have an elevation of CA-125 (greater than 30 U/ml). Studies have not yet been performed to demonstrate the ability of CA-125 to improve survival of patients with ovarian cancer.

Of course, the only way to positively assess if a growth in the pelvis is cancerous requires a biopsy.

Prognosis

Recovery and treatment depend on the patient's age, overall health, type and size of tumor, and the actual stage of the cancer. Survival is directly related to stage, grade, and the amount of tumor that remains after surgery (Table 1). Total response to treatment is also an important prognostic factor and is assessed by tumor markers.[2] For patients with more positive health factors, five-year survival in stage 1 can be as high as 90 percent, and in stage 2 approximately 70 percent to 80 percent.[2] While contemporary management produces a 20 percent to 30 percent long-term survival in stage 3 and approximately 5 percent in stage 4.[2]

Clinical findings

Functional and inflammatory lesions develop between the years of menarche to menopause. They may cause local discomfort, menstrual dysfunction, impairment of fertility, or rarely, debility and death due to local problems such as intestinal or ureteral obstruction.[4]

Most neoplastic ovarian tumors produce few symptoms. Abdominal pain may be due to pulsion, traction, torsion, distention or inflammation. The mere size of the pelvic mass can cause the sense of increased weight or pressure. Menstrual aberrations occur in only about 15 percent of patients with primary ovarian neoplasia.[4]

Any palpable enlargement of the ovary in infancy or childhood is distinctly abnormal. Precocious puberty is commonly considered to be evidence of a functioning ovarian tumor, but 90 percent of such problems are due to focal premenarcheal follicular ripening and thus need no surgical therapy unless they persist. During the menstrual years, temporary functional ovarian cysts are common; if they are persistent (60 days or longer), with normal menstrual cycles, the enlargement should be considered neoplastic.[4] But if the tumor should disappear during that time, it is most likely a functional cyst. If the patient is postmenopausal, any ovarian enlargement should be investigated promptly regardless of size. (See sidebar on ovarian cysts).

In premenopausal patients, 95 percent of adnexal masses are benign. Even after menopause, some 70 percent of adnexal masses are benign, but enlargement in post menopause is an indication for surgical exploration.

In postmenopausal patients with a pelvic mass, serum CA-125 level (95 U/ml or greater) is markedly elevated and distinguishes malignant from benign disease with a positive predictive value of 96 percent.[4] Elevated levels of CA-125 in a patient with a pelvic mass should prompt her referral for an initial exploration at an institution capable of proper staging of early ovarian cancer and of cytoreductive surgery for advanced disease.

Progressive enlargement of localized ovarian cancer can produce urologic or gynecologic symptoms, including urinary frequency, dysuria, obstruction or constipation.[3] Rarely torsion of an ovarian mass can produce acute abdominal symptoms. Vaginal bleeding or discharge is not frequently associated with primary ovarian cancer.[3]

Approximately two-thirds of patients present with stage 3 or 4 disease (Table 1). Symptoms include abdominal distention from ascites and ill-defined abdominal pain. Paracentesis usually is not required in women with a scites and an adnexal mass, since prompt surgical exploration is already indicated. Besides a workup, physical exam, other tests include a complete blood-count, serum CA-125 determination, a transvaginal sonogram, a chest film, a mammogram and in patients greater than 40 years of age, a barium enema or colonoscopy.

Therapeutic considerations

In stages 1 and 2 with low risk ovarian cancer, treatment consists of bilateral salpingo-oophorectomy (BSO) and total abdominal hysterectomy (TAH), along with surgical staging with careful observation.[2] Patients with lesions that have progressed to stages 1 or 2 will receive some type of adjuvant therapy following surgery. This may include intraperitoneal radionucleotide, total abdominal irradiation, single alkylating agents, or a combination of cytotoxic drugs (Table 2).[2]

In stages 3 and 4, treatment is more advanced, consisting of TAH-BSO, omentectomy, surgical cytoreduction, and platinum-based chemotherapy for three to six months.[2] After chemotherapy a second-look laparotomy is usually performed. With current therapy, more than half of the patients will have no evidence of disease. By noninvasive evaluation at the completion of chemotherapy, only 30 to 40 percent will be free from disease. But, when reevaluated with multiple biopsies at second look and disease is found, investigational therapy may be attempted.[2] This includes intraperitoneal administration of cisplatin and other compounds such as Taxol, and high-dose therapy with hematopoietic stem cell support.[2]

Cytotoxic chemotherapy

Several different cytotoxic drugs have produced at least temporary regression of ovarian cancer. Alkylating agents have proven to be the most active. With optimal cytoreduction of tumor, the usage of cytophosphamide and cisplatin in combination has produced greater long-term survival than has cisplatin alone.[2] Current therapy for ovarian cancer includes cisplatin or carboplatin in combination with cyctophamide at three to four-week intervals for six to eight cycles. A clinical response rate of 70 percent can be anticipated in patients with advanced epithelial ovarian cancer who have not been previously treated.[2]

Intraperitoneal therapy

Intraperitoneal (IP) therapy produces a substantial pharmaco kinetic advantage that depends on the more rapid clearance of the compounds from the peripheral blood than from the abdominal cavity. Once administered into the abdominal cavity, cisplatin exposes tumor to higher concentrations of the drug than can be achieved safely by intravenous administration.[2] Patients with small tumors (less than 5 mm) who have responded to intravenous cisplatin are most likely to respond to IP cisplatin.[2] As many as 40 percent of the patients will have a complete response following IP administration of cisplatin.[2]

Autologous bone marrow transplantation

Using high doses of multiple alkylating agents followed by stem cell and cytokine support, has achieved response rates of 54 percent to78 percent in patients who had failed all conventional therapy.

Conclusion

Often there are no early symptoms of cancer of the ovary, and only one quarter of ovarian cancers are detected in the early stages. The best prevention is early detection and yearly pelvic examination beginning at age 18. This exam can reveal any changes in the size and shape of the ovaries. Women are also advised to limit their intake of high fat foods and increase foods from plant sources, such as fruits, vegetables and whole grain products.

Most women will experience one or more of the risk factors and should consult their personal physicians if a family history of cancer exists.

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