Ovarian Cancer: Part I

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This is the first part of a two-part feature. Part II will appear in the January/February 1980 issue of Ca.

Introduction

Ovarian cancer—increasing in the highly industrialized countries—presents the most frustrating problem in gynecology. The ovary is unique in that it not only gives rise to a great number of primary cancers but is also a recipient of metastases from many primary cancers: This fact justifies a thorough preoperative evaluation (metastatic work-up) in any patient presenting with a suspected ovarian cancer.

Ovarian neoplasms are difficult to diagnose; at the time of initial diagnosis approximately 60 to 70 percent are either stage III or IV. Treatment also leaves a great deal to be desired: only 15 to 25 percent of patients with invasive cancer live five years or more and treatment results are no better today than those reported for the previous two decades. With new modalities of therapy (hyperalimentation, multiple drug chemotherapy, and immunotherapy) patients are living longer and hopefully more comfortably, but the five-year survival rate has not improved.

Unlike patients with other pelvic cancers, a high percentage of patients with ovarian cancer remain alert up to the moment of death. Despite impaired gastrointestinal functioning, these patients suffer greatly from ravenous hunger and thirst, although only a small amount of food or water precipitates bouts of prolonged vomiting. Women with advanced ovarian cancer pose a dilemma to therapeutic nihilists who argue that patients should be left to "die with dignity." We cannot abandon these patients, driving them to seek the help of quacks. In caring for these women the art of medicine must take over when the science of medicine fails.

For most gynecologic cancers the cause of death has been recorded. However, the picture is less clear for those patients who have died as a result of ovarian cancer. It is widely assumed that the repeated bowel obstructions result in inanition and malnutrition; these patients literally vomit themselves to death. However, on closer observation, this assumption is difficult to accept. Some patients have a large volume of cancer yet live on despite it; others with bowel obstruction die even though they are kept...
in good nutritional, fluid and electrolyte balance. Close observation indicates that most of these patients have infection and some have sepsis. Lowered immunocompetence interferes with the host's ability to respond normally to infection.

The overall management of the patient with ovarian cancer has come full cycle. In the 1950s aggressive surgical programs were carried out but the morbidity and mortality that resulted decreased the enthusiasm of the profession for this approach. Chemotherapy was not sophisticated enough to insure a predictable chance for either cure or palliation for those surviving the postoperative period. Recently, the improved and expanded role of hyperalimentation has permitted a more aggressive plan of management, and the improved understanding of and new regimens for anticancer chemotherapy have increased the survival rate for these patients.

Incidence

Ovarian cancer is the sixth leading cancer in women and accounts for about five percent of all female cancers. Only cancer of the skin, breast, colon and rectum, uterus, and lung account for more new cases of female cancer than cancer of the ovary. On the basis of the Third National Cancer Survey, it is estimated that about 1.4 percent or one of every 70 newborn girls will develop cancer of the ovary sometime during their lives. Ovarian cancer accounts for about 25 percent of all gynecologic cancer but accounts for about 47 percent of all genital cancer deaths!

The specific incidence rates for ovarian cancer show a steady rise with age up to age 75, where the rate begins to drop off slightly, indicating that while the ovary gets too old to function, it never gets too old to form a cancer. This observation should be considered when making a judgment on whether or not to preserve the ovaries at the time of hysterectomy in women 40 years of age or older. The greatest number of cases is found in age groups 50 to 59 years. The mean age is 62.3 and the median age is 59.0 years.

Mortality

In 1979, the estimated incidence of ovarian cancer was four percent; estimated mortality in women was six percent. Ovarian cancer accounted for 24 percent of genital cancers among white women and 12 percent among black women. (Estimated number of new cancers of the ovary in blacks for 1979 is 1,100.) Ovarian cancer accounted for 47 percent of all gynecologic cancer deaths. The mean age of death was 62.3 years, and the median age was 63.7 years.

In the age groups 30 to 34, and 65 to 69 years, cancer of the ovary is either the third, fourth or fifth leading cause of cancer deaths. At 75 and older, cancer of the ovary is the ninth leading cause of death, if not higher.

The death rates by age for cancer of the ovary show a steady increase as the risk population gets older until ages 70 to 75 followed by a slight decline in the older ages. The rates for nonwhites are lower than those for whites in each age group for ages over 20 years.

The rates for all ages in white women have risen slowly and steadily through the years. The rates for ages over 55 have shown a general increase. In the age groups 35 to 44 and 45 to 54, there is a general leveling off. The trends in age-standardized death rates for major sites show that the rate for ovarian cancer is increasing: the death rate from cancer of the ovary has tripled in the past 40 years. In a given 10-year period there are over 100,000 deaths from ovarian cancer. The median survival time for ovarian cancer is listed in Table 1.

Clinical Manifestations

Usually there are no early manifestations of ovarian cancer; this alone is considered a major contributing factor to the poor therapeutic results. The usual manifestations of abdominal swelling, pain,
and a mass recorded in the hospital charts are associated with advanced cancer.

The earliest manifestations are generally insidious and include vague abdominal discomfort, dyspepsia, indigestion, gas with constant distension, flatulence, eructations, a feeling of fullness after a light meal, slight loss of appetite, and other mild digestive disturbances. Although the manifestations are certainly not specific, these gastrointestinal complaints are not uncommon. They are suggestive of ovarian cancer unless another definitive explanation is identified and may signal difficulty. Unfortunately, such complaints are usually not considered significant. Patients with ovarian cancer have an acid reaction of their peritoneal fluid, unlike patients without disease or with a benign process. This may explain the early gastrointestinal symptoms.

The gastrointestinal manifestations may precede other symptoms by months. It is imperative to rule out ovarian cancer in women over age 40 who present with gastrointestinal symptoms that cannot be definitely diagnosed. Elderly women without pelvic complaints but with symptoms referable to the intestinal tract are more apt to consult their internist, family doctor or primary care physici

![Table 1](image)

**TABLE 1**

| Age         | Median Survival (Years) |
|-------------|-------------------------|
| All ages    | 1.4                     |
| Under 45    | 5.4                     |
| 45-54       | 1.8                     |
| 55-64       | 1.3                     |
| 65-74       | 0.9                     |
| 75 and over | 0.8                     |

2. Persistent gastrointestinal symptoms in the patient 40 years of age or older that cannot be definitely diagnosed.

3. A long history of ovarian dysfunction or malfunction.

**Clinical Diagnosis**

The early diagnosis of ovarian cancer is a matter of chance rather than a triumph of scientific approach. Means of early detection are extremely limited. It is the capacity of cancer to grow and disseminate that makes early detection of the disease so important. The cancerous tumor of one cc (approximately 1/16 in³) in size, weighing about one gm (approximately 1/30 oz), is about the smallest that can be detected by palpation or by x-rays, yet it contains about a billion cancer cells, each potentially capable of originating a new focus of disease. Dis-
functioning stroma in the ovarian cancer. Ascites with malignant cells is a sign of advanced disease.

In terms of function, it must also be emphasized that a variety of paraendocrine effects, such as hypercalcemia, hypoglycemia, Cushing's syndrome, as well as disorders such as hemolytic anemia, on rare occasions may relate to the presence of an ovarian cancer.

Pelvic Findings

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 carcinomas versus five percent in benign lesions);
- An omental cake, nodular hepatomegaly and ascites, common findings in advanced disease.

Indications for
Exploratory Laparotomy

Prime indications for doing exploratory laparotomy are:
- Any pelvic mass that 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 (functional cysts seldom get this large);
- A mass that cannot be definitively diagnosed as either a fibroid or carcinoma.

The work-up for ovarian cancer is listed in Table 2.
Laboratory Diagnosis

The Pap smear has been reported to be positive in 40 percent of advanced cases and positive cells are found in 90 percent of cases on cul-de-sac taps. The author's results are very poor when compared to these figures.

Neither sonography nor CT scan has been helpful in making an early diagnosis but both play a role in monitoring therapy. Laparoscopy has been helpful in staging patients with ovarian cancer, but has not been helpful in making an early diagnosis.

Carcinoembryonic antigen (CEA), lactic dehydrogenase, Regan isoenzyme and chorionic gonadotropins have not been helpful in making an early diagnosis but, if elevated, play a role in monitoring the response to therapy. Alphafetoprotein is elevated in endodermal sinus tumors and is perhaps the only marker specific for diagnosing an ovarian tumor.

One of the most exciting areas of gynecologic oncology is the effort now being made to diagnose ovarian cancer by means of immunologic techniques. The potential for a serologic test is great.

Tumor-Specific Ovarian Cancer Antigens

The ectopic production of human chorionic gonadotropin by neoplasms is being explored in great detail at the present time. Since the individual starts as a single cell it is reasonable to believe that the cell contains the potential for producing every type of enzyme and protein needed for the differentiation of cells into tissues and organs. This differentiation is accomplished by a constant interplay between the repression and derepression of genes. However, when a cell mutates and there is loss of genetic control (with derepression of normally repressed cells), enzymes and proteins that were originally produced but later held in abeyance are produced once again and start to function. This may explain reports that 40 percent of all cancers produce chorionic gonadotropin; some embryonal tumors have been found to produce chorionic gonadotropin in 100 percent of cases. This probably represents a retrogeneic expression from derepression of genes following the dedifferentiation of cells.

Several research groups have identified a candidate antigen—unique for epithelial ovarian cancers—that can produce an antibody when injected into rabbits. The absorbed antiserum has a very high specificity for epithelial ovarian cancer, but it may not be sensitive enough to diagnose early lesions. Radioimmunoassay studies are necessary to screen a large number of women. However, it will be necessary to first determine: (1) whether the antigen will remain bound to the tumor; and (2) whether it will be secreted as an antigen or as an antigen-antibody complex. The prospects are promising.

With modern technology it has been possible to isolate a homologous and very pure antibody from ascitic fluid. In splitting the antigen-antibody complex that is so abundant in the fluid, it has also been possible to isolate a much purer antigen than has been available previously. The Nepelometer has helped identify complexes as well as antigens in the ascitic fluid and has cut down on the time required for this step, while also improving the accuracy of the test.

“...newer advances offer hope that the long sought-after blood test for diagnosing ovarian cancer is moving towards realization.”

plexing the autologous anti-ovarian antibody to a staphylococcus A protein, a sensitive blocking test has been developed that permits identification of minute amounts of the candidate ovarian cancer antigen. The potential for a serologic diagnosis of ovarian cancer is encouraging. These newer advances offer hope
that the long sought-after blood test for diagnosing ovarian cancer is moving towards realization.

Teratomas containing significant vitelline component (endodermal sinus and polyvesicular vitelline tumors) have been shown to give rise to a serum alphafetoprotein. The fetal antigen has also been identified in the ascitic fluid.

Cytogenetics

In malignant ovarian tumors, the chromosome distribution varies with the degree of invasiveness. Ovarian carcinomas differ from other gynecologic cancers in their ploidy distribution and the frequency of marker chromosomes. Wa-konig-Vaartaja and Auersperg reported that differentiated and undifferentiated cancers of the ovary had 59 percent in the hypodiploid (2n-x) group and 41 percent in the triploid (3n±x) group, while the undifferentiated had 100 percent in the triploid group. Ovarian cancers that were localized had a high diploid mode, while those that had metastasized had a high triploid mode. The evidence suggests that a spread outside the ovary is associated with a change from the diploid to the triploid mode. The same authors report that a high incidence of larger marker chromosomes is present in ovarian cancer. Since benign, borderline and invasive areas may be present in the same tumor, it is obvious that wide sampling must be carried out to accurately determine the chromosomal content of the cancer.

Early Detection and Prevention

In the last five years ovarian cancer has become the leading cause of death among gynecologic cancers. There are only two methods available to lower the mortality rate: (1) early diagnosis; and (2) prophylaxis.

Unfortunately, there is no method available for making an early diagnosis, and there is a strong resistance on the part of the patient as well as the physician to prophylaxis. However, when a hysterectomy is indicated in a patient over 40 years of age, it is important to explain to her that ovarian cancer is on the increase, that it is the leading cause of death from gynecologic cancer and that most cases are in stages III and IV when the diagnosis is made. Bilateral salpingo-oophorectomy should also be advised.

In evaluating patients admitted with the diagnosis of ovarian cancer it was found that the incidence of cancer in the retained ovary of patients who had previous pelvic surgery was reported as approximately three percent thirty years ago. In 1962, it was reported as seven percent; in 1967 as 8.9 percent; and in 1971 as 20 percent by Gibbs. Since ovarian cancer is on the increase and is the leading cause of death from gynecologic cancer it would be interesting to know what the figure is today. There is no indication that the risk of ovarian cancer is lessened by removing one ovary. Currently, more than 800,000 hysterectomies are performed each year and most of these are carried out in women over 40 years of age. These are the patients at risk to develop ovarian cancer (Fig. 1).

Postmenopausal Palpable Ovary Syndrome

Barber and Graber reported an early sign of ovarian cancer that has proved most valuable in diagnosis, i.e., 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 postmenopausal palpable ovary syndrome should not be followed and re-evaluated but must be investigated promptly for the presence or absence of an ovarian tumor. The only method of diminishing the mortality rate from ovarian cancer is the acceptance of more liberal indications for surgery. To wait until one feels a solid tumor mass of up to five cm and then expect a cure is unrealistic. A review of the median survival time by age emphasizes the importance of vigilance.
Classification
In 1973, the World Health Organization published a monograph (edited by Drs. Sirov, Scully and Sobin), establishing standards for the histologic typing of ovarian cancers. This is a very complete breakdown of the common epithelial tumors, gonadal stromal tumors (formerly termed sex cord cells), germ cell tumors, metastatic tumors, as well as unclassified tumors. In addition, it goes further and differentiates the common epithelial tumors not only into the usual three groups of benign, borderline and malignant, but also according to whether the adenomatous of fibrous element is dominant (Table 3).

The World Health Organization reports that borderline cancer can be defined as a tumor that has some, but not all, of the morphologic features of cancer, including, in varying combinations: (1) stratification of the epithelial cells; (2) apparent detachment of cellular clusters from their sites of origin; and (3) mitotic activity and nuclear abnormalities intermediate between those of clearly benign and unquestionably malignant tumors of a similar cell type. On the other hand, obvious invasion of the adjacent stroma is lacking. Tumors with epithelial cell proliferation or atypicality of a minor degree should be placed in the benign category.

Surface papillomas are included as a separate entity since there is increasing evidence to suggest that they are more prone to spread than the completely encapsulated tumor, even though both are in the same clinical stage.
### Table 3
HISTOLOGICAL CLASSIFICATION OF OVARIAN TUMORS

#### I. Common Epithelial Tumors

**A. SEROUS TUMORS**
1. **Benign**
   - cystadenoma and papillary cystadenoma
   - surface papilloma
   - adenofibroma and cystadenofibroma
2. **Of borderline malignancy (carcinomas of low malignant potential)**
   - cystadenoma and papillary cystadenoma
   - surface papilloma
   - adenofibroma and cystadenofibroma
3. **Malignant**
   - adenocarcinoma, papillary adenocarcinoma, and papillary cystadenocarcinoma
   - surface papillary carcinoma
   - malignant adenofibroma and cystadenofibroma

**B. MUCINOUS TUMORS**
1. **Benign**
   - cystadenoma
   - adenofibroma and cystadenofibroma
2. **Of borderline malignancy (carcinoma of low malignant potential)**
   - cystadenoma
   - adenofibroma and cystadenofibroma
3. **Malignant**
   - adenocarcinoma and cystadenocarcinoma
   - malignant adenofibroma and cystadenofibroma

**C. ENDOMETRIOID TUMORS**
1. **Benign**
   - adenoma and cystadenoma
   - adenofibroma and cystadenofibroma
2. **Of borderline malignancy (carcinomas of low malignant potential)**
   - adenoma and cystadenoma
   - adenofibroma and cystadenofibroma
3. **Malignant**
   - carcinoma
     - adenocarcinoma
     - adenoacanthoma
     - malignant adenofibroma and cystadenofibroma
   - endometrioid stromal sarcomas
   - mesodermal (Müllerian) mixed tumors, homologous and heterologous

**D. CLEAR CELL (MESONEPHROID) TUMORS**
1. **Benign**: adenofibroma
2. **Of borderline malignancy (carcinomas of low malignant potential)**
3. **Malignant**: carcinoma and adenocarcinoma

**E. BRENNER TUMORS**
1. **Benign**
2. **Of borderline malignancy (proliferating)**
3. **Malignant**

**F. MIXED EPITHELIAL TUMORS**
1. **Benign**
2. **Of borderline malignancy**
3. **Malignant**

**G. UNDIFFERENTIATED CARCINOMA**

**H. UNCLASSIFIED EPITHELIAL TUMORS**
### TABLE 3 (Continued)

#### II. Sex Cord (Gonadal Stromal) Tumors

| A. GRANULOSA-STROMAL CELL TUMORS |
|-----------------------------------|
| 1. Granulosa cell tumor           |
| 2. Tumor in the thecoma-fibroma group |
| (a) thecoma                       |
| (b) fibroma                       |
| (c) unclassified                  |

| B. ANDROBLASTOMAS; SERTOLI-LEYDIG CELL TUMORS |
|-----------------------------------------------|
| 1. Well differentiated                        |
| (a) tubular androblastoma; Sertoli cell tumor (tubular adenoma of Pick) |
| (b) tubular androblastoma with lipid storage; Sertoli cell tumor with lipid storage (folliculome lipidique de Lecene) |
| (c) Sertoli-Leydig cell tumor (tubular adenoma with Leydig cells) |
| (d) Leydig cell tumor; hilar cell tumor       |
| 2. Of intermediate differentiation            |
| 3. Poorly differentiated (sarcomatoid)        |
| 4. With heterologous elements                 |

| C. GYNANDROBLASTOMA                         |
| D. UNCLASSIFIED                             |

#### III. Lipid (Lipoid) Cell Tumors

#### IV. Germ Cell Tumors

| A. DYSGERMINOMA                             |
| B. ENDODERMAL SINUS TUMOR                  |
| C. EMBRYONAL CARCINOMA                     |
| D. POLYEMBRYOMA                            |
| E. CHORIOCARCINOMA                         |
| F. TERATOMAS                                |
| 1. Immature                                |
| 2. Mature                                  |
| (a) solid                                  |
| (b) cystic                                 |
| (i) dermoid cyst (mature cystic teratoma)  |
| (ii) dermoid cyst with malignant transformation |
| 3. Monodermal and highly specialized       |
| (a) struma ovarii                          |
| (b) carcinoid                              |
| (c) struma ovarii and carcinoid            |
| (d) others                                 |

| G. MIXED FORMS                              |

#### V. Gonadoblastoma

| A. PURE                                     |
| B. MIXED WITH DYSGERMINOMA OR OTHER FORM OF GERM CELL TUMOR |

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It is usually not difficult to determine whether or not serous tumors have invaded the stroma. Although diagnosis is generally made without difficulty in clear cell or endometrioid cancers, it is not as clear-cut as reported among the serous cancers. Benign, borderline and malignant forms of any of these neoplasms may coexist in any one tumor. This has been confirmed in work carried out with the electron microscope and may explain the importance of studying many sections before reporting the tumor karyotype.

Mucinous tumors are commonly multilocular and parvilocular, often making it impossible in a given patient to accurately determine whether glandular structures lying within the stroma are the result of budding from a larger gland or cyst, or whether they indicate invasion of the stroma. The documentation of invasion of this group may have to await the results of studies of histologic and nuclear grading as well as stromal response. Currently, if the epithelium is four cells high it is considered invasive.

**Staging**

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

- **Stage I.** Growth limited to the ovaries.
  - **Stage Ia.** Growth limited to one ovary; no ascites.
  - **Stage Ib.** Growth limited to both ovaries; no ascites.

- **Stage II.** Growth limited to the pelvic cavity.
  - **Stage IIA.** Growth limited to one ovary; capsule intact.
  - **Stage IIB.** Growth limited to both ovaries; capsule intact.

- **Stage III.** Growth limited to the pelvic cavity and peritoneal cavity.
  - **Stage IIIA.** Growth limited to one ovary; capsule intact.
  - **Stage IIIB.** Growth limited to both ovaries; capsule intact.

- **Stage IV.** Metastases outside the peritoneal cavity.
  - **Stage IVA.** Metastases to solid organs.
  - **Stage IVB.** Metastases to some other site.
Parenchymal tissues.

Stage Ic. Tumor either Stage Ia or Ib but with ascites* or positive peritoneal washings.

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

Stage IIa. Extension and/or metastases to the uterus and/or tubes.

Stage IIb. Extension to other pelvic tissues.

Stage IIc. Tumor either Stage Ila or IIb, but with ascites* or positive peritoneal washings.

Stage III. Growth involving one or both ovaries with intraperitoneal metastases outside the pelvis and/or positive retroperitoneal nodes; or tumor limited to the true pelvis with histologically proven malignant extension to small bowel or omentum.

Stage IV. Growth involving one or both ovaries with distant metastases. If pleural effusion is present there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastases equal Stage IV.

Special Category. Unexplored cases thought to be ovarian carcinoma.

Diagnosis and Management of an Adnexal Mass

Age is an important consideration in the management of a patient with an adnexal mass or suspected ovarian tumor. A mass in the very young and the very old is presumed to be abnormal. The best management consists of a careful work-up and exploratory laparotomy. There is no time or place for observation and procrastination with patients in these age groups. Management of an adnexal mass diagnosed during pregnancy or in patients between 20 and 40 may arouse controversy. The patients have been divided into three age groups: birth to 20, 20 to 40, and over 40 years.

Birth to Age 20

Although ovarian tumors account for only one percent of new growths in children under 16, they remain the most frequent genital neoplasm of childhood and adolescence. Ovarian neoplasms may occur at any age in childhood and adolescence, but they tend to be most common at puberty (between 10 and 14). The genital organs migrate from the abdomen to the pelvis at the time of puberty. In the prepubertal child the genital organs are located in the abdomen. The most common tumors seen in this age group are germ cell tumors, particularly cystic teratomas (dermoids). Among the malignant tumors, dysgerminoma is the most common. The key to treatment is to be conservative. However, any spread beyond the ovary demands a more aggressive approach.

Age 20 to 40

In this group, controversy may arise over management of an adnexal mass. As the patient approaches age 40 there is little controversy: a more aggressive approach is followed. However, as the age moves towards 20 there is controversy about management. In this age group germ cell and gonadal stromal tumors are found with an occasional common epithelial cell tumor. The treatment should be individualized according to the type of tumor, stage of the disease and age of the patient. In the younger patient, conservatism, unless it jeopardizes the patient's chances for a cure, is desirable.

Age 40 and Older

Patients 40 years and older comprise the high risk group because they are either premenopausal or postmenopausal. Metastatic cancer to the ovaries is more common in this high risk group. Observation is not indicated; the patient should have a thorough work-up and management should be carried out without delay.