Ovarian Cancer

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The management of patients with ovarian cancer presents a constant challenge to the clinician. This challenge is reflected not so much in the incidence of the disease (23.5 percent of gynecologic cancers), but rather in its high mortality rates (46.7 percent of all deaths from cancers of the genital tract). Thus, while 10 out of every 1,000 women in the United States over the age of 40 will develop ovarian cancer, only one or two will be cured. The remainder will suffer repeated bouts of intestinal obstruction as the tumor spreads over the surface of the bowel, develop inanition, malnutrition and literally vomit to death. This pathology, described as carcinomatosis ileus, is one of the few indications for the intermittent use of a nasogastric tube as definitive therapy to decompress the bowel. Those therapeutic nihilists who plead that patients should be left to “die with dignity” must face a dilemma when forced to apply their philosophy to the care of women with advanced ovarian cancer.

How can the high mortality rates associated with cancer of the ovary be reduced? Statistics show that prophylactic oophorectomy at the time of pelvic surgery has little influence on overall survival. Nor is there any indication that the risk of ovarian cancer is lessened by removing only one ovary. Eight to nine percent of patients with cancer of the ovary have had previous hysterectomies with preservation of the ovaries; deaths in this group could have been prevented by prophylactic oophorectomy. Recent studies, however, show encouraging results. Gibbs suggests that a radical approach to pelvic surgery in women over the age of 35 years could reduce the incidence of ovarian carcinoma by 20 percent.

We have reported an early sign of ovarian cancer that has been most valuable in diagnosis, the Postmenopausal Palpable Ovary Syndrome. It is simply that palpation of what is interpreted as a normal sized ovary in the premenopausal woman represents an ovarian tumor in the postmenopausal woman. Patients with the PMPO syndrome should not be followed and re-evaluated, but rather the presence or absence of an ovarian...
tumor must be investigated promptly. To save more women and diminish the mortality rate from ovarian cancer, more liberal indications for operation must be accepted. Waiting until one feels a solid tumor mass of up to five centimeters in size and then expecting a cure is an exercise in fancy and futility. A review of the median survival time by age for patients with ovarian cancer emphasizes the importance of vigilance. (Table 1.)

As in other cancers, early diagnosis is the most effective means of increasing survival rates for women with ovarian cancer.

**Diagnosis**

Unfortunately, the diagnosis of ovarian cancer is more a matter of chance than a triumph of scientific method. Because there are limited means of detection, careful evaluation combined with constant suspicion are essential, especially in high-risk patients. Peak incidence of ovarian cancer is found in women between 40 to 65 years of age. The ovary may get too old to function, but it is never too old to form tumors. Women at high risk usually have a long history of ovarian imbalance or malfunction, including increased premenstrual tension, heavy menstruation with marked breast tenderness, a tendency for spontaneous abortions, infertility and nulliparity as well as an early menopause.

The insidious onset of ovarian cancer needs no elaboration. It is time, however, to change the generally accepted notion that there are no early symptoms of ovarian carcinoma. Symptomatology includes often vague abdominal discomfort, dyspepsia and other mild digestive disturbances which may be present for several months prior to diagnosis. Unfortunately, such complaints are usually not recognized as anything more than middle-age indigestion; many ovarian cancers have been nurtured in a sea of bicarbonate of soda. It is imperative, therefore, to rule out ovarian cancer in women between 40 and 60 years of age who present with persistent gastrointestinal symptoms which can not be definitively diagnosed. (Table 2.)

**Pelvic Examination**

Routine pelvic examination will detect only one ovarian cancer in 10,000 examinations of asymptomatic women. In addition, since tumors
cannot be palpated abdominally until they reach 15 centimeters in size, pelvic findings are often minimal or uncertain even in patients with advanced disease. The tumor may be deep in the pelvis; the patient may be obese, heavy-muscled, uncooperative or aged with an inelastic and conical vagina. Pain in the early stages is associated with a complication, such as torsion, rupture or infection. Vaginal bleeding may occur in the postmenopausal patient and has been attributed to functioning stroma in the cancer. Ascites with positive cells is a sign of advanced disease; five-year survival is reported in only about eight percent of these patients.

Although pelvic findings are of limited value in diagnosis, the physician must be alert to:

- A mass in the ovary;
- Relative immobility due to fixation and adhesions;
- Irregularity of the tumor;
- Shotty consistency with increased firmness;
- Tumors in the cul-de-sac described as “a handful of knuckles”;
- Relative insensitivity of the mass;
- Increasing size under observation;
- Bilaterality (70 percent in ovarian carcinoma versus five percent in benign lesions);
- An omental cake, nodular hepatomegaly and ascites, common findings in advanced disease.

Other Diagnostic Procedures

The Pap smear has been reported positive in 40 percent of patients with advanced disease. Positive cells on cul-de-sac taps were found in 90 percent of patients; the authors’ results are very poor when compared to these figures, however. The value of laparoscopy must still be determined. Nevertheless, it is generally advised when a normal sized ovary is palpated in a patient three to five years postmenopausal. Other indications, according to Gusberg and Frick, include:

- Any pelvic mass which has appeared after the menopause, particularly an adnexal mass;
- An adnexal mass in a woman of any age that progressively enlarges beyond five cm. while under observation;
- An adnexal mass 10 cm. or more in size;
- A mass which cannot be definitively diagnosed as either a fibroid or carcinoma.

Staging

The Cancer Committee of the International Federation of Gynecology and Obstetrics has recommended the following stage grouping:

| Table 2. Complete Workup for Ovarian Cancer |
|-------------------------------------------|
| Careful history                          |
| Physical examination                     |
| Pelvic exam and pap smear                |
| Proctosigmoidoscopy, as indicated        |
| CBC and urinalysis                       |
| SMA-12 (Blood chemistries)               |
| Chest X-ray                              |
| Intravenous pyelogram                    |
| GI series                                |
| Barium Enema                             |
| Paracentesis, laparoscopy and lymphangiogram (optional) |

This workup documents the extent of disease and determines whether the cancer is primary or metastatic. About 5-10 percent are metastatic.
Primary Carcinoma of the Ovary

Stage I. Growth limited to ovaries.
Stage Ia. Growth limited to one ovary; no ascites
(1.) Capsule ruptured
(2.) Capsule not ruptured
Stage Ib. Growth limited to both ovaries; no ascites
(1.) Capsule ruptured
(2.) Capsule not ruptured
Stage Ic. Growth limited to one or both ovaries; ascites with malignant cells
(1.) Capsule ruptured
(2.) Capsule not ruptured

Stage II. Growth involving one or both ovaries with pelvic extension.
Stage IIa. Extension and/or metastases to uterus/tubes/other ovary
Stage IIb. Extension to other pelvic tissues
Stage IIc. Extension and/or metastases to other organs

Stage III. Growth involving one or both ovaries with widespread intraperitoneal metastases.

Stage IV. Growth involving one or both ovaries with distant metastases.

Special Category. Unexplored cases thought to be ovarian carcinoma.

Treatment of Epithelial Cancers

Tumors of surface epithelial and ovarian stromal origin constitute approximately 90 percent of ovarian cancers. (Table 3.) Only about eight percent occur in women under the age of 35; most develop in patients between 40 to 60 years old. In the latter group, conservative surgery is not indicated and treatment consists of total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy and instillation of P32. In patients with cancers at Stages I through IV, postoperative irradiation is added to the protocol.

Stages Ia, Ib, Ic
Total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy and instillation of P32 is the recommended treatment. Caution must be exercised using P32 in women who have not had previous surgery since bowel complications including perforation have been observed. All patients should have any free fluid aspirated and cytologically examined according to the Papanicolaou technique. Although there is considerable controversy over the value of omentectomy, in its defense, islands of tumor cells will occasionally be found, advancing the stage from I to III. In addition, the omen-

| Cells of Origin | Type of Tumor |
|-----------------|---------------|
| Epithelial cells| Primary epithelial tumors |
|                 | Serous |
|                 | Mucinous |
|                 | Endometrioid |
|                 | Mesonephric |
| Germ cells      | Dysgerminoma |
|                 | Endodermal sinus |
|                 | Embryonal teratoma |
| Sex cord cells  | Adult teratoma |
| Germ cells + Sex cord cells | Mesenchymal tumors |
|                 | Granulosa cell tumors (female) |
|                 | Sertoli-Leydig (male) |
|                 | Gonadoblastoma |

The ovary gives rise to a great variety of cancers and is also a favorite site for metastases from other organs. Epithelial tumors constitute about 85-90 percent of all ovarian tumors.
tumor interferes with the even distribution of P³² and is best removed if P³² is used. Reports indicate that metastatic disease may be found in the omentum even in an apparently early, encapsulated ovarian cancer.

Stages IIa, IIb

Here, too, the treatment of choice is total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy and P³² instillation. External irradiation is included, especially if the disease extends beyond the ovaries or if it is not possible (or doubtful) that all gross disease can be removed. Adhesions surrounding the tumor should be biopsied to determine the presence or absence of cancer and to further document the extent of disease.

Stage III

If possible, the surgical approach is the same as that used for Stage I and II cancers, namely total hysterectomy, bilateral salpingo-oophorectomy, appendectomy and omentectomy. Total abdominal radiation therapy, chemotherapy or both are now being employed with greater frequency. Tumor masses larger than two centimeters do not respond as well to irradiation as smaller nodules because of a central anoxic area and should be treated with chemotherapeutic agents.

Stage IV

The ideal management is to remove as much cancer as possible through total abdominal hysterectomy, bilateral salpingo-oophorectomy, appendectomy and omentectomy. Radiation therapy and chemotherapy are adjunctive measures.

Role of Extended Surgery and Pelvic Exenteration

In patients with advanced disease, the cancer is usually widely disseminated over the peritoneal surfaces of the pelvis, upper abdomen and omentum. Frequently, both ovaries are involved due either to metastases or bilateral primary growths. Advanced ovarian cancer is not a surgical disease. However, this concept may be revised if and when immunotherapy is adopted as standard treatment. Since tumor mass must be reduced below a certain volume before this form of treatment is effective, it is possible that future patients will be treated in stepwise fashion—first by surgery, then radiation and chemotherapy, and finally by immunotherapy. The "second look" operation may play a new role in finding...
those patients with reduced tumor masses who are good candidates for immunotherapy.

On theoretical grounds the natural history of ovarian cancer contraindicates these radical surgical procedures. However, in rare instances when tumor recurrence is late and limited entirely to the pelvis, more radical surgery may be chosen. Endometrioid cancer, for example, which appears to be less aggressive than other epithelial ovarian cancers, especially in its potential for metastases, may lend itself to this approach. Long and Taylor reported that only 30 percent of cases were bilateral and metastases were noted in 45 percent of cases to the upper abdomen. In general, however, patients with advanced ovarian cancer should not undergo extended surgery or pelvic exenteration except in extremely rare instances.

**Treatment of Nonepithelial Cancers**

Nonepithelial lesions comprise 10 percent of all ovarian tumors and are the most common gynecologic tumor in children and adolescents. One in 10 is malignant, arising generally from germ cells. The cancer rapidly progresses and is susceptible to torsion due to the long infundibulopelvic ligament.

**Germ Cell Tumors**

The management of germ cell tumors (Table 4) must be based on a knowledge of their natural history. The dysgerminomas resemble sexually undifferentiated germ cells of the early gonad. Some patients have subnormal gonadal development and pseudohermaphroditism, but these findings are not caused by the tumor and the patient's ambiguous sexual status is not altered after removal of the lesion. In a patient over the age of 35 years with a tumor which has spread beyond the ovary or in those with testicular feminization, ideal treatment is total hysterectomy, bilat-
biopsy of the other ovary and of the para-aortic nodes as well as cytologic examination of pelvic fluid. The patient should be followed every two to three months for the first three years and then every six months thereafter. Ideally, she should undergo a "second look" operation approximately eight months after the initial procedure was performed.

Endodermal sinus, embryonal teratomas, choriocarcinomas and polyvesicular vitelline tumors of the ovary are highly malignant. Management is generally total hysterectomy and bilateral salpingo-oophorectomy, but no strong argument can be made for this treatment over a more conservative approach since the survival rate from each is near zero. These tumors are not radiosensitive, but triple chemotherapy has shown some encouraging results. A "second look" operation is recommended in patients surviving more than six months on a three drug regimen.

The solid adult teratoma is a benign lesion and commonly occurs in patients over 35 years of age. Conservative treatment is not indicated despite the fact that the lesion is benign. The cystic teratoma, which accounts for 50 percent of ovarian tumors in childhood, has a malignancy rate below the two percent reported in adults and is bilateral in less than 10 percent of patients. Conservative management is recommended in children and adolescents.

Mesenchymal Tumors (Gonadal Stromal)

Female sex cord lesions are often referred to as feminizing tumors, although a certain number are nonfunctioning. The granulosa tumor, the most important in this category, is bilateral in five percent of patients. Diagnosis is not infrequently made following rupture with resultant hemoperitoneum. In women over 35 years old, treatment involves total hysterectomy and bilateral salpingo-

![Fig. 5: Granulosa cell tumor.](image1)

![Fig. 6: Krükenberg tumor.](image2)

oophorectomy. In children and adolescents, the tumor is usually unilateral and encapsulated, and unilateral salpingo-oophorectomy is sufficient treatment.

Male sex cord lesions such as the Sertoli-Leydig cell tumors always produce masculinization. This tumor occurs most commonly in patients between the ages of 20 and 30 years. Its management and response is generally similar to that reported for granulosa cell tumors.

Gonadoblastoma

Gonadoblastoma, a rare ovarian tumor, is composed of germ cells.
(dysgerminoma) and sex cord cells (granulosa-Sertoli). Sex chromatin studies usually show a negative nuclear pattern (46 XY) or a sex chromosome mosaicism (XO/XY). Most patients are intersexual with a phenotypic habitus, amenorrheic and possibly virilized. The malignancy rate is near zero, but the gonads are useless and both ovaries should be removed.

**Metastatic Ovarian Cancer**

Approximately 10 percent of ovarian cancers are metastatic and the survival rate is very low. Most arise from the bowel, breast or thyroid. Krükenberg tumors usually originate from the upper gastrointestinal tract, specifically the stomach and pylorus, but may develop from any mucous secreting organ. On microscopic examination they have signet ring cells and a cellular stroma derived from the ovary. As much of the tumor as possible should be removed, primary as well as metastatic disease. Since bilateral ovarian tumors may represent metastatic disease, a thorough exploration should be performed.

**Radiation Therapy**

In patients with Stage I disease, radioactive phosphorus $^{32}$P in 15 milli-curie doses given intraperitoneally has improved survival rates, while external radiation therapy has not. Stage IIa cancers are usually treated as those in Stage I, but if there is any doubt about the extent of disease or its complete removal, pelvic irradiation is recommended. Stage IIb tumors require postoperative pelvic radiation therapy; in Stage III the whole pelvis and abdomen are irradiated, care being taken to avoid radiation to the kidneys. When liver involvement is present, however, chemotherapy is indicated.

Delclos at M.D. Anderson Hospital and Tumor Institute in Houston uses a moving strip technique in which areas 2.5 cm. in width are marked on the front and back of the patient. Each day a segment is treated first on the front and then the back, afterward advancing to the next 2.5 cm. strip. Approximately 2,600 to 2,800 rads are delivered in 12 treatments over 30 to 40 days. This high dose has a greater biologic effect than the static field technique, yet the side effects are less.

Kottmeier reports that by adding postoperative irradiation to the treatment regimen he has increased the survival rate from 16.7 percent (sur-
surgery only) to 61.5 percent (surgery plus irradiation). In those cases where it was impossible to remove all the disease or in inoperable patients, postoperative irradiation increased survival from zero to 2.4 percent. Forty-five percent of these patients had marked clinical improvement. Thirty-five percent had no noticeable improvement and died within six months of therapy. Kottmeier administers radiation through two large anterior and two corresponding posterior fields and keeps the total dose to 2,000 rads delivered over six weeks. Once the cancer has been completely removed, radiation is restricted to the pelvis and lower abdomen; in the presence of an incompletely removed tumor, ascites or metastases throughout the abdomen, the full course is delivered. A daily dose of 200 rads to the lower abdomen is well tolerated, but it is advisable not to exceed 100 rads per day to the upper abdomen. Six weeks after the completion of therapy the patient should be re-examined. If there has been general and local improvement, additional irradiation is repeated with slightly smaller doses. If there is no obvious response, no additional treatment is given.

Chemotherapy

Whether chemotherapy has increased the overall survival is difficult to estimate, but it has made life more comfortable for a great number of these unfortunate patients. Each center has its own criteria but, in general, patients with metastases and ascites have been chosen for chemotherapy. Chemotherapy given in a well-controlled manner does not produce as much morbidity as radiation to the upper abdomen. Following response and in the absence of palpable disease, repeat surgery may be undertaken to determine whether the patient is a candidate for: (1) excision of any remaining cancer; (2) radiation therapy; or (3) continued chemotherapy. Alkylating agents have proven most valuable for the treatment of ovarian cancer. The authors commonly use cyclophosphamide (cytoxan) which, after a pretreatment workup, is given in 200 mg. doses intravenously for five days followed by 50 mg. twice a day by mouth. The WBC and differential as well as the hemoglobin should be checked after two to three weeks and the drug discontinued if the white blood count drops below 3,000. Although the platelets are not often affected by cytoxan, it is wise to do a platelet count every six weeks. The M.D. Anderson Hospital group uses L-phenylalanine mustard (melphalan), 1 mg./kg. of body weight given in divided doses over five to six days and repeated monthly. Combination chemotherapy does not produce better results than the alkylating agents, except in the treatment of embryonal tumors. Nor has chemotherapy and radiation combined proven any more successful than each given alone and, in fact, there is increased morbidity.

Summary

Early diagnosis is the most effective means of reducing the currently high mortality rate associated with ovarian cancer. The palpation of what appears to be a normal sized ovary in a premenopausal woman suggests an ovarian tumor in a postmenopausal woman. Also, rule out ovarian cancer in any 40-60 year old woman who presents with persistent, unexplained GI symptoms. Ninety percent of all ovarian tumors are of epithelial origin. Treatment consists of total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy and instillation of P₃₂. In Stage II through IV cancers, post-operative irradiation is added to the protocol.