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Survival After Second-look Laparotomy in Advanced Ovarian Epithelial Cancer

Study of 86 Patients

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Abstract—*Second-look laparotomy (SLL) was performed after chemotherapy in 86 patients with advanced epithelial ovarian cancer. Seventy-one patients received cisplatin-based regimens. Median follow-up was 66 months. Negative SLL was found in 32 patients who had a 5-year survival rate of 48.3% after SLO. Microscopic residual disease was present in seven patients whose 5-year survival rate was 35.7%. Maximum residual tumor of 2 cm or less was found in 13 patients with a 5-year survival rate of 30%. Residual tumor larger than 2 cm after secondary cytoreduction was present in 20 patients; their 3-year survival rate was 19.7%. Fourteen patients with bulky residual disease who did not have cytoreduction were all dead within 17 months. Patients with initial residual tumor at first laparotomy <2 cm had a nearly significant advantage in survival rate over patients with residual disease >2 cm and stage IV (P = 0.07). Non-responders to initial chemotherapy had a survival rate similar to that of partial responders.*

These findings justify discontinuation of conventional systemic chemotherapy for patients showing residual disease after SLL and secondary tumor removal in case of residual tumor at SLL. Therapeutic trials are needed in advanced ovarian cancer testing initial aggressive surgery or early debulking to avoid bulky residual disease, and consolidation therapy in patients who achieved complete pathological response or minimal residual disease.

INTRODUCTION

SECOND-LOOK LAPAROTOMY (SLL) in advanced epithelial ovarian cancer has been performed to stop chemotherapy when negative, to remove residual cancer and to plan further treatment when positive [1]. SLL appears to be necessary because clinical evaluation is too inaccurate, more than half of the patients clinically disease-free having persistent disease at SLL [2–5].

However, a negative SLL does not always mean a cure. Recent reports have shown that half of the patients who had a negative SLL died of their disease [6]. This demonstrates the need for further treatment in this situation. Furthermore, in some reports, patients macroscopically disease-free but with microscopic disease at SLL had a similar survival rate to that of patients with negative SLL [6–8]. These findings question the importance of demonstrating a negative SLL.

This study was done to evaluate the survival rate and prognostic factors in patients according to SLL results and to evaluate the value of secondary cytoreductive surgery.

PATIENTS AND METHODS

This retrospective study included 86 patients who had advanced ovarian epithelial cancer eligible for second-look laparotomy from March 1976 to February 1986. Median follow-up time was 66 months.

Patients were FIGO stage III or IV and stratified according to residual tumor after initial laparotomy: (1) all macroscopic lesions were removed; (2) largest residual tumor was 2 cm or less; (3) largest residual tumor was more than 2 cm.

SLLs were performed in patients initially treated

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with systemic chemotherapy and considered as clinically disease-free through regular physical examination which included normal chest X-ray and normal abdomino-pelvic echography or scanner.

The SLL procedure consisted of median laparotomy, biopsies of any suspicious lesions, systematic multiple biopsies of peritoneum and peritoneal washing in case of negative macroscopic findings. In cases where residual disease was found a maximum cytoreduction was performed.

Negative SLL was defined as the absence of residual disease, proven by negative biopsies and peritoneal washing. Complete response (CR) was defined as a negative SLL in patients with residual disease at first laparotomy. Partial response (PR) was defined as a decrease of at least 50% in the sum of the products of the diameters of measurable lesions. Stable disease (SD) was defined as a decrease not reaching 50% or an increase of less than 25% and progressive disease (PD) was defined as an increase of no less than 25%.

Patients were also classified according to residual disease after SLL: (1) negative SLL; (2) microscopic residual disease; (3) largest residual tumor 2 cm or less after cytoreduction; (4) maximum residual tumor >2 cm in patients in whom cytoreduction was performed; (5) maximum residual tumor >2 cm in patients who could not have tumor removal.

Characteristics of the patients are summarized in Table 1. The mean interval between initial and second-look laparotomy was 8.9 ± 3.6 months. The results and details of initial chemotherapy have been previously described [9, 10]. Briefly, patients who received doxorubicin–cisplatin had SLL after nine monthly courses; those in the sequential cisplatin–doxorubicin and in the hexamethylmelamine–5-fluorouracil–doxorubicin–cisplatin groups after six courses; and most of the remaining patients at 12 months.

Ten of 32 patients with negative SLL continued therapy after SLL, three received systemic chemotherapy and seven reeived three courses of intraperitoneal chemotherapy. Therapy was completed in other patients. All 54 patients with residual disease continued on salvage therapy: alkylating agents (33 patients), cisplatin-based regimens (15), other chemotherapy regimens (five), radiotherapy (one). Abdominal and pelvic radiotherapy was associated with chemotherapy in three patients. Relapses after

Table 1. *Characteristics of the patients*

Number	86
Mean age	55.1 years S.D. 9.6 (range 29–78)
Stage	
III	68
III microscopic disease	1
III residual mass <2 cm	25
III residual mass >2 cm	37
III residual mass not specified	5
IV	18
Performance status (WHO)	
0	21
1	30
2	9
3	4
Not specified	22
Histology	
serous	51
mucinous	1
endometrioid	5
mixed	5
brenner	1
undifferentiated	23
Initial chemotherapy	
AP	36
PAC	21
HFAP	10
Other with cisplatin	4
Without cisplatin	15

AP: doxorubicin–cisplatin: PAC: cisplatin–doxorubicin–cyclophosphamide:

HFAP: hexamethylmelamine–5-fluorouracil–doxorubicin–cisplatin.

CR were treated with cisplatin-based regimens (eight patients) or alkylating agents (eight) or cyclophosphamide–doxorubicin–5-fluorouracil (one).

Survival was measured in months from second-look until February 1988 and curves established according to Kaplan and Meier. Comparisons were made using the log-rank test.

RESULTS

Second-look laparotomy

Negative SLL was observed in 32 patients (37.2%) and microscopic residual disease in seven patients (8.1%). After SLL, 13 patients (15.1%) had residual disease 2 cm or less; 20 patients (23.3%) had residual disease larger than 2 cm after surgical cytoreduction; and 14 patients (16.3%) had residual mass larger than 2 cm and could not have cytoreduction. Complete pathological response was found in 31 evaluable patients. Partial responses to chemotherapy were observed in 24 patients (27.9%) and stable or progressive disease in 30 (34.9%). Twenty-three patients remained with bulky residual disease (larger than 2 cm) after SLL when initial stage was IV or initial residual mass >2 cm (41.8%); and eight when initial mass was <2 cm (30.7%). The difference was not significant (log-rank = 0.91).

Survival after second-look

Survival was calculated according to restaging based on residual disease after SLL. Survival curves are presented in Fig. 1. The 5-year probability of survival from SLL was 48.3% when SLL was negative, 35.7% when residual disease was microscopic and 30.1% when residual disease was <2 cm (from diagnosis, respectively 49, 35.7 and 34.8%). Median survival was 36 months in patients with negative SLL, 21 months with microscopic residual disease and 26 months in residual disease <2 cm. Differences were not significant. The entire group of 52 patients with negative SLLs or residual disease <2 cm had a 5-year survival rate of 42% and a median survival of 32 months (from diagnosis, 43.5% at 5-year, median survival 43 months). Three-year and 5-year survival rates were respectively 19.7 and 0% in patients with residual mass >2 cm and 0% in patients who could not have tumor removal. Median survival was 17 months in patients with residual mass >2 cm and only 10 months when no cytoreduction was performed.

Differences in survival after SLL were significant among patients with negative SLL or residual mass <2 cm and residual mass >2 cm ($P = 0.001$); among patients with negative SLL or residual mass <2 cm and patients who could not have surgical cytoreduction ($P = 10^{-7}$); and among patients with residual mass >2 cm and patients who could not have surgical cytoreduction ($P = 0.001$).

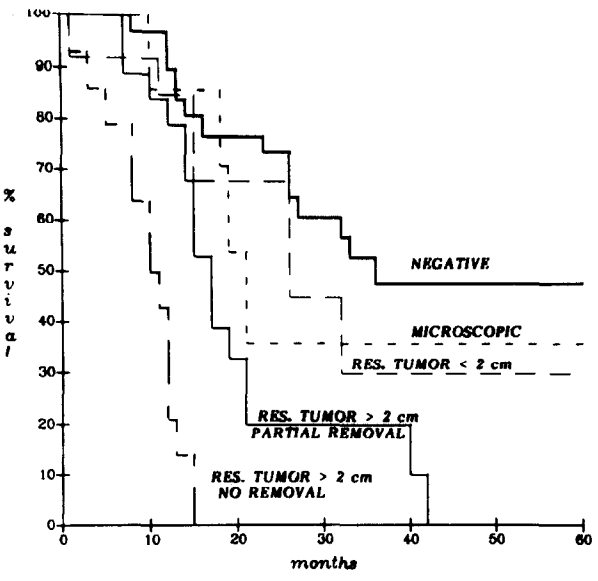

Fig. 1. Survival according to findings at second-look laparotomy in advanced ovarian epithelial cancer

Prognostic factors

The main prognostic factor was residual disease after SLL as previously shown. The prognostic value of diagnostic features and response to chemotherapy have also been studied in patients with identical findings.

In patients with negative SLL or residual mass <2 cm, age at diagnosis and serous or non-serous histology were not prognostic factors. An initial residual mass at first laparotomy <2 cm indicated a better survival rate than stage IV or residual disease >2 cm with an almost significant difference ($P = 0.07$). Survival rates were similar in partial and non-responders to initial chemotherapy.

In patients with bulky residual disease, age and serous or non-serous histology had no prognostic value. An initial residual mass at first laparotomy <2 cm again had a better survival rate than stage IV or residual disease >2 cm with an almost significant difference ($P = 0.10$). The survival rate was also similar in partial and non-responders to initial chemotherapy. These results are shown in Table 2.

DISCUSSION

Negative SLL in advanced ovarian cancer after systemic chemotherapy, including cisplatin, is achieved in 20–40% of patients [9, 11–16]. However, negative SLL does not mean a cure; 5-year survival after negative SLL ranges from 42 to 80% (Table 3). Our results and Neijt's are similar, with a 5-year survival after SLL of 42 and 48%. Such a survival rate after negative SLL is disappointing. Residual disease in relapsing patients could persist either inside or outside the abdomen, limiting the value of SLL.

Table 2. Prognostic factors at second-look laparotomy in patients with advanced ovarian cancer

	n	Median survival (months)	χ^2	*P*
Residual tumor at SLL				
None or <2 cm	52	32	10.46	0.001
>2 cm after tumor removal	20	17	12.25	0.001
>2 cm without tumor removal	14	10		
Residual mass <2 cm *at SLL*				
Residual mass <2 cm at first laparotomy	18	Not reached	3.35	0.07
Residual mass >2 cm at first laparotomy	32	26		
Age <55 years	27	36	0.18	NS
Age >55 years	25	27		
Serous	35	32	0.06	NS
Non-serous	13	32		
Partial response	17	26	0.983	NS
No response	6	Not reached		
Residual mass >2 cm *at SLL*				
Residual mass <2 cm at first laparotomy	8	15	2.78	0.07
Residual mass >2 cm at first laparotomy	23	12		
Age <55 years	15	14	0.10	NS
Age >55 years	19	14		
Serous	16	12	1.94	NS
Non-serous	18	15		
Partial response	8	14	0.01	NS
No response	26	11		

NS: non significant.

Table 3. Survival after second-look laparotomy in patients with advanced epithelial ovarian cancer in complete pathologic response

n	Percentage survival 3-year	5-year	Median follow-up (months)	Initial stage	Consolidation therapy	Reference
85	90	80	—	75% III <2 cm	—	[2]
41	55	42	60	—	Systemic	[6]
30	78					[7]
20	90					[7]
17	93		<60	100% III		[11]
12	65	65	—	—	6/12 IP	[12]
63	85	72	—	—	—	[17]
17	85					[18]
45	70		<42	7% IIB, IIC 78% III, 15% IV	21/45 Radiotherapy	[19]
32	48.3	48.3	66	40% III <2 cm 60% III >2 cm IV	10/32	Present study

IP: intraperitoneal chemotherapy.
Survival rates after SLL has been evaluated from survival curves.

In our experience, which corroborates that of others [6, 8], survival in patients with macroscopic residual disease or minimal residual disease is not significantly different from survival in patients with negative SLL. In the literature (Table 4), median survival ranges from 12 to 60 months in patients with minimal residual disease. The small number of patients in each study and differences in prognostic factors can explain such a large variation. A difference in therapy could also explain this variation. However, in most studies systemic chemotherapy or total abdominal radiotherapy was continued after SLL [15, 22–25].

Residual disease with mass >2 cm in diameter

Table 4. Survival after second-look laparotomy in patients with minimal residual disease

n	Percentage survival 3-year	median (months)	Initial stage	Reference
Microscopic residual disease				
9	20	16		[3]
13	70	60		[6]
11	47	31		[7]
5	50	19		[7]
50	80	—	80% III <2 cm	[8]
13	27	30		[11]
39	43	24	—	[17]
6	45	34		[18]
7	35.7	21	33% III <2 cm	Present study
Larger residual mass 2 cm *or less in diameter*				
36	28	24		[17]
12	5	20	(mass <1.5 cm)	[20]
14	(64) follow-up 15.5 months	(48)	Partial (<2 cm)	[21]
13	30.1	26		Present study

Table 5. Survival after second-look laparotomy in patients with bulky residual disease

n	Percentage survival 3-year	median (months)	Surgery	Reference
11	0	5	None	[3]
14	10	19	Partial	[11]
23	8	12	Partial	[17]
14	25	15	None	[17]
20	0	5	Partial (>1.5 cm)	[20]
13	0	11	Partial	[21]
20	19.7	17	Partial	Present study
14	0	10	None	Present study

means a poor survival rate (Table 5), with a median survival between 5 and 12 months. However, in our experience patients did benefit from even a limited surgical cytoreduction. Similar findings have been recently reported [21].

While residual disease after SLL is usually the main prognostic factor [26, 27], this study points to two other factors which it is also important to consider for optimal management of ovarian cancer. The first is residual disease after initial laparotomy. Whatever the situation after SLL, negative, minimal residual disease or bulky residual disease, there is a survival advantage in patients with no residual disease or tumor <2 cm at first laparotomy over patients with residual tumor >2 cm or stage IV. Relapses have been more frequently found after negative SLL in patients with bulky residual disease at first laparotomy [2, 17]. The impressive survival after negative SLL in the series of Gersherson *et al.* [2] could be, for the most part, attributed to a large proportion of patients (75%) with negative SLL or residual tumor <2 cm, against only 40% in our study. The importance of a minimal residual tumor mass left after initial therapy can be resolved either by aggressive initial surgery as suggested [28] or by an early surgical cytoreduction after one to three courses of chemotherapy in patients with bulky residual disease as performed by some authors [16].

The second factor is the response to initial therapy. In our experience, achieving a partial response to initial chemotherapy is not a good prognostic factor for survival after SLL compared to stable and progressive disease. Goldhirsh *et al.* recently published identical findings [19]. Second-line systemic chemotherapy after failure of a cisplatin-based regimen has no proven efficacy and cannot explain the poor results in partial responders. In another study, the best survival was found in a subset of patients who were non-responders to initial therapy [22]. This observation supports the hypothesis of two different evolutive patterns in ovarian cancer: (1) some cancers demonstrate early chemotherapy resistance and a slow rate of growth; (2) other cancers respond to chemotherapy for a rela-

tively short duration and exhibit a secondary chemotherapy resistance with a fast growth rate if complete pathologic response has not been achieved. The results presented here do not justify continuing conventional systemic chemotherapy after SLL, even in the case of PR.

Management of advanced ovarian cancer can be optimized from the experience in SLL: Initial aggressive surgery or early debulking surgery in the case of a residual tumor >2 cm should be performed to avoid bulky residual disease. Patients with negative SLL should receive consolidation therapy to reduce the relapse rate. Intraperitoneal chemotherapy needs to be evaluated in this situation and in the case of minimal residual disease. High doses of cytotoxic drugs in contact with residual cells or tumors have shown interesting results in patients resistant to conventional chemotherapy [29, 30]. Other alternative procedures are intensive systemic chemotherapy and abdominal radiotherapy which appears to be controversial [15, 24, 25]. After SLL partial responders should not be maintained on the same first-line regimen.

Even limited surgical cytoreduction should be considered at SLL if bulky residual disease is present in order to prolong survival.

In our opinion, the goals of SLL, in advanced ovarian cancer, should move away from the original ones. Negative SLL is no longer a valuable indicator to stop chemotherapy. Being an important prognostic factor, residual disease at SLL must be carefully measured. Indication of SLL should be extended to all patients who could also benefit from secondary tumor removal. Patients with minimal residual disease limited to the peritoneal cavity could benefit from intraperitoneal chemotherapy.

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