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Localized Ovarian Cancer: Surgery plus Chemotherapy

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Abstract—*Fifty-four patients were referred to Medical Oncology after operation for "limited" ovarian cancer; 7 were excluded because immediate restaging showed evidence of macroscopic spread to structures outside the true pelvis, and 10 will be considered separately because of microscopic spread shown only by cytology.*

Thirty-seven patients (31 stage I and 6 stage II) were accordingly accepted as "localized", because peritoneal cytology and diaphragm and omental plus parietal peritoneum histology could rule out the spread to the large abdominal cavity. Some of the referred patients had been operated in nearby hospitals; the Padua GYN Cin. performed 14 of the 37 first surgery operations and 30 of the 37 second look operations.

All patients soon after surgery underwent first-line chemotherapy with 5 courses of high dose adriamycin plus cyclophosphamide for 4 months, then surgical second look, and second-line non-cross-resistant chemotherapy for 3 months.

During the second look the organ and tissue removal was completed in those 21 patients having received "limited" first surgery.

Two patients died within 5 years from admission, so that the overall 5 year actuarial survival from referral is 93% for the entire group with 11 patients still at risk; 87% are disease free 5 years after the second look with 7 at risk.

Subdivision of the patients according to "adequate" vs. "limited" first surgery, may select a group (the "adequate" one, composed of 16 patients) completely free from relapses, up to now.

The complex therapeutic program described seems to offer long term relapse-free survival to the majority of patients, while the few failures seem closely related with inadequacies of the initial surgical procedure.

INTRODUCTION

EPITHELIAL ovarian tumors occur primarily in adult women, are frequently bilateral, and have a high incidence of diaphragmatic metastases (11–23%), a frequent involvement of pelvic and paraaortic nodes (12–60%), positive cytology in peritoneal washings (13–22%); and omental infiltration has also been frequently shown [1].

Accordingly, most patients with ovarian cancer are treated only at an advanced stage of disease and this is probably the cause of the high overall mortality rate: this tumour indeed is the major killer among the gynecological malignancies.

Conversely a cure is frequently obtainable in truly early stages; here surgery is the mainstay of therapy, but additional postoperative treatment with chemotherapy or radiotherapy is usually applied even in stage I and II of the disease [2–4].

Stage I, although credited with a favorable prognosis, still shows 12–45% of surgically treated patients relapsing within 5 years [5–6].

Several factors may influence the recurrence rate, such as: (a) age of the patient, (b) extent of the first surgery, (c) histologic type, (d) histologic grade, (e) type of adjuvant treatment.

(a) Youth is associated with a better prognosis [7], while the reasons for this behaviour are obscure [8].

(b) In relation to the type of primary surgical treatment we must recall that only a very thorough procedure may reveal occult involvement of paraaortic lymph nodes, or tumor on the undersurface of the diaphragm, grafting of esfoliated cells onto the peritoneal cavity, or omental involvement; and each one of this findings will deeply influence survival [9–11].

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The actual spread of disease is often underscored at first surgery: in a study of the Ovarian Cancer Study Group, (NCI; M.D. Anderson; Mayo Clinic; Roswell Park Memorial) 50 patients with stage I or II ovarian cancer, described as free of postoperative residual malignancy, underwent surgical restaging after referral to the above Institutions, within 2 months of first surgery [9].

Local residuals were found in 5% of these 50 patients, paraaortic lymph node metastases in 15%, omental metastases in 7% and pelvic lymph node metastases in 12%. A total of 24% of the 50 women, described as disease free after initial surgery, were found to have microscopic disease at the restaging laparotomy.

(c) Regarding histology; clear cell type is associated with earlier relapse and mortality [13].

(d) Some studies have shown that tumor grade is inversely related to survival, although the types of postoperative treatment and the sites of failure were not fully analyzed [14, 15]. Only a few patients with stage I carcinoma bearing high-grade tumor have been reported [16, 17] and such condition may have a more ominous prognosis than the favourable stage would indicate [5].

In patients with stage I ovarian carcinoma, subgroups with poor prognostic features may be identified.

Webb *et al.* found 5-year survival possible for 90% patients with tumor confined to the ovary, 68% for patients with capsular invasion, 56% if the tumor had ruptured by the time of surgery, and 51% if the tumor adhered to (but did not invade) non-gynecological pelvic structures [18].

Cytological evidence of peritoneal disease or presence of ascitic fluid also negatively influence survival [6, 11, 19].

Regarding the sites of relapse and modalities of relapse prevention, Dembo has conducted a randomized study in 54 women with ovarian cancer stage IA; the 9 observed tumor relapses where randomly distributed between the "observation only" group and the group receiving 4.500 cGy pelvic radiation in 20 fractions [20].

This suggests that even in stage IA, the entire peritoneal cavity is at risk for relapse (when relapse occurs) and pelvic irradiation does not reduce the overall risk of relapse. The peritoneal site of most relapses after complete "pathological" remission has been shown in one of our previous reports [21].

PURPOSE OF THIS REPORT

We wish to present here a retrospective analysis of 47 patients with stage I and II carcinoma of the ovary, identifying especially the group of 37 really "localized" ones (stage I and II a and b), undergoing adriamycin and cyclophosphamide treatment as an adjuvant to operation, in a sequential non-randomized series. A separate discussion for 9 patients in stage I c will be attempted (+1 II c). Chemotherapy has already been reported by Hreshchyshyn *et al.* [4] as an effective adjuvant to surgery, comparing favourably with radiotherapy also for Ovarian Cancer Stage I.

MATERIALS AND METHODS

(a) Referral

Between January 1979 and March 1985, 54 patients having "limited" ovarian cancer were referred to the Department of Medical Oncology of the Padua General Hospital and/or to the GYN clinic, Padua University. The median age was 52 years (range 18–72). All patients had been submitted before chemotherapy to midline umbilicopubic incision, salpingo-oophorectomy (SO) and/or total abdominal histerectomy (H).

(b) Exclusions

Excluded from the study were patients who had already received radiotherapy or chemotherapy as well as patients affected with impairment of renal and/or hepatic function, heart failure, or other conditions preventing the completion of treatment or follow-up, and patients with a second tumor other than skin cancer.

No patient had "visible tumor" when beginning chemotherapy except 2 stage IIb patiens with single minimal deposits.

(c) Restaging and grouping

In 21 of the 54 patients all or some of the surgical procedures required for accurate staging (Table 4) had been omitted during the first operation, and in these an attempt to complete the pathological staging was performed with echo- and CT-scan, plus laparoscopy: (with random biopsies of the diaphragm, omentum, peritoneum; also some mesenteric lymph node specimen was obtained, besides saline washing for peritoneal cytology). 7 patients were upgraded to stage III at laparoscopy and will not be further discussed here; of the remaining 47 accountable patients, 40 were assigned to stage I, of which 9 were Ic, and 7 to stage II (1 to IIc).

The "c" patients (stages Ic+IIc) are consequently 10 patients with microscopically evidenced peritoneal spread, and these will be analyzed separately, being the survival curves of this report restricted to the truly "localized" 37 patients, of which 31 stage I and 6 stage II.

There were 13 patients with grade 3 (or undifferentiated) tumors, of which 5 in the serous papillary type and 4 in the endometrioid group. Moreover 10 patients had grade 2 tumors.

Table 1. Distribution of tumors by epithelial cell type and grade, stage 1 and 2

	Total	Borderline	1	2	3
Cell type					
Serous tumors	21	1	9	6	5
Mucinous tumors	13	2	7	3	1
Endometrioid tumors	10	—	5	1	4
Clear cell tumors	—	—	—	—	—
Undifferentiated carcinoma	3	—	—	—	3

Table 2. Stage by grade in 47 patients

	Borderline	1	2	3
1Ai	—	1	2	—
1Aii	2	13	4	5
1Bi	—	1	—	1
1Bii	—	—	2	—
1C	1	4	2	2
2A	—	2	—	2
2B	—	—	1	1
2C	—	1	—	—
Total	3	22	11	11

The quality and amount of chemotherapy had been the same for all patients throughout the study while the quality and extent of first surgery was variable as described below.

In 16 patients the initial surgical procedure was considered "adequate", having removed all the internal genitalia, the appendix, the omentum, and obtained sample biopsies of the retroperitoneal lymph nodes, of the diaphragm and of the peritoneum; for these patients accordingly the stage was accepted as I in 14 and II in 2. Further details regarding stage subcategories, histology (cell type) and histological grading are described in Tables 1 and 2.

The pathology was reviewed in all patients, and each tumor was categorized as to cell type and grade using the WHO classification [16].

(d) Treatment

Within 1 month from surgery, the patients received chemotherapy with adriamycin, (55 mg/m^2) and cyclophosphamide (1200 mg/m^2) every 21 days, times 5; the same chemotherapy was applied in the groups with "adequate" or "limited" first surgery: they were evaluated for gastrointestinal toxicity, bone marrow damage, peripheral neuropathy, nephrotoxicity, cardiac efficiency, local damage to tissues from adriamycin injection (Table 3). All the patients have been exposed to ACy chemotherapy as previously described; only two patients had a dose reduction for both drugs, because of moderate heart disease. No long-term side-effects of chemotherapy have been observed until now.

(e) Follow up

Frequent clinical follow up (every 3 months) was based on physical examination, serum alkaline phosphatase, lactic dehydrogenase (LDH) carcinoembryonic antigen (CEA), fibrinogen dosage, colposcopy plus colpocytology plus abdominal echotomography.

Table 3. Ovarian cancer stage 1 and 2

	Toxicity from Chemotherapy (evaluated acc. NCOG)				
	0	1	2	3	4
Nausea and vomiting	38	2	13	16	2
Alopecia	0	4	1	6	60
Neuropathy					
Nephrotoxicity					
Allergy	70	1	0	0	0
Local toxicity	67	1	1	2	0
Infection	64	2	4	1	0
Cardiac	68	3	0	0	0
Hematologic toxicity*	25	3	10	7	2

*Every patient with Hb or WBC or PLT drops has been accounted for as "toxic"; the higher degree of her toxicity has been expressed in this table. For instance a patient with no drop of hemoglobin and white blood cells, but with a grade 2 platelet fall has been plotted as grade 2 toxic. Platelet and hemoglobin drops were uncommon (4 and 5 cases, respectively) while WBC nadirs of 1.000/mm or less were observed in 9/47 patients.

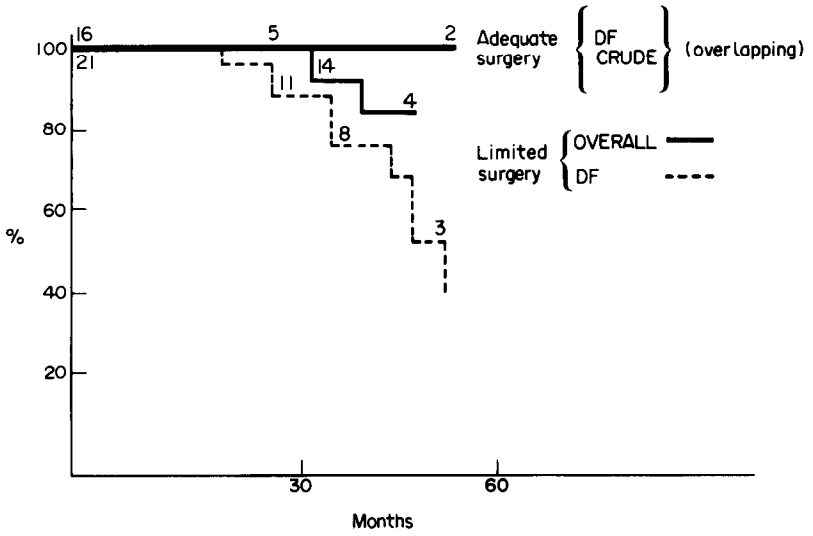

Fig. 1. *Survival for stage* 1A, 1B, 2A, 2B.

Patients were fully evaluated as disease-free-to-follow-up after a full assessment inclusive of laparoscopy and peritoneal washings, computerized axial tomography and echotomography and chest X-rays; this reassessment was performed regularly at 12, 40 and 60 months. The median follow-up has been 40 months (range 2–78).

RESULTS

(a) Fate of the 37 truly localized patients

The total overall survival for the entire group of 37 patients was 93% at 36 months (S.E. ± 0.047; 19 pts still exposed to risk) and 93% at 5 years (11 exp to risk). The disease free survival (dfs) is 84% at 36 and 60 months with 15 and 7 patients at risk respectively, (S.E. of 0.074: the risk was calculated from first surgery for overall survival and from the second look for dfs).

The actuarial disease free survival in the group of 16 patient with "adequate" first surgery is 100%; at risk at 60 months however are only 2 patients from this group; no relapse has occurred up to now in this "adequate initial surgery" series (Fig. 1).

In the group of 21 women with "limited initial surgery" the percentage of disease free survival is 77% at 38 months with 8 patients at risk (S.E. = 0.012) and 40% at 60 months, with 3 patients at risk (S.E. = 0.017) (Fig. 1). Overall survival at 34 months is 93% (S.E. = 0.064) with 14 at risk and S.E. = 0.064.

The 21 patients (stages I and II) of the group with "limited" first surgery may be subdivided as follows: 9 women underwent BSOH, 6 underwent BSOH and appendectomy (3 of whom had been previously exposed to appendectomy for acute inflammation), 1 underwent omentectomy with bilateral salpingo-oophorectomy, 2 had partial omentectomy and BSOH, 1 other patient was submitted to total omentectomy and right salpingo-oophorectomy as results from Table 4. All these patients after the first surgery just described received the combination of adriamycin and cyclophosphamide, followed by a surgical second look; during the second operation the first line surgery was completed with total omentectomy and/or appendectomy, and/or total abdominal hysterectomy, and/or salpingo-oophorectomy on the residual organs and tissues.

Table 4. *Stage by first surgery*

Type of surgery	Total	1Ai	1Aii	1Bi	1Bii	2A	2B
Adequate (BSOH total omentectomy, appendectomy	16	2	11	1	1	1	—
Limited:	21	1	13	1	1	3	2
BSOH	9	—	5	1	—	3	2
BSOH, appendectomy	6	—	5	—	1	—	—
BSOH, total omentectomy	1	—	1	—	—	—	—
BOSH, partial omentectomy	2	—	2	—	—	—	—

In conclusion the second-look surgery was not only exploratory but integrative of the first surgical operation.

Nonethelesss treatment failures occurred only in patients undergoing "limited" initial surgery: the relative weight of initial surgery clearly overwhelms any later attempt to complete the procedure.

The toxicity of the Acy regimen is acceptable (Table 3).

Distribution of histology and grade is not statistically different in the subgroups that may be obtained stratifying for "adequate" versus "limited" surgery; cell type and grade are detailed in Tables 1 and 2. One patient with a mucinous tumor of borderline malignancy, stage Ic, has relapsed in the peritoneal cavity 37 months after pathological complete remission. The two relapsing Ic patients had been submitted to "limited" first surgery plus chemotherapy as usual and second look inclusive of radical omentectomy.

The outcome of localized stage I and II with adequate first surgery and adjuvant chemotherapy, should also be compared with the survival of "c" patients and especially 9 stage Ic patients undergoing exactly the same treatment.

In this group however chemotherapy should not be considered "adjuvant" but "therapeutic" for the presence of cytologically positive ascites. All but 2 showed pathologically confirmed complete remission after the first line-chemotherapy at second look with random biopsies and never relapsed (Fig. 1); 2 of the stage Ic patients did not respond to the Acy regimen, and actually one of these has relapsed in the peritoneal cavity 15 months after reaching complete remission with the second line chemotherapy inclusive of hexamethylmelamine and cis-diamino-dichloroplatinum; the other obtained a complete remission after the combination of fluorouracyl + platinum and has not relapsed up to now.

The influence of initial surgery has been analyzed separately in order to exclude the effect of an irregular distribution of histological grade between the "adequate" and "limited" surgery groups. In the "adequate" group, (exempt from relapses) there were 4 patients with grade 3 and 3 pts with grade 2 tumors: that is 6 high grade on a total of 16 pts. In the "limited" surgery group there have been 4 relapses, in patients of grades 1; 1; 2 and 3, while the 3 year disease free survivals in this group have been 4/5 for grade; 4/6 for grade 2 and 5/7 grade 1. From this profound analysis it becomes clear that poor initial surgery is a risk factor also for low grade tumors, and that high grade tumors may not recur provided all the treatment sequence is very accurate.

DISCUSSION

Very accurate and extensive surgery may provide a group of patients with "localized" stage I and II: this group has a rather good postoperative prognosis, but more than 20% of them may be expected to relapse within 2 years, if submitted to surgery alone. Applying aggressive chemotherapy to 16 such patients, we have observed no relapse up to now, after a 26 month median observation, and with 2 patients still at risk at 5 years.

In a contemporary series of 31 patients undergoing suboptimal primary surgery (that is ablative surgery, with omitted omentectomy or random biopsies or removal of an apparently healthy controlateral adnexum) despite the attempted completion of staging through laparoscopy and despite application of the same postoperative chemotherapy, the relapse rate at 3 and 5 years is 56%. It seems that the policy of completing staging with laparoscopy and providing organ removal at second-look surgery has not succeeded in preventing the "loss of probability of cure" caused by a "less thorough" first surgical operation.

Two reasons may account for this undue relapse rate: (a) less careful patient selection; (b) larger residual tumor burden. No data are at present available to clarify the independent contribution of these two factors: the importance however of a "complete" first line surgery is indisputable.

It is clearly possible that a larger removal of "tissues at risk" may reduce the invisible burden of tumor cells to the abdomen of the patient, increasing the chances of a "total kill" of the tumor from chemotherapy, but it cannot be easily proven.

Conversely we may admit that a procedure capable of identifying the "true" stage I and II tumors with no residuals is the only and unique opportunity to detect those patients who do not need so aggressive and costly procedures as second-look surgery and second line non-cross-resistant chemotherapy.

The only firm conclusion to be drawn until now is that a first line surgery of very high quality and extent is an irreplaceable prerequisite for previewing a long disease free survival.

A second statement could be that aggressive, short term chemotherapy after appropriate initial surgical management, may reduce near to zero the five year relapse rate for truly localized stage I and II ovarian cancer, whatever the "grade" or aggressiveness of the tumor; further confirmatory studies are, however, needed on this point.

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