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Analysis of failures and clinical outcome of advanced epithelial ovarian cancer in patients with microscopic residual disease at second-look reassessment following primary cytoreductive surgery and first-line platinum-based chemotherapy

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Summary

Aim: to assess the pattern of failure and survival of advanced ovarian cancer patients with microscopic residual disease at second-look following cytoreductive surgery and platinum-based chemotherapy. *Materials and Methods:* Nine-five women were retrospectively analyzed. Residual disease after initial surgery was > one cm in 58 (61.1%) patients, first-line chemotherapy was paclitaxel/platinum-based in 70 (73.7%) patients, second-look findings showed no macroscopic residuum but positive random peritoneal biopsies and/or positive washing ("true" microscopic residual disease) in 79 (83.2%) patients, and a macroscopic residuum which was completely resected (converted complete response) in 16 (16.8%) patients. *Results:* Eight-one (85.2%) patients developed recurrent disease after a median time of 14 months (range four to 51). The abdomen (29.6%) and the pelvis (28.4%) were the most common sites of failure. Two- and five-year survival after second-look were 78.1% and 31.0%, respectively. The clinical and pathological features with prognostic relevance at presentation (age, histotype, and tumor grade), as well as type of first-line chemotherapy and treatment after second-look were not related to the clinical outcome. There was a trend for a better survival in patients with optimal primary cytoreduction compared with those with suboptimal primary cytoreduction (five-year survival = 42.7% vs 23.4%). There was no significant difference in survival between the converted complete responders and the patients with "true" microscopic residual disease. *Conclusions:* These data confirm the unsatisfactory clinical outcome of patients with microscopic residual disease after first-line chemotherapy and the limited benefit of second-look reassessment.

Key words: Epithelial ovarian cancer; Surgical cytoreduction; Chemotherapy; Second-look surgery; Survival.

Introduction

Epithelial ovarian cancer is the leading cause of gynecologic cancer death in Western countries [1]. Survival is highly-dependent on tumor Stage. As far as patients with advanced disease are concerned, the International Federation of Gynecology and Obstetrics [FIGO] Annual report n. 26 showed that the five-year overall survival ranged from 46.7% for Stage IIIa, to 41.5% for Stage IIIb, 32.5% for Stage IIIc, and 18.6% for Stage IV [2]. Cytoreductive surgery followed by paclitaxel/platinum-based chemotherapy is the standard treatment for advanced disease, which is able to achieve a clinical complete response rate of 50% approximately, a pathological complete response rate of 25%-30%, a median progression-free survival of 15.5 to 22 months, and a median overall survival of 31 to 44 months [3-6]. Almost 75% of the clinically complete responders and 30% to 50% of pathologically complete responders will ultimately relapse after a lead time of 12.5 to 52.5 months [6-12]. Most recurrences develop within the initial two years. Advanced stage, high grade, and large residual disease after initial surgery are strong predictors of recurrence in complete responders [7, 9-12]. Further limited data are currently available for the clinical outcome of patients with microscopic residual disease, i.e. with positive random biopsies and/or positive cytological washing at second-look reassessment [13-22].

The aim of this retrospective investigation was to assess the pattern of failure and the survival rates of advanced epithelial ovarian cancer patients with microscopic residual disease at second-look laparotomy or laparoscopy following primary cytoreductive surgery and first-line platinum-based chemotherapy.

Materials and Methods

This retrospective study was conducted in 95 patients: i) who underwent primary cytoreductive surgery followed by platinum-based chemotherapy for advanced epithelial ovarian cancer at Departments of Gynecology and Obstetrics of the University of Pisa and Brescia between 1985 and 2011 and at the Department of Gynecologic Oncology of the European Institute of Oncology of Milan between 1996 and 2003; ii) who underwent a second-look laparotomy or laparoscopy after the

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completion of chemotherapy; and iii) who had no macroscopic residuum but positive random peritoneal biopsies and/or positive peritoneal washing ("true" microscopic residual disease) at second-look, or who had a macroscopic residuum which was completely resected during the second-look (converted complete response). Patients who underwent neoadjuvant chemotherapy followed by interval debulking surgery were not included in the present analysis.

The hospital records, including surgical notes and pathological reports of the 95 women, were collected using a common form with standardized items and a common database. Some of these patients had been enrolled in phase II multicenter Italian study (After-6 Protocol 2) aimed to assess the efficacy of weekly 60 mg/m^2 paclitaxel as maintenance treatment in patients who had microscopic residual disease after six cycles of paclitaxel/platinum-based chemotherapy [22].

At presentation, tumor Stage and histological diagnosis were determined according to FIGO criteria and the histological typing system of the World Health Organization (WHO), respectively. Tumors were graded as well (G1), moderately (G2), or poorly (G3) differentiated. The histological material was reviewed by the same pathologists in each center. Additional therapy after second-look was given according to local protocols, and changed at the long-term interval of the study.

The evaluation of the course of disease was based on clinical examination, serum CA 125 assay, chest X-ray, abdominal-pelvic ultrasound, and/or computed tomography (CT) scan. Further investigations were performed where appropriate.

An asymptomatic patient with rising CA125 levels and negative clinical and imaging examinations was no longer considered to have recurrent disease and underwent a more stringent follow-up program.

The median follow-up of survivors was 74 months (range 8 to 137).

Statistical methods

The SAS statistical package (release 8.2) was used for computations. The time from second-look surgery to death or last observation was defined as survival after second-look. The analysed prognostic variables included patient age, histological type, tumor grade, residual disease after initial surgery, first-line chemotherapy (paclitaxel/platinum-based chemotherapy vs other), second-look findings ("true" microscopic residual disease vs converted complete response), and treatment after second-look (platinum-based chemotherapy vs weekly paclitaxel vs other). Survival analyses were performed according to the Kaplan-Meier product-limit method. Differences between groups were evaluated by the log-rank test.

Results

Patient characteristics at initial diagnosis are summarized in Table 1. Median age was 53 years, FIGO Stage was IIIC in 82 (86.3%) cases, histological type was serous in 72 (75.7%) cases, tumor grade was G3 in 64 (67.3%) cases, and residual disease was > one cm in 58 (61.1%) cases. First-line chemotherapy consisted of paclitaxel/platinum-based regimens in 70 (73.7%) cases. Second-look reassessment was performed by laparotomy in 42 (44.2%) and by laparoscopy in 53 (55.8%) cases. Second-look findings showed a "true" microscopic residual disease in 79 (83.2%) cases, and a converted complete response in 16 (16.8%) cases. Nine-two (96.8%) patients received additional chemotherapy .

Table 1. — *Patient characteristics.*

Variable	Patients: 95
Age (median, range)	53 years (range 31 to 82)
FIGO Stage	
IIIA-IIIB	5
IIIC	82
IV	8
Tumor grade	
G1	3
G2	28
G3	64
Histological type	
Serous	72
Endometrioid	9
Mucinous	0
Clear cell	2
Undifferentiated	4
Mixed	7
Carcinosarcoma	1
Residual disease after first surgery	
0-1 cm	37
> 1	58
First line chemotherapy	
Platinum-based non taxane-combination	16^
Single-agent platinum	9
Paclitaxel + platinum-based CT	70^^
Second-look findings	
"True" microscopic residual disease	79
Converted complete response	16
Treatment after second-look	
Chemotherapy	92
Platinum-based non taxane-combination	13*
Single-agent platinum	7
Paclitaxel + platinum-based CT	12**
Weekly paclitaxel (up to 21 cycles)	31
Other agents	29***
No treatment	3

^Carboplatin + gemcitabine, 1; platinum + cyclophosphamide ± doxorubicin or epidoxorubicin, 15.
^^Paclitaxel + carboplatin, 61; paclitaxel + cisplatin, 5; docetaxel + carboplatin, 2; Ifosfamide + paclitaxel + cisplatin, 2.
*Platinum + topotecan, 4; platinum + doxil, 5; platinum + cyclophospha-mide ± doxorubicin or epidoxorubicin, 4 **.
**Paclitaxel + carboplatin, 11; paclitaxel + cisplatin, 1.
***Doxil, 4; topotecan + doxil, 1; doxorubicin or epirubicin, 7; paclitaxel, 13; unknown, 4.
G_1: well-differentiated; G_2: moderately-differentiated; G_3: poorly-differentiated.

Nine patients did not develop recurrent disease and were still alive after a median time of 37 months (range 9 to 114) from second-look, five patients died due to intercurrent disease with no evidence of recurrent tumor after a median time of 29 months (range two to 84), and 81 (85.2%) patients developed recurrent disease after a median time of 14 months (range four to 51). The abdomen (29.6%) and the pelvis (28.4%) were the most common sites of recurrent disease (Table 2).

Treatment at recurrence consisted of chemotherapy in 62 patients, surgery plus chemotherapy in 16 patients (with additional radiotherapy in one patient), and best supportive case in three patients.

Among the 81 relapsed patients, 69 died after a median

Table 2. — *Sites of first recurrence after second-look surgery.*

Sites	Patients (n, %)
Pelvis	23 (28.4%)
Abdomen	24 (29.6%)
Retroperitoneal nodes	13 (16.0%)
Distant sites *	10 (12.3%)
Multiple sites **	11 (13.6%)

* pleura, 1; axillary nodes, 1, liver + spleen 1; liver 4; liver + pleura 1; lung 1; SNC 1; **abdomen + pelvis 3; pleura + abdomen 1; pelvis+retroperitoneal nodes 1; pelvis + retroperitoneal nodes + abdomen 2; pelvis + liver 2; abdomen + retroperitoneal nodes, 1; abdomen + sovraclavicular nodes, 1.

Table 3. — *Survival of patients with microscopic residual disease after second-look.*

Variables	Patients	Two-year OS	Five-year OS	*p* value
Whole series	95	78.1%	31.0%	
Patient age				
≤ 53 years	48	85.0%	28.5%	0.455
> 53 years	47	71.1%	34.0%	
Histological type				
Serous	72	80.9%	37.4%	0.058
Not serous	23	69.6%	11.6%	
Tumor grade				
G_1-G_2	31	79.2%	39.7%	0.089
G_3	64	77.5%	26.8%	
Residual disease after first surgery				
0-1 cm	37	74.5%	42.7%	0.127
> 1 cm	58	80.4%	23.4%	
First-line chemotherapy				
Platinum/paclitaxel-based	70	77.0%	32.0%	0.526
Platinum non-paclitaxel-based	25	82.1%	28.4%	
Second-look findings				
"True" microscopic residual disease	79	76.4%	29.3%	0.472
Converted complete response	16	86.7%	39.3%	
Treatment after second-look				
Platinum-based chemotherapy*	32	77.4%	19.7%	0.455
Weekly paclitaxol	31	76.8%	33.4%	
Other	32	88.3%	39.6%	

*Platinum-, non-paclitaxel based, 13; platinum- and paclitaxel based, 12; single-agent platinum, 7.
OS: overall survival; G_1: well-differentiated; G_2: moderately-differentiated; G_3: poorly-differentiated.

time of 17 months (range two to 51) from recurrence, seven were still alive with clinical evidence of disease after a median time of 22 months (range two to 98), and five were still alive with no clinical evidence of disease after a median time of 39 months (range 30 to 91).

Two- and five-year overall survival rates after second-look were 78.1% and 31.0%, respectively (Table 3). There was a trend for a better survival for patients with optimal primary cytoreduction (macroscopic residual disease ≤ one cm after initial surgery) and microscopic residual disease at surgical re-evaluation compared with those with suboptimal primary cytoreduction and microscopic residual disease at surgical re-evaluation (five-year survival = 42.7% vs 23.4%). There was no significant difference in survival between the converted complete responders and the patients with "true" microscopic residual disease.

Discussion

Carboplatin plus paclitaxel is the standard regimen for advanced epithelial ovarian cancer able to achieve a clinical complete response in approximately 50% of the cases [3-6]. Second-look laparotomy or laparoscopy has long been used for the reassessment of disease status in clinically complete responders. However, this surgical procedure has been less and less employed in the last decade due to its limited clinical benefit. Two randomized trials failed to detect a survival advantage with second-look, although both studies had drawn criticism for their design or for the chemotherapy regimen used [23, 24]. More recently, a non-randomized comparison, using an explanatory analysis of the optimally debulked women enrolled in the Gynecologic Oncology Group (GOG) 152 trial, confirmed that the performance of a second-look laparotomy was not associated with longer survival [25]. At second-look reassessment, only 50% of clinically complete responders are in pathological complete response, whereas 15% have a microscopic residual disease, and 35% have a subclinical macroscopic residuum [26]. Approximately, 30%-50% of pathologically complete responders will ultimately relapse [6-12], and consolidation treatments with intra-peritoneal [27] or systemic [28-31] chemotherapy, immunotherapy [32], whole abdomen irradiation [17], and intraperitoneal phosphorus (P^{32}) [33] do not improve the prognosis of these patients. The management and the clinical outcome of women with microscopic residual disease after second-look represent an even more debated problem, and different therapeutic modalities have been tested with uncertain results [13-22]. Whole abdomen irradiation has been largely used, with five-year overall survival rates ranging from 29% to 66% [15, 17, 19, 21]. Intraperitoneal ^{32}P or systemic and/or intraperitoneal chemotherapy have obtained conflicting, inconclusive, and generally disappointing results [14, 16, 18, 20]. For instance, Spanos *et al.* [14], who administered intraperitoneal ^{32}P to 52 patients with Stage III epithelial ovarian cancer after second-look surgery, reported a five-year survival of 75% for the 23 pathologically-complete responders, 48% for the 15 patients with microscopic residual disease, and 32% for the 14 patients with macroscopic residual disease. McCreath *et al.* [20] reviewed 262 clinically complete responders who had persistent disease after second-look surgery and who further received systemic and/or intraperitoneal chemotherapy. Median survival ranged from 5.9 years for the patients with optimal primary cytoreduction (macroscopic residual disease ≤ one cm after initial surgery) and microscopic residual disease after second-look, to 3.4 years for those with suboptimal primary cytoreduction and microscopic residual disease after second-look, to 2.1 years for those with suboptimal primary cytoreduction and macroscopic residuum after second-look ($p < 0.001$), and no salvage chemotherapy regimen was associated with a survival advantage. A Swedish-Norwegian study reported a five-year survival of 40.5% for the women who had microscopic residual disease after four cycles of first-line epidoxorubicin/ plat-

inum-based chemotherapy and who underwent six additional cycles of the same regimen as maintenance treatment [17].

In the present study, 81 (85.2%) of the 95 patients developed recurrent disease after a median time of 14 months from second-look, and the abdomen and the pelvis were the most common sites of failure. Among the 81 relapsed patients, 69 (85.2%) died after a median time of 17 months from recurrence. Two- and five-year survival rates after second-look were 78.1% and 31.0%, respectively. The clinical and pathological features with prognostic relevance at presentation (age, histological type, tumor grade), as well as type of first-line chemotherapy and treatment after second-look, were not related to the clinical outcome. In agreement with the data of McCreath *et al.* [20], there was a trend towards a better survival for the patients with optimal primary cytoreduction when compared with those with suboptimal primary cytoreduction (five-year survival = 42.7% vs 23.4%). These data confirm the unsatisfactory clinical outcome of patients with microscopic residual disease after first-line chemotherapy, and the limited benefit of second-look reassessment. Nonetheless, it is noteworthy that patients with a macroscopic residuum, which was completely resected during second-look, had the same survival of those with no macroscopic residuum but positive random peritoneal biopsies and/or positive peritoneal washing. Similarly, in a GOG study including women with persistent epithelial ovarian cancer at second-look, no difference in survival was detected between the 29 patients who had microscopic disease and the 36 patients who had macroscopic residuum and who were surgically cytoreduced to microscopic disease [34].

Attempts to improve the prognosis of patients with advanced epithelial ovarian cancer should be addressed to the identification of both new first-line regimens able to obtain higher complete response rates and effective treatments to consolidate or maintain the response achieved by first-line chemotherapy [35]. The good results obtained with the addition of bevacizumab during and after carboplatin- and paclitaxel-based chemotherapy appear to offer new interesting perspectives for the treatment of these patients and to further reduce the role of second-look surgery [36, 37].

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