CARCINOMA OF THE OVARY

DISCUSSION OF 230 CASES

Dr. GEORGE T. SCHNEIDER, M.D. (**)

Ovarian carcinoma remains one of the most deadly malignant diseases of women. Therapeutic results have not improved significantly during the past twenty years, and certainly have not kept pace with advances in the diagnosis and therapy of other gynecologic malignant diseases. For this reason, it is important to review our experience with the disease periodically in the hope that the universally low five year survival rates, ranging from 18 to 33 per cent (1-4), can be improved.

Our experience with this problem at the Ochsner Clinic and Ochsner Foundation Hospital in New Orleans, Louisiana, covering the twenty year period ending in 1963 was therefore reviewed. During this time, 175 patients with various stages of ovarian carcinoma were treated. An additional 55 "functioning" tumors of the ovary (31 granulosa cell and 24 theca cell tumors), considered to be of lower grade malignancy (5), which were encountered at the Ochsner Clinic and Charity Hospital in New Orleans, Louisiana, were also analyzed so that the series comprises 230 cases.

AGE AND PARITY

Sixty-two per cent of the 230 patients were between the ages of 40 and 60 years. The youngest was 25 and the oldest 82 years of age. Thirty per cent were childless.

SYMPTOMS

Unfortunately, an enlarging ovary may be asymptomatic for a considerable period of time, and this accounts to a great extent for the difficulty of early detection. Later, pelvic pain or pressure develops, along with abdominal swelling. Menstrual abnormalities or postmenopausal bleeding may also occur.

(*) Presented at the Segundo Congreso Peruano de Obstetricia y Ginecologia in Lima, Peru, Sept. 6-10, 1964.
(**) From the Department of Gynecology and Obstetrics, Ochsner Clinic, and Ochsner Foundation Hospital, New Orleans
Sixty per cent of all tumors in our series were papillary cystadenocarcinomas, 23 per cent were primary solid adenocarcinomas, and 7 per cent were of the mucinous variety. The remaining 10 per cent consisted of teratomas, mesonephromas, and Krukenberg tumors. The 55 "functioning" tumors were not included in these statistics because they have a lower malignant rate.

**PROGNOSIS**

Because our institution is a referral center, a large number of our patients with malignant disease are first seen with far advanced lesions. Fifty per cent of the patients in our series had such extensive disease as to be non-resectable or the tumor was incompletely removed because of extensive intra-peritoneal metastases.

In order to give a more specific prognosis and to permit comparison with other large series, some degree of uniformity of classification of the extent of the lesion at the time of operation must be established. For example, the following simple but adequate classification (6) may be used:

**Stage I.**—Cancer confined to one ovary. Includes solid as well as cystic lesions.

**Stage II.**—Presence of superficial excrescences or a ruptured cyst. The gross tumor is resectable but microscopic seeding is probably present. Bilateral ovarian involvement is in this category.

**Stage III.**—Involvement of the pelvic peritoneum, the pelvic viscera, or both.

**Stage IV.**—Spread beyond the pelvis into the abdominal cavity with involvement of the omentum, abdominal viscera and/or peritoneum.

With adequate therapy the five year survival rate can be expected to be: 70 to 90 per cent for stage I, 45 to 60 per cent for stage II, 18 to 25 per cent for stage III, and 0 to 5 per cent for stage IV. Among our 31 patients with granulosa cell carcinoma, the five year survival rate was 84 per cent, and only one of 24 patients (96 per cent) with a thecoma died.

**THERAPY**

Once the probable diagnosis of an ovarian tumor or cyst has been made, hysterectomy with bilateral salpingo-oophorectomy is the generally accepted method of treatment in the United States. Preoperative pelvic irradiation by deep roentgen-ray or cobalt is used in the occasional case in which extensive ovarian carcinoma can be diagnosed before operation by cytologic examination of ascitic fluid or by inguinal lymph node biopsy. Irradiation may re-
duce the size of the tumor to the extent that subsequent surgical resection can be more extensive.

The more radical Wertheim hysterectomy with pelvic node dissection has not yet proved to offer better long term results and is therefore not recommended except in selected circumstances. Omentectomy reduces the size of the tumor and delays further regional abdominal extension in many cases.

Involved localized segments of intestine, especially if obstruction is imminent, should be resected. This type of palliative therapy has occasionally been of value, especially if the cancerous tissue is sensitive to radiation or chemotherapy (7).

Re-exploration or a "second look" operation after about six months in patients with extensive metastases has been advocated by a number of authorities. We have performed this in a number of selected patients, with satisfactory palliation after removal of recurrent malignant tissue, especially in those who have strong host resistance to the tumor, and in whom the lesion tends to remain localized in the abdominal cavity.

In a number of patients in whom we encountered incompletely removable anaplastic lesions, the uterus was not removed if it was not grossly involved, because this organ provides an effective site for intrapelvic implantation of radium. In such cases this has proved gratifying.

Radioactive Isotopes. Since 1952 we have instilled radioactive gold (Au\(^{198}\)) intraperitoneally as an adjunct to surgical therapy. From three to nine days postoperatively, 125 to 150 millicuries of Au\(^{198}\) is instilled into the peritoneal cavity with 500 cc. of physiologic saline solution through a polyethylene tube, inserted at operation or later. We believe this is especially valuable in patients in whom surgical cure is considered feasible. With adequate diffusion, superficial tumoricidal irradiation (usually between 4500 and 7000 r) to the entire peritoneal cavity is possible. Since irradiation by this method is accomplished with the short bate ray with maximum irradiation of 1.5 to 2 mm., gross or deep metastatic spread is not affected. For this reason, Au\(^{198}\) is not recommended in such cases, unless ascites is a serious problem. Formation of ascitic fluid can be well controlled by intraperitoneal instillation of radioactive isotopes.

More recently, we have utilized radioactive chromic phosphate (CrP\(^{32}\)O\(_4\)) instead of Au\(^{198}\) because of its lack of gamma radiation, its ease of handling, and its longer half life (14 1/2 days as contrasted with 2.7 days for Au\(^{198}\)). The dosage of CrP\(^{32}\)O\(_4\) is 15 to 20 millicuries.

If the patient has deeper metastatic spread which is considered to be not resectable, we give high voltage roentgen-ray or cobalt therapy in a dosage of 3000 to 5000 r over a period of four to six weeks postoperatively.
Chemotherapy. When surgical treatment and radiation are no longer of benefit, we have found that certain chemotherapeutic agents may prolong the life of some of these patients, or at least make them more comfortable. Drugs currently employed for this purpose have been classified according to their structural similarity, mechanism of action, or common origin, such as alkylating agents, antimetabolites, or antibiotics. The designation "alkylating" stems from the ability to alkylate, i.e., to bind an alkyl group (methyl, —ethyl—) to a receptor substance of the neoplastic cells, such as intracellular enzymes or nucleic acids, thus disrupting the cellular metabolic processes. Antimetabolites are structurally similar to normal metabolites, such as purines, or pyrimidines, and when accepted into a metabolic system, disrupt it by interfering with the function of normal compounds. The mode of action of antibiotics, most of which are obtained from various species of Streptomyces, is poorly understood.

Of the many chemotherapeutic agents that have been explored, only a few of the alkylating agents have established clinical value in ovarian carcinoma. Nitrogen mustard (HN$_2$) was the first alkylating agent studied extensively in the treatment of various neoplastic diseases and is still the most widely used agent in the chemotherapeutic attack on ovarian carcinoma. It can be administered intraperitoneally in a dosage of 0.4 mg./kg. of body weight for control of peritoneal effusion when radioactive materials are unavailable. In patients with far advanced disease in whom further surgical treatment or irradiation is not suitable, nitrogen mustard can be injected intravenously in doses of 0.2 mg./kg. body weight on two successive days, followed in two weeks by a maintenance dose of 0.1 mg./kg. body weight at weekly intervals. The predominant adverse reaction of vomiting can be diminished by prophylactic administration of antiemetics.

Other agents which have not proved significantly more advantageous than nitrogen mustards are Thio-Tape®R, given intravenously, and chlorambucil, which can be given orally.

With our present knowledge of chemotherapeutic drugs, we believe that they should be employed only in patients in whom definite resection or radiation is not indicated. Approximately one-fourth of the patients treated palliatively, may be expected to derive some temporary benefit (8). Toxic effects are extremely dangerous, especially on the hematopoietic system, and only physicians thoroughly familiar with the effects of these drugs should prescribe them.

COMMENT

Delay of the asymptomatic patient in seeking therapy is one of the major problems in ovarian cancer. Survival rates are directly proportional to
the stage of the disease when correct surgical therapy is instituted. Postoperative intraperitoneal instillation of radioactive gold or chromic phosphate should improve results in the early stages. For this reason women must have pelvic examinations at regular intervals to discover ovarian enlargement. This applies particularly to those older than 40 years, in whom the incidence of carcinoma of the ovary is highest.

In spite of the deadliness of ovarian cancer and the difficulty of detecting it early, we do not perform bilateral oophorectomy at the time of hysterectomy for benign disease in premenopausal women between the ages of 40 and 50 years with the view to preventing development of ovarian cancer. Synthetic estrogens have not yet proved the equal of a woman's endogenous hormones.

REFERENCES

1.—HENDERSON, D.N. and BEAN, J.L.—Results of treatment of primary ovarian malignancy. Am. J. Obst. & Gynec. 73:657-663 (March) 1957.