

Ovarian Cancer: Diagnosis and Treatment

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Ovarian cancer is not an entity but a group of diseases. Studies of the result of treatment must be based on homogenous groups of tumors and not on mixtures of histologically and biologically different tumor types. Furthermore, there still exists a considerable degree of confusion as to which tumors should be considered true carcinomas. Experience has shown that between obviously benign and obviously malignant neoplasms there exists a group of well-differentiated tumors that, in their clinical behavior, resemble true carcinomas, inasmuch as they give rise to implantation metastases and ascites and cause the death of the patient, but yet have quite a different course. The lack of generally accepted definitions of the various histological forms has resulted in the extreme differences in long-term results given by various authors. The importance of elaborating a standardized, internationally accepted classification of ovarian tumors so that the results of different clinics may be accurately compared is obvious. The International Federation of Gynecology and Obstetrics has adopted a histopathologic classification of ovarian tumors related to the Müllerian epithelium. They consist of the serous, mucinous, and endometrioid types. The so-called endometrioid carcinomas resemble adenocarcinoma of the endometrium. In general they are well differentiated, while the majority of serous carci-

nomas are more or less undifferentiated.

Table 1 gives the histologic classification of the primary epithelial tumors. Figure 1 presents the survival rates of serous cystomas. From the figures given it is obvious that well-differentiated tumors of low potential malignancy ought to be separated from true carcinomas. We all share the opinion that, in general, the prognosis is poor. Ovarian carcinomas are frequently not discovered until the growth has extended to surrounding organs or has given rise to metastases. The treatment becomes progressively less effective with increasing anatomic extent of the disease.

The necessity of an early diagnosis is obvious. Laparoscopy has proved to be of value in many cases and can promote an early diagnosis. Hysterosalpingography, arteriography, and needle biopsies through the vagina or the rectum may help in this respect. The routine use of cul de sac aspiration may result in the detection of occult carcinomas as brilliantly demonstrated by the Grahams (1964). Sometimes a laparotomy is necessary to permit a final diagnosis.

Explorative laparotomy facilitates the outlining of the borders of growth by direct inspection and palpation, and should be routinely carried out whenever there is the slightest suspicion of an ovarian tumor. Some years ago gynecologists considered it appropriate to apply conservative treatment in patients

with physiologic enlargements or cysts of the ovary. It is often difficult to decide whether an enlargement of the ovary is physiologic or neoplastic. Since today laparotomy is quite a safe procedure, it is wise to perform this operation on the slightest suspicion of an ovarian neoplasm.

Surgery

During laparotomy the surgeon should outline in detail the extension of the growth and take several, rather large, biopsies from areas that seem to be suspicious. The establishment of the anatomical extent of the carcinoma is important in planning further therapy. Experience has proved that serous carcinomas grow fast and give rise to extensive metastases at an early stage, whereas mucinous tumors are confined to the ovary for a long time, and endometrioid carcinomas tend to be multicentric, but remain to the true pelvis for a long time. Metastases above the pelvis were diagnosed in 147 of 276 cases (53.3%) of serous carcinoma, in 9 of 51 cases (17.6%) of mucinous carcinoma, and in 29 of 168 cases (17.2%) of endometrioid carcinoma. The carcinoma was limited to the ovaries and uterus in 55 of 276 cases (19.9%) of serous neoplasm, in 30 of 51 cases (58.8%) of mucinous neoplasm, and in 58 of 168 cases (34.5%) of endometrioid neoplasm.

It should be stressed, though,

OVARIAN CANCER: DIAGNOSIS AND TREATMENT

TABLE 1
Histologic Classification of Common Primary Epithelial Tumors of the Ovary

- I. Serous cystomas
 - a. Serous benign cystadenoma.
 - b. Serous cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (low potential malignancy).
 - c. Serous cystadenocarcinomas.
- II. Mucinous cystomas
 - a. Mucinous benign cystadenomas.
 - b. Mucinous cystadenomas with proliferating activity of epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (low potential malignancy).
 - c. Mucinous cystadenocarcinomas.
- III. Endometrioid tumors (similar to adenocarcinomas in the endometrium)
 - a. Endometrioid benign cysts.
 - b. Endometrioid tumors with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrative destructive growth (low potential malignancy).
 - c. Endometrioid adenocarcinomas.
- IV. Concomitant carcinoma, unclassified carcinoma
Tumors which cannot be allotted to one of the groups I, II, or III.

that the excision of an ovarian carcinoma should be performed to the greatest possible extent. Every effort should be made to keep the capsula intact. Even if the tumor is unilateral, it is advisable to remove the opposite ovary. In young patients and in those who want to have children, a unilateral oophorectomy may be considered. If, however, the tumor is a serous type, a relaparotomy is indicated, as the normal ovary may frequently harbor microscopic metastases.

An extended operation, for instance with resection of the small or large bowel, is indicated at least in carcinomas that are likely to be mucinous, as at a late stage these neoplasms give rise to metastases and evidently are radioresistant. Whether this management is advisable in serous and endometrioid carcinomas is doubtful. It is our experience that extensive surgery in such neoplasms smears cancer cells over the peritoneum, opens lymph and blood vessels, and favors implantations and metastases. The removal of serous or endometrioid carcinomas fixed to surrounding tissue by firm adhesions destroys the defensive reaction of the body. Recurrences appear rapidly and do not, as a rule, respond to radiation, nor to any other therapy. Although we cannot prove so at present, it seems logical to try radiotherapy prior to excisional surgery. Consequently, the laparotomy should be restricted to an exploratory operation. Biopsies should be taken and irradiation administered to the area outlined on surgery. It is not appropriate to exceed a dose of 4,000 rad in five weeks. Re-operation should be carried out 10 to 14 days after completion of radiotherapy.

Most gynecologists prefer to perform a panhysterectomy in addition to oophorectomy because of possible transtubal metastases to the endometrium. I am not convinced that, as a rule, a hysterectomy is to be recommended. Intrauterine application of radioactive sources renders a treatment to the

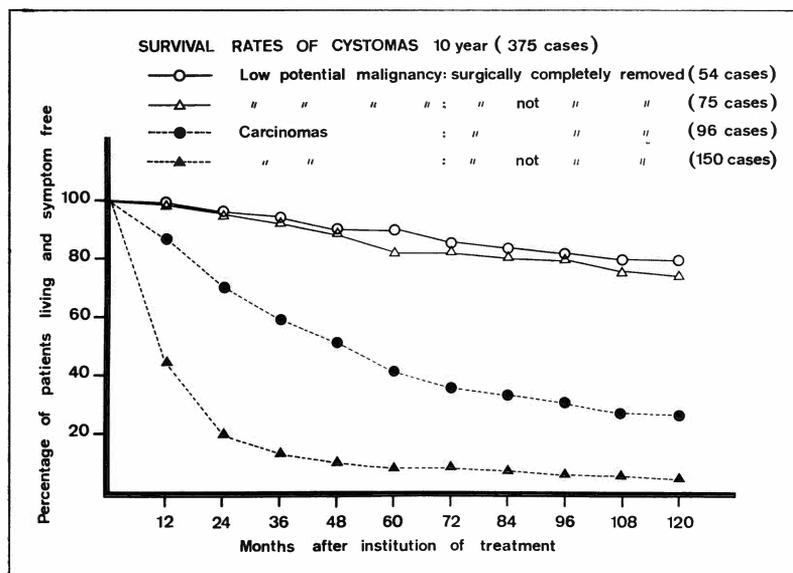


Fig. 1—Ten-year survival rates of cystomas (375 cases).

cul de sac possible. Metastases or pelvic recurrences appear first and foremost in the cul de sac. A heavy dose of radiation can be given to this area if external irradiation is combined with intrauterine radium. Insertion of radium into the vagina is not valuable.

Resection of the omentum has been recommended whenever any surgical procedure for ovarian cancer is performed. Metastases to the omentum are diagnosed in many cases. At Radiumhemmet we have not been convinced that prophylactic omentectomy is valuable and will improve the outcome. In cases of metastases to the omentum, a resection lessens the degree of ascites accumulation. Yet, a stipulation is that a cutting of the omentum is not made through carcinomatous tissue.

Application of Radioactive Sources

Intraperitoneal examination or removal of an ovarian carcinoma will spread cancer cells to various parts of the peritoneal cavity. It is likely that such superficial peritoneal transplants are eradicated by the intraperitoneal application of colloidal radioactive sources. Müller (1959) has for years applied radioactive gold intraperitoneally after surgery. His results support the value of this method. Radiumhemmet, and many others, has substituted chemotherapeutic agents such as Nitrogen mustard, ThioTEPA, Cytoxan, etc., for the isotope. The effect of intra-abdominal application of isotopes or of chemical drugs has so far not been as satisfactory as we had expected.

Radiation Therapy

The survival rate in true ovarian carcinoma is dependent on the anatomical extent of the carcinoma. Serous carcinomas have a tendency to give metastases above the pelvis and distant metastases, while en-

dometrioid carcinomas are often limited to the pelvis. Radiation should start as soon as possible after surgery if laparotomy and further examination have proved that the cancer is incompletely removed, but yet is limited to the true pelvis. Many authors have reported an increase of survivors if radiotherapy is given postoperatively. At Radiumhemmet a five-year survival rate of 17.1% has been reached in 35 cases of serous, and 50.0% in 24 cases of endometrioid carcinoma with non-resectable metastases in the true pelvis. The corresponding three-year survival rates are 23.6% in 55 cases of serous, and 50.0% in 50 cases of endometrioid carcinoma. These figures suggest that endometrioid carcinomas do respond better to irradiation than serous ones.

In these patients conventional x-ray therapy with a half value layer of 1 to 2 mm Cu has been administered through two large opposing fields in addition to intrauterine application of radium.

Irradiation of the pelvis can be achieved more efficiently with supervoltage radiation than with conventional roentgen therapy. As a consequence of our experience that endometrioid carcinomas possibly respond better to irradiation than serous carcinomas do, cases of serous and endometrioid neoplasms with extension to tissues in the true pelvis are at present receiving cobalt beam therapy with a dose of 4,500 to 5,000 rad to the midpelvis over a period of six to seven weeks. Two large opposing portals or a three-field technique are being used in these cases. The latter method is chosen for cases in which the extent of the carcinoma is outlined in detail, and, thus, a reduced dose can be given to the bladder, rectum, and small bowel partly with the use of wedge-filters. The radiation is delivered through one large anterior and two lateral fields.

The radiation technique mentioned is applied *also in cases of true ovarian carcinoma in which*

the tumor was removed completely. However, in such cases the dose from external radiation is decreased to about 3,000 rad.

The radiation therapy described has been used at Radiumhemmet since 1964. For the time being it is impossible to draw any conclusions, but we do believe that results will be improved.

I have mentioned previously that at Radiumhemmet radiotherapy was also given to *cases of true ovarian carcinoma with metastases above the pelvis.* Only two of 114 such patients with serous carcinoma are living symptom-free at five years. The corresponding number of endometrioid carcinoma is four of 24. It is likely that radiotherapy will bring about a palliation in advanced cases of true ovarian carcinomas, but it is questionable whether the five-year survival in six of 138 cases can be attributed to the radiation delivered in rather small doses. Possibly, the survival is due to a slow growth of the disease. However, we have tried recently to deliver dosages of 3,500 to 5,000 rad to the total abdominal cavity in selected cases of ovarian carcinoma with extensive metastases over the entire peritoneal cavity. The radiation has been applied through six fields with central doses of 700 rad over a period of five days. Remarkably enough the patients have withstood the radiation satisfactorily. Their general condition has improved, the ascites has disappeared, and sometimes the tumor has decreased considerably in size. However, it is yet doubtful whether the survival in cases of serous carcinoma has been prolonged. Such a radiation as mentioned may be tried as an experiment but should not be applied routinely.

Another attempt to increase the dose to the entire abdomen has been made at the M. D. Anderson Hospital, Houston. Megavoltage irradiation was given through multiple narrow horizontal strips. Actually, this is a modification of the

overlapping x-ray strip technique recommended by Patterson for radiation of the trunk. The realization of this radiation technique is difficult in cases of carcinoma with ascites.

Table 2 gives the survivals in 555 cases of ovarian carcinoma treated five years ago or earlier.

Chemotherapy

Great attention has been drawn to radiomimetic substances in the hope that they may delay the growth of the carcinoma. Experience has shown that the use of compounds similar to Nitrogen mustard have been a success in causing regression of ovarian carcinoma. Since the publications by Bateman (1955; Bateman and Winship, 1956) and others, Thio-TEPA has been reported to be useful in the management of ovarian carcinomas, but Chlorambucil, E-39, Endoxan, Sarcylisin, Hemisulphur mustard, etc., have also produced good palliation in many cases. At Radiumhemmet we have chosen Thio-TEPA in the treatment of ovarian carcinoma and have used it exclusively or in combination with irradiation.

The intracavitary application of cytotoxic agents has also been used to a large extent at Radiumhemmet. For years we nourished the hope that intraperitoneal instillation of Nitrogen mustard or similar drugs would lead to palliative results similar to those achieved by colloidal

radioactive substances. Unfortunately, experience has shown that this does not hold valid for ascites. Nor does prophylactic installation of Thio-TEPA into the peritoneal cavity after laparotomy seem to be valuable, whether it is administered continuously or by injection.

From 1960 through 1962, an investigation was carried out to explore whether chemotherapy given in addition to radiation would improve survival rates (Kottmeier, 1967). Thio-TEPA was given intravenously in moderate doses in 32 cases in which the ovarian carcinoma had been incompletely removed, but no extrapelvic metastases were traced. The follow-up of these cases has not revealed any benefit attributable to chemotherapy.

With the purpose of studying the effect on cases of ovarian carcinoma that were either completely inoperable or had given rise to several unresectable metastases above the pelvis, Thio-TEPA was injected intravenously in 131 patients, whereas 88 patients received only radiation. The aim was to maintain a combined therapy until depression of the bone marrow had appeared. In 42 of the 131 patients, therapy was given until the leucocytes and thrombocytes were depressed to very low levels. Table 3 presents the distribution of the cases in regard to the histopathological type of the growth. The serous carcinomas amount to 38% in the irradiated group and 56% in that

which had received combined therapy.

From the study (Fig. 2, table 4) it is obvious that combined treatment has proved to be effective in producing a prolonged survival and a noticeable subjective improvement in many cases of extensive ovarian carcinoma in which chemotherapy was given in large doses.

As a consequence of this trial we give Thio-TEPA intravenously to patients with extensive ovarian carcinoma, especially if the growth is the serous type. It is important to continue chemotherapy until a depression of the bone marrow occurs. It is, therefore, not sufficient to keep the blood count under close observation. Repeated bone marrow biopsies must be made during the course of therapy, especially as occasionally the blood count does not correspond to the cellular pattern of the bone marrow taken from the sternum.

Thio-TEPA is given intravenously with a dose of 10 mg daily or every second day. The initial dose varies considerably. The patient is kept under close observation also for several weeks after the completion of therapy, as a severe late depression of the leucocytes and platelets may sometimes occur two to four weeks later. The patients have a depressed immunity to infections. The treatment involves a risk of aplastic marrow or septicaemia. Five patients have died as a sequel of therapy.

For the time being we do not know whether a combined treatment of irradiation and chemotherapy is preferable to chemotherapy alone in cases of true ovarian carcinoma with extension above the pelvis. We suppose that a combined treatment is appropriate in cases of endometrioid carcinoma. In this respect I call attention to the fact that therapy should begin with radiation, and chemotherapy should be given subsequently. Investigations carried out have shown that apparent hyperplasia of the

TABLE 2
Five-Year Survival of Patients with Ovarian Carcinomas

Type of Carcinoma	No. Patients Treated	No. Patients Surviving After:				
		1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.
Serous	276	149	95	68	48	41
Mucinous	51	39	35	33	32	32
Endometrioid	168	138	115	106	102	93
Unclassified	60	29	18	17	14	13

cellular pattern in marrow from the sternum occurs during the first two weeks of irradiation.

Recent observations support the opinion that chemotherapy alone is preferable to combined treatment in cases of extensive serous and mucinous carcinomas. Provided initial treatment has yielded a good effect, further chemotherapy with Thio-TEPA or Endoxan in moderate doses should be given, under observation, though, of the blood count. In our experience, however, the platelets will never return to normal level. In addition blood transfusions and testosterone in large doses should be given.

Repeated Surgery

One important question remains: Should surgery be carried out in cases of extensive ovarian carcinoma that, on initial examination and/or laparotomy, were considered completely inoperable and that had responded satisfactorily to treatment applied? Radiumhemmet has advocated for years that in these cases a laparotomy should be made with removal of as much of the disease as is possible. In the years 1958 through 1962, this was carried out in 45 cases of serous carcinoma, in eight cases of endometrioid carcinoma, and in 10 cases of unclassified true carcinoma. Six, two, and three patients respectively have survived three years after initial therapy. Five patients are living at five years; only one survived of the 45 patients with serous carcinoma. However, in 24 of the 63 patients operated upon, the disease exploded following surgery. As a consequence of these poor results, we only occasionally advocate surgery in cases of extensive ovarian carcinoma that from the beginning are considered completely inoperable. However, we do agree with Rutledge that modern therapy with application of chemical drugs in repeated series may widen the indications for repeated surgery.

TABLE 3
Histopathological Distribution of 219 Cases of Inoperable Ovarian Carcinoma. Results of Treatment with Irradiation Alone and in Combination with Chemotherapy

Pathologic Type	Treatment Applied			
	Irradiation		Irradiation and Chemotherapy	
	No.	Cases	No.	Cases
Serous	33	(38%)	74	(56%)
Mucinous	2		1	
Endometrioid	15	(17%)	18	(14%)
Unclassified	14	(16%)	22	(17%)
No microscopic examination	24	(27%)	16	(12%)
Total	88		131	

INOPERABLE OVARIAN CARCINOMAS 1960-1962

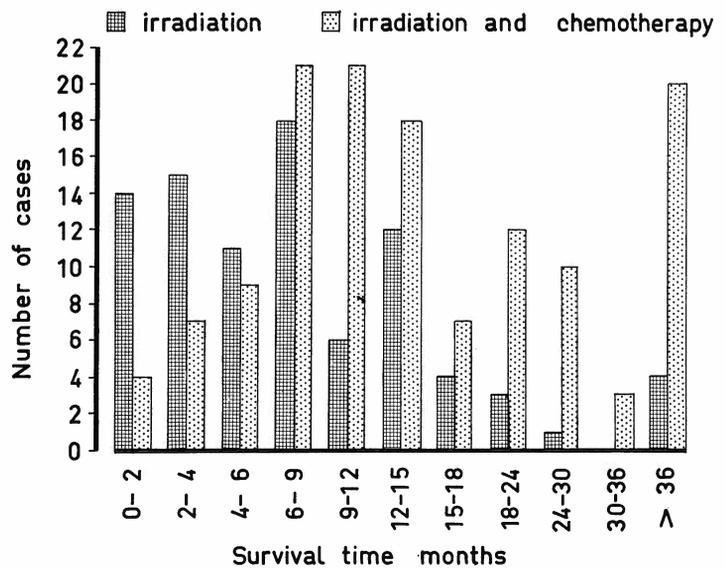


Fig. 2—Inoperable ovarian carcinomas, 1960-1962. A randomized study to establish the value of chemotherapy as an adjunct to irradiation.

TABLE 4
Sustained Palliation in 219 Cases of
Inoperable Carcinoma of the Ovary

Irradiation		Irradiation and Chemotherapy	Effect
No. Cases	No. Cases		
47	17		None
41	116		Good

Ovarian Carcinoma of Low
Potential Malignancy

Regarding 121 cases of so-called "questionable" carcinomas treated five years ago and 156 cases treated at least three years ago, I have not much to add. In cases of unilateral growth, surgery with preservation of the normal ovary may be adequate therapy. Radical excision is important especially in cases of mucinous tumor, as fragments of neoplastic tissue left behind may lead to pseudomyxoma peritonaei. Radiotherapy with doses not exceeding 3,000 rad is expedient in all other cases in which the tumor could not be completely removed. Relaparotomy is indicated in cases initially considered inoperable which improved after radiation therapy. A five-year survival rate of 79.6% has been attained in 49 cases of low potential carcinomas with metastases. The corresponding three-year survival rate in 67 cases is 85.1%.

Summary

I have made it my task with this paper to outline principles for the treatment of ovarian carcinoma. Emphasis has been laid on pathology and on anatomical extent of the growth. The extension of the tumor should be outlined in detail at clinical examination and at laparotomy. Excision of the carcinoma should be performed to the greatest possible extent. Every effort should be made to keep the capsule intact.

In cases of serous and endometrioid carcinoma fixed to surrounding tissue by firm adhesions, it may be appropriate to restrict the operation to an explorative laparotomy and to operate on the patient again 10 to 14 days after completion of radiation.

Intraperitoneal application of colloidal radioactive sources following surgery seems to decrease the risk of peritoneal implants and is superior to radiomimetic substances in the palliation treatment of ascites. Removal of the primary malignancy is occasionally followed by regression of disseminated metastases.

Radiotherapy with adequate doses should be administered to all cases of true ovarian carcinoma limited to the pelvis. Endometrioid carcinomas may respond better to radiation than serous tumours. In advanced cases of carcinoma with unresectable metastases above the pelvis, chemotherapy should be administered either as the only treatment or in combination with radiation. Chemotherapy should be applied in doses that lead to depression of the bone marrow. Recent experience has shown that many times the palliative effect from chemotherapy is superior to that from radiotherapy.

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