CARCINOMA OF THE OVARY

DISCUSSION OF 230 CASES

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Ovarian carcinoma remains one of the most deadly malignant diseases of women. Therapeutic results hove not improved significantly during the past twenty years, and certainly have not kept pace with advances in the diognosis and therapy of other gynecologic malignant diseases. For this reasan, 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.

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PATHOLOGIC CLASSIFICATION

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 veriety. The remaining 10 per cent consisted of teratomas, mesonephromas, and Krukenberg tumors. The 55 "functioning" tumors were not included in these statistics because the 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 nanresectable or the tumar was incompletely removed because of extensive intraperitoneal metastases.

In order to give a more specific prognosis and to permit comparison with ather large series, some degree of uniformity of classification of the extent of the lesion at the lime 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 superficiol excrescences or a ruptured cyst. The gross tumar is resectable but microscopic seeding is probably present. Bilateral ovarian involvement is in this category.

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

Stage IV.— Spread beyond the pelvis into the abdominal cavity with involvement af the omentum, abdominal viscero and/or peritoneum.

With adeguate therapy the five year survival rate can be expected to be: 70 to 90 per cent for stage I, 45 ta 60 per cent for stage II, 18 to 25 per cent for stoge III, and 0 to 5 per cent for stage IV. Among aur 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 thecama died.

THERAPY

Once the prabable diognasis of an ovarian tumor or cyst has been made, hysterectamy with bilateral salpinga-oopharectamy is the generally accepted method af treatment in the United States. Preoperative pelvic irrodiation by deep roentgen-ray or cobalt is used in the occasional case in which extensive ovarian carcinoma can be diagnosed before operation by cytologic examinotion of ascitic fluid ar by inguinal lymph node biopsy. Irradiatian moy re-

duce the size of the tumor to the extent that subsequent surgical resection can be more extensive.

The more radical Wertheim hysterectamy 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 polliative therapy has occasionally been of value, especially if the cancerous tissue is sensitive to radiation or chemotheropy (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 malignont tissue, especially in those who have strong host resistance to the tumor, and in whom the lesion tends to remoin locolized in the obdominal covity.

In a number of patients in whom we encountered incompletely removable anaplastic lesions, the uterus was not removed if it was not grossly involved, becouse 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 rodioactive gold (Au ^{198}) intraperitoneally os an adjunct to surgicol 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 especiolly valuable in patients in whom surgical cure is considered feasible. With adeguate diffusian, superficiol tumoricidal irrodiation (usuolly between 4500 ond 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 contralled by intraperitoneal instillation of radioactive isotopes.

More recently, we have utilized radioactive chromic phosphote ($CrP^{32}O_4$) 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 dasage 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 voltoge roentgen-ray or cobolt therapy in a dosage of 3000 to 5000 r o ver a period of four ta six weeks postoperatively.

Chemotherapy. When surgical treatment and radiotion are no longer of benefit, we have found that certain chemotherapeutic ogents may prolong the life of some of these potients, or at leost 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, o rantibiotics. 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 af 40 and 50 years with the view to preventing development of ovarian cancer. Synthetic estrogens have not yet proved the egual of a woman's endogenous hormones.

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