Ovarian carcinoma; second-look laparotomy postchemotherapy

Preliminary report

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The proper staging and extent of disease in carcinoma of the ovary cannot be determined without an exploratory laparotomy.[1] In some cases, reexploration after an interval of treatment helps the physician to determine whether the therapy has been successful. Exploratory laparotomy for this purpose, or second-look operation, has become a common practice at the Cleveland Clinic. With this ongoing evaluation new treatment schedules will be designed and others modified.

Advanced ovarian cancer should be treated surgically when diagnosed. In many cases radical resection is accomplished with total removal of all known cancer.[2] In other cases as much cancer is removed as possible to decrease the tumor cell population.[3] In either case chemotherapy is used postoperatively.

In 1951, Wangensteen et al[4] reported the second-look operation for patients with cancer of the colon. With the development of new chemotherapeutic agents and combinations of these agents, second-look operations are performed on advanced ovarian cancer at this institution.

Twenty-two patients with advanced cancer of the ovary, on whom second-look operation was performed after chemotherapy are the subjects of this study. When no tumor was found in several

biopsy specimens and results of peritoneal cytologic studies were negative, chemotherapy was discontinued. Patients with residual disease continued to receive chemotherapy. One patient received P^{32} intraperitoneally.

Patients and methods

Sixty-two patients have been treated for advanced ovarian cancer in the Cleveland Clinic Gynecologic Oncology Section. Advanced ovarian cancer includes Stage IIB or greater according to the International Federation of Gynecologists and Obstetricians (FIGO) staging system. These patients were treated from January 1978 to August 1981. Twenty-two patients with complete clinical response to chemotherapy after ten or more courses of chemotherapy underwent second-look operations.[1] All patients had had an initial laparotomy with removal of as much tumor as possible. Eleven of the 22 patients had the initial operation at another hospital before referral. Some patients had only a partial resection or biopsy of the tumor mass because the cancer was thought to be too extensive.

In the second-look operation, peritoneal washings of the pelvis and right and left abdominal gutters are performed for cytologic study. A careful sampling of the entire abdomen is made with biopsies of the omentum, both pelvic walls, cul-de-sac, lateral abdominal gutters, paraaortic nodes, and diaphragm (*Table 1*). Serosal surfaces of the small and large intestines including the mesentery must be inspected. Thick adhesions and small plaquelike formations may contain aggregates of tumor cells. Biopsy specimens of residual round ligament and infundibulopelvic ligaments can be the source of residual microscopic cancer. We use the proctoscope with light source to visualize the diaphragm and serosal surface of the liver. If on initial evaluation at laparotomy a tumor plaque or nodule is discovered, it is excised or a biopsy is obtained and submitted for frozen section. If all suspected areas are negative on frozen section, the meticulous search must continue until the previously mentioned biopsy sites have been submitted for histologic study. The upper paraaortic area should be thoroughly palpated and biopsies should be obtained on any palpable or enlarged nodes.[5] An average of 22 biopsies were done in the patients who had no palpable or visible evidence of residual cancer.

Table 1. Second-look laparotomy

Site of biopsy
Adhesions or thickened areas
Plaque formation on parietal or visceral peritoneum
Right and left pelvic wall (2 each). Residual round and infundibulopelvic ligaments
Cul-de-sac (3)
Bladder peritoneum (3)
Right and left lateral gutters (2 each)
Excision residual omentum
Paraaortic and pelvic lymph node sampling
Diaphragm (2)

The average age of this group of patients was 51 years with a range of 32 to 67. Three patients had been treated for carcinoma of the breast and one patient had associated superficial adenocarcinoma of the endometrium at the time of the original operation. Four other patients had family histories of cancer.

All but two of the patients who had second-look operations had epithelial cancers according to the classification of the World Health Organization (WHO) (*Table 2*). Fifteen had serous carcinomas and 10 of the 15 had undifferentiated or Grade III cancers. Two mucinous carcinomas were Grade I and one was Grade II. The mixed epithelial cancer and endometrial cancer were Grade III.

Table 2. Second look; classification of ovarian cancer

Type	Grade I	Grade II	Grade III	No. of patients
Serous	0	5	10	15
Mucinous	2	1		3
Mixed			1	1
Endometrioid clear cell				
Endometriod			1	1
Malignant squamous teratoma			1	1
Mixed mesodermal			1	1
			Total	22

A 38-year-old patient had teratocarcinoma with a poorly differentiated squamous component of the teratoma with metastases to the small intestine. The involved segment of the small intestine was resected. One mixed mesodermal cancer of the ovary was included in this series.

All cases were reviewed to determine the amount of residual cancer at the time of the original operation. This information was obtained by telephone communication with the referring physician and careful review of operative notes and pathology reports. Cases with residual tumor nodules 2 cm or less were classified as surgically optimal. Cases with visible or palpable tumor nodules greater than 2 cm were classified as suboptimal.

All patients received at least ten courses of chemotherapy. With the availability of cis-platinum and reports of higher response rates in advanced ovarian cancer with cis-platinum in combination with other agents, the combination of cis-platinum, doxorubicin hydrochloride (Adriamycin), and cyclophosphamide (Cytoxan) was most commonly used in this series.[6,7] Cis-platinum was given, 50 mg/m^2 via 2-hour infusion with 12.5 mg mannitol preceded by overnight hydration. Adriamycin was given by rapid infusion, 40 to 50 mg/m^2 and Cytoxan, 500 mg/m^2 rapid infusion. This combination was repeated every 4 weeks. Adriamycin was discontinued after a total dose of 450 mg/m^2.

Only two patients received single agent alkylating chemotherapy. Melphalan (Alkeran) was given, 0.2 mg/m^2 orally on 5 consecutive days every 4 weeks. Cytoxan was administered via bolus infusion, 1000 mg/m^2 every 4 weeks.

Four patients received hexamethylmelamine, Adriamycin, and Cytoxan. Hexamethylmelamine was given orally, 4 mg/kg/day for 7 days; Adriamycin, 40 mg/m^2, day one and Cytoxan, 500 mg/m^2, day one. This combination was also repeated at 4-week intervals. Adriamycin was discontinued after 450 mg/m^2 were given.

The Adriamycin-Cytoxan combination was received by two patients at 4-week intervals. Adriamycin, 50 mg/m^2 and Cytoxan, 500 mg/m^2 were given intravenously. A total of 450 mg/m^2 of Adriamycin was given.

Vincristine, Adriamycin, and Cytoxan were administered to both patients with nonepithelial cancers. The patient with mixed mesodermal cancer received vincristine, 1.5 mg/m^2 intravenously weekly for 6 weeks, then in combination with Adriamycin, 45 mg/m^2, and Cytoxan, 400 mg/m^2 intravenously at 4-week intervals. The patient

with teratocarcinoma received vincristine, 1.5 mg/m^2 weekly for 12 weeks; Adriamycin, 50 mg/m^2 every 4 weeks for nine times; and Cytoxan, 500 mg/m^2 every 4 weeks for nine times. Following completion of Adriamycin, 450 mg/m^2, the patient continued to receive Cytoxan and actinomycin-D, 0.5 mg intravenously daily for 5 days; 500 mg/m^2 intravenously on day one, until a total of 12 courses of chemotherapy had been administered.

Results

Twelve patients, the largest group, received cis-platinum, Adriamycin, and Cytoxan chemotherapy (*Table 3*). Seven patients had suboptimal disease and four had Stage IV; two had pulmonary nodules and two had positive cytologic findings in the pleural fluid. The effectiveness of this combination chemotherapy becomes evident when only three of seven suboptimal cases had residual cancer at second look. All of the suboptimal patients represent complete clinical responses, since none had clinical evidence of disease before reexploration. Macroscopic disease refers to visible or palpable residual cancer, and microscopic disease refers to disease proved by histologic section on random biopsy. All patients with negative findings are living and well except one who died of brain metastasis 11 months after negative abdominal exploration. The others are living and well 3 to 14 months after surgery. Four patients with residual cancer are alive. Three have received additional chemotherapy. The only patient with palpable disease has received two courses of Platinum-Cytoxan and two courses of Platinum-Velban. One of the four patients with positive findings at second-look operation had one positive microscopic section in the residual omentum, and because no adhesions were present she received 15 mCi P^{32} intraperitoneally postoperatively. P^{32} was not used in the other three patients

Table 3. Ovarian carcinoma treated with platinum, Adriamycin, Cytoxan

Patient	No. courses	Stage	Class	Findings	Status
1	12	III	Subopt.	Negative	NED 6 months
2	11	IV	Subopt.	Positive (macro)	NED 3 months
3	11	III	Subopt.	Positive (macro)	Persistent disease 4 months
4	12	III	Opt.	Negative	NED 6 months
5	11	IV	Opt.	Negative	NED 11 months
6	12	III	Subopt.	Negative	NED 6 months
7	14	III	Opt.	Negative	NED 14 months
8	12	IV	Opt.	Negative	NED 11 months
9	4 PAC 8 HAC	IV	Subopt.	Negative	NED 5 months
10	11 PAC 7 HMM Cytoxan	III	Opt.	Positive (micro)	NED 11 months
11	6 PAC 6 Adriamycin-Cytoxan	III	Subopt.	Negative	Died 11 months (Brain met.)
12	11	III	Subopt.	Positive (macro)	NED 2 months

NED = no evidence of disease; PAC = platinum, Adriamycin, Cytoxan; HAC = hexamethylmelamine, Adriamycin, Cytoxan; HMM = hexamethylmelamine.

Table 4. Ovarian carcinoma treated with Adriamycin, Cytoxan

Patient	No. courses	Stage	Class	Findings	Status
13	12	III	Optimal	Negative	NED 36 months
14	12	IIC	Optimal	Positive (micro)	NED 17 months

Table 5. Ovarian carcinoma treated with hexamethylmelamine, Adriamycin, Cytoxan

Patient	No. courses	Stage	Class	Findings	Status
15	12	IIB	Optimal	Negative	NED 7 months
16	12	III	Optimal	Negative	NED 6 months
17	13	III	Subopt.	Positive (micro)	NED 6 months
18	12	IIC	Optimal	Negative	NED 15 months

Table 6. Ovarian carcinoma; chemotherapy—single agent

Patient	Agent	No. courses	Class	Stage	Result	Status
19	Alkeran	10	Optimal	IIC	Negative	NED 34 months
20	Cytoxan	12	Optimal	IIB	Negative	NED 12 months

because of macroscopic disease and adhesions. Only one patient with surgically optimal disease had microscopic residual cancer indicating that maximum tumor reduction at initial surgery may be important.[8, 9]

Both patients receiving Adriamycin-Cytoxan are living and well (*Table 4*). The one patient with positive microscopic residual cancer received nine courses of Platinum-Cytoxan after second-look operation and is without clinical evidence of cancer 8 months later. She did not undergo a third-look laparotomy. The M.D. Anderson Hospital series indicates that a third-look procedure is not indicated for positive microscopic findings for patients who undergo second-look operations.

The evaluation of hexamethylmelamine, Adriamycin, and Cytoxan is shown in *Table 5*. The one patient with suboptimal disease had residual microscopic disease and is receiving Platinum-Cytoxan chemotherapy. She has no palpable disease at 6 months.

Both patients receiving single-agent therapy had negative findings at second-look operations (*Table 6*). Single alkylating agents are presently used only in Stage I or early Stage II epithelial cancers with favorable grade.[8]

Vincristine, Adriamycin, and Cytoxan chemotherapy proved effective in patients with both the mixed mesodermal carcinoma and teratocarcinoma, since both are clinically free of disease 12 months after reexploration with negative findings.

Cytologic washings were positive only in cases with positive biopsies. One patient with macroscopic disease (paraaortic node) did not have positive washings. The one patient with a single microfocus

Table 7. Ovarian carcinoma; positive second look

Patient	Agent	Class	Positive biopsy	Cytology
2	PAC	Subopt.	Anterior peritoneum, cul-de-sac, serosa of cecum (macro)	Positive
3	PAC	Subopt.	Omentum, mesentery, diaphragm, gutter (macro)	Positive
10	PAC	Optimal	Microfocus omentum	Negative
12	PAC	Subopt.	Paraaortic node (macro)	Negative
17	HAC	Subopt.	Cul-de-sac, diaphragm (micro)	Positive
14	AC	Optimal	Round ligament, cul-de-sac (micro)	Positive

of residual cancer in an omental remnant also had negative cytologic findings.

Table 7 shows the site of positive biopsy at the second-look operation. Two of these patients who underwent operation had visible or palpable disease in an area that could be visualized by laparoscopy. Therefore, preceliotomy laparoscopy would have spared only two patients from definitive laparotomy.

Discussion

Reasons for a second-look operation: (1) The patient has had ten or more courses of chemotherapy and clinically is free of disease. (2) An upstaging procedure is done for reliably staging the patient when sufficient biopsies or thorough exploration were not accomplished at the first operation. (3) Original unresectable tumor masses respond to chemotherapy and can be removed. (4) A suspected tumor mass serving as a guide during chemotherapy becomes suspected as something other than a neoplastic mass.

The second-look operation is not a simple laparotomy but a well-planned systematic operation. If cancer is found, the findings are carefully documented and future treatment may be modified. If disease is not apparent, a complete sampling is done of the peritoneal cavity, the pathway by which ovarian carcinoma spreads.

If the patient is free of cancer, chemotherapy is discontinued. In this study metastases developed in only one patient who had been free of cancer at second-look operation. The patient died. Patients with residual cancer should continue chemotherapy. Patients with microscopic disease receive six to nine courses of Platinum-Cytoxan chemotherapy. P^{32} given intraperitoneally can be considered if there are no adhesions and the disease is microfocal. If cancer is found, as much as possible should be removed. In vitro tumor cell culture with drug sensitivities may then be used to modify future chemotherapy.[10]

Summary

Twenty-two patients with advanced ovarian carcinoma were studied by a second-look operation after chemotherapy. None of the patients had clinical evidence of cancer before the procedure. All patients had received at least ten courses of chemotherapy after an initial laparotomy, at which time as much tumor as possible was removed. The second-look procedure was done to determine whether chemotherapy should be continued. Sixteen patients had no microscopic or cytologic evidence of disease and had discontinued chemotherapy. The type of chemotherapy received, findings at laparotomy, and treatment of patients with residual cancer are discussed.

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