EJGO European Journal of Gynaecological Oncology

Evaluation of residual tumor locations in advanced ovarian cancer patients after incomplete primary cytoreduction

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Summary

Background: Nowadays complete primary cytoreduction can be achieved in a large number of patients suffering from advanced ovarian cancer. However, there is a group of patients in whom complete tumor resection remains impossible. The authors analyzed the intraoperative limiting factors in patients with residual tumor after primary surgery treated in the present institution. *Materials and Methods:* Patients with advanced epithelial ovarian cancer (FIGO Stage IIIB-IV), who underwent primary incomplete surgery in the present institution between 2006 and 2008 were included in this study. Patients' records were evaluated regarding to intraoperative findings and final surgical results. *Results:* The authors identified 39 eligible patients in their registry. Twenty-six (66.7%) patients underwent surgery with residual tumor < 1 cm and 13 (33.3%) ≥ 1 cm. The most frequent location of residual tumor limiting complete surgery was disseminated bowel carcinomatosis in 34 (87.2%) patients. Moreover significant differences in tumor residuals locations and operative time between patients with residuals < 1 cm and ≥ 1 cm were reported ($p < 0.05$). *Conclusions:* The most frequent reason for incomplete primary cytoreduction remains disseminated carcinomatosis. However, in patients with residuals under one cm, its frequency is significantly higher. The complication rate is comparable in patients independently of residual tumor < 1 cm and ≥ 1 cm. Therefore the cytoreductive efforts should be made even in primarily not completely operated patients in order to achieve residuals under one cm.

Key words: Primary ovarian cancer; Advanced ovarian cancer; Incomplete cytoreduction.

Introduction

Ovarian cancer is the leading cause of death due to gynecologic malignancies in the United States and the European Union [1, 2]. The majority of patients with ovarian cancer are diagnosed in advanced stage of disease [3]. The completeness of primary cytoreduction is the single most important prognostic factor for the outcome in advanced ovarian cancer [4-6]. Median overall survival of 99.1 months in patients with complete resection compared to 29.6 months for patients with residuals of more than one cm in diameter were reported [5].

A substantial number of cancer patients receive sub-standard treatment incompatible with current guidelines [7]. Comprehensive surgery for advanced ovarian cancer requires a high degree of specialization, appropriate skills, and an optimized infrastructure, which are often not available outside of gynecologic oncology centers [7-9]. The rate of optimal debulking surgery resulting in macroscopic complete resection remains very heterogeneous between institutions, and incomplete cytoreduction is a common situation. A quality assurance program in Germany has shown that on national level approximately 40% of ovarian cancer patients are operated with remaining lesions of more than one-cm diameter [10, 11] that corresponds to international data [12]. Several studies in gynecological oncology centers showed that quality-control programs can increase the percentage of macroscopic complete resection during primary surgery to over 65% and < 1 cm residual tumor to 90% or more [6, 13-14]. The best prognosis was observed in completely operated patients. However, even tumor mass reduction to residuals under one cm in advanced ovarian cancer cases showed prognostic impact [5, 6, 15].

The authors analyzed the intraoperative limitations for complete tumor resection in advanced ovarian cancer patients treated at the Department of Oncology, Division of Gynecologic Oncology, Poznan University of Medical Sciences in Poland.

Materials and Methods

All consecutive patients with invasive epithelial ovarian cancer, treated in Department of Oncology, Division of Gynecology, Poznan University of Medical Sciences in Poland between 2006 and 2008 were considered for enrolment. Eligibility criteria included primary diagnosis of advanced epithelial ovarian cancer FIGO Stage IIIB-IV and primary macroscopic incomplete cytoreduction. Patients who received neo-adjuvant chemotherapy were excluded. Further exclusion criteria included recurrent disease, non-epithelial ovarian neoplasm or borderline tumors.

Revised manuscript accepted for publication October 15, 2014

Table 1. — *Perioperative findings in studied patients.*

Criterion		Number	Percent (%)
FIGO Stage	IIIC	37	94.9
	IV	2	5.1
Histological type	Serous	36	92.3
	Endometrioid	2	5.1
	Clear-cell	1	2.6
Grading	G1	4	10.3
	G2	10	25.6
	G3	23	59,0
	n/a	2	5,1

Table 2. — *Outcome of surgery performed in this center.*

Criterion	Number	Percent (%)
< 1 cm in diameter	26	67
≥ 1 cm in diameter	13	33
Location of residual tumor		
Intestines/mesentery	34	87.2
Lymph nodes	20	51.3
para-aortic	14	35.9
pelvis	6	15.4
Liver (capsule, hilus)	10	25.6
Spleen (capsule, hilus)	8	20.5
Others (stomach, pancreas)	6	15.4

Gynecological examination, vaginal ultrasound, and additional radiological imaging were standard diagnostic procedures prior to planned surgery.

The patients' individual records were reviewed and the following information was abstracted: age at the time of surgery, operative findings, residual disease at the completion of the procedure, blood loss, final pathologic diagnosis, and postoperative complications. The primary surgeon in all cases was a gynecologist oncologist.

End point of the present study was the evaluation the residual disease locations after primary cytoreduction in advanced epithelial ovarian cancer patients. All other statistical analyses were performed using SPSS 18.0.

Results

Ninety-six patients treated at the Department of Oncology, Division of Gynecology, Poznan University of Medical Sciences were considered for inclusion in the present study. Twenty-six early ovarian cancer cases FIGO Stage I-IIIA were directly excluded. Among 70 patients with advanced ovarian cancer FIGO Stage IIIB-IV, five women received neo-adjuvant chemotherapy initiated by an outside institution and therefore were excluded. Complete primary cytoreduction could be achieved in 26 (37%) of those patients inclusive all FIGO Stage IIIB patients. Finally, 39 patients (aged 39 - 86, median 65 years) met the aforementioned criteria and were enrolled in the study. Twenty-six (67%) of studied patients underwent the surgery with residuals < 1 cm and 13 (33%) ≥ 1 cm in diameter.

Table 3. — *Outcome of surgery with regards to postoperative tumor residuals.*

Criterion	Residuals < 1 cm (%)	Residuals ≥ 1 cm (%)	*p*
Location of residual tumor regarding to performed surgery			
Intestines/mesentery	24 (92.0%)	10 (77.0%)	< 0.05
Lymph nodes	9 (34.6%)	11 (84.6%)	< 0.05
para-aortal	7 (26.9%)	7 (53.8%)	< 0.05
pelvis	2 (7.7%)	4 (30.8%)	< 0.05
Liver	4 (15.4%)	6 (46.1%)	< 0.05
Spleen	3 (11.5%)	5 (38.5%)	< 0.05
Others (stomach, pancreas)	3 (11.5%)	3 (23.1%)	< 0.05
Complications	3 (11.5 %)	1 (7.7%)	> 0.05
Postoperative bleeding	1 (3.8%)	0 (0.0%)	
Re-laparotomy	1 (3.8%)	0 (0.0%)	
Infection	1 (3.8 %)	1 (7.7%)	
Median blood loss (range) in ml	182 (100 – 300)	93 (20 – 200)	< 0.05
Median duration of surgery (range) in minutes	110 (90 – 165)	70 (35 – 120)	< 0.05

Thirty-four (87.2%) patients were in good performance status Eastern Cooperative Oncology Group (ECOG) 0 or 1 when five (12.8%) women were classified with ECOG 2.

The majority of patients (37 women) had FIGO Stage IIIC ovarian cancer and two women were classified as FIGO Stage IV due to malignant pleural effusion. However in both cases, no radiologic signs of pleural carcinomatosis were described (Table 1). Thirty-six (92.3%) patients had serous pathology, followed by mucinous – two (5.1%) and clear cell – one (2.6%). Grade was determined in 37 (95%) patients; among these, four (10.3%) had G1, ten (25.6%) had G2, and 23 (51.3%) had G3 (Table 1).

The most frequent localization of residual disease was bowel, followed by peritoneum, and para-aortic lymph nod es. Detailed localizations of residual tumor are presented in Table 2. Furthermore, the authors analyzed the residual tumor localization according to residual disease < 1 cm versus ≥ 1 cm. According to this subanalysis, they found differences in residual tumor localizations between both groups (Table 2). Although intestines remained the most frequent localization, in patients with residuals < 1 cm its frequency was significantly higher ($p < 0.05$). Involvement of para-aortic lymph nodes, liver and stomach was significantly higher in patients with residuals ≥ 1 cm ($p < 0.05$).

In five (12.8%) cases, patients' performance status limited complete surgery. Two (7.7%) and three (23.1%) cases in < 1 cm and ≥ 1 cm groups, respectively.

Statistically significant differences were identified between surgeries with regards to operative time. In patients with postoperative residuals ≥ 1 cm, surgery was significantly shorter in comparison to women with residuals < 1 cm ($p < 0.05$) (Table 3). Major postoperative complications

occurred in four (10.3%) patients (Table 3). The authors observed significantly higher incidence of postoperative complications in cases with residual tumor < 1 cm versus ≥ 1 cm, respectively, three (11.5%) and one (7.7%) ($p < 0.05$). No significant difference in hospital stay was reported. Patients with residuals under one cm required 8.1 (range 6 – 12) days hospitalization and patients with residuals > one cm, 7.3 (range 5-10) days.

Discussion

Postoperative tumor-mass remains the most important prognostic factor in ovarian cancer patients. The current data shows that patients treated in specialized gynecological oncology departments more frequently receive treatment according to guidelines [11]. Furthermore, recent studies showed significantly higher incidence rate of residual tumor in non-specialized departments, which could have been removed during reoperation in gynecological oncology centers [16, 17]. Nevertheless, in substantial number of patients, complete cytoreduction remains not possible, even in specialized units.

At the time of the present study, primary cytoreduction with residuals under one cm was an established optimal operative treatment in advanced ovarian cancer cases. Even thought complete tumor resection constituted substantial number of operated cases [6, 8, 18]. Altogether, the optimal surgery in ovarian cancer patients reaches 80% [18]. Results from the present center correspond with international data in regard of the surgery completeness [6, 8, 18].

In the present study the authors analyzed only not pretreated patients with advanced ovarian cancer. Thirty-nine patients had residual tumor after primary surgery and among those, majority (74%) with residuals under one cm. Analogically to available data, a disseminated bowel and/or mesenteric carcinomatosis was the most frequent limiting factor for complete cytoreduction in studied patients [18]. Aletti *et al.* [18] reported that patients' performance status, carcinomatosis, and surgeon are independent factors associated with optimal residual disease. In the present study, five patients due to performance status could not be completely operated. Furthermore, bowel involvement was the most frequent localization of residual tumor, as well as the main reason for incomplete tumor resection indicated by the surgeons.

Subsequently, the authors performed a sub-analysis to evaluate the localizations of residuals regarding to postoperative size of the rest tumor, accordingly below and over one cm in diameter. Significant differences in frequency of residual tumor localization were observed. In the group of patients with residuals < 1 cm, a disseminated intestinal/mesentery tumor spread was significantly higher. Other localizations were significantly more frequent in the group with residuals ≥ 1 cm. Similarily, the operative times were significantly different. The authors presume that the differences result from intraoperative tumor spread and therefore estimated operability. Patients were classified as inoperable according to the assessment of abdominal cavity more quickly in those with residuals over one cm. Respectively in subgroup with residuals up to one cm in diameter, the main tumor mass appeared resectable and therefore the surgical efforts was reasonable. It is in accordance to patients' surgical documentation. Therefore, surgeon tendency to employ radical procedures differ with regards to intraoperative findings. Accordingly, the duration of surgery differed between both subgroups. Fotopoulou *et al.* [19] introduced in 2010 an intraoperative Mapping of Ovarian Cancer (IMO) based on evaluation of quadrants involved with carcinomatosis in order to evaluate the predictability of tumor resection. Tumor dissemination pattern and maximal tumor load were significantly different between complete and incomplete operated patients, with less extrapelvic tumor involvement in the first group. Tumor spread involving multiple abdominal quadrants was the major negative predictor for complete tumor resection in primary ovarian cancer patients. The most frequent residual tumor localization reported by Fotopoulou *et al.* was bowel/mesentery. This observation complies with postoperative findings in the present patients.

The present authors observed postoperative complications in 10.2% of patients, which is comparable with other authors [19 - 22]. Moreover, no difference in complication rate between patients with residuals < 1 cm and ≥ 1 cm were noticed. Although blood loss was significantly higher in patients that underwent optimal cytoreduction, median value of 182 ml remained acceptable for this kind of operation.

Although the frequency of complete cytoreduction in advanced ovarian cancer increases (10, 11), certain tumor localizations remain inoperable even by gynecologists oncologists. As a consequence, the prognosis of those patients is significantly worse. The exact assessment of abdominal cavity in specialized center results in a cytoreduction with residuals < 1 cm in majority of cases. This approach combined with acceptable complication rate has a positive impact on prognosis. Nevertheless, further investigation in a larger group of patients is needed.

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