

Predictive Factors in Relapsed Ovarian Cancer for Complete Tumor Resection

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Abstract. *Aim: The aim of this study was to identify predictive factors for complete tumor resection in patients with relapsed ovarian cancer. Patients and Methods: All patients with first relapse of ovarian cancer who underwent secondary cytoreduction at our center between September 2000 and April 2006 were evaluated according to a validated intraoperative documentation tool. Predictive factors were identified by logistic regression following the Cox regression model. Results: Overall, 177 consecutive patients (pts) were analyzed. The median age at first diagnosis was 55 years (range, 23-83 years). The complete tumor resection rate was 44.6%. Predictive factors that correlated with an adverse surgical outcome in terms of residual tumor were ascites <500 ml (Odds ratio, OR=0.3; 95% Confidence interval, CI=0.1-0.8 $p<0.05$), tumor involvement of the small bowel (OR=0.22; 95% CI=0.07-0.71 $p<0.05$), tumor spread in the upper abdomen (OR=0.33; 95% CI=0.1-0.9 $p<0.05$) and platinum resistance (OR=0.1, 95% CI=0.06-0.5 $p<0.01$). Serous tumor histology (OR=5.8) appeared to have a protective effect. Age and initial FIGO stage were of no predictive significance. Conclusion: Platinum-sensitive patients without ascites, no intestinal tumor involvement, tumor restricted to middle and lower abdomen, and of serous papillary histology have significantly higher complete tumor resection rates. Prospective studies are warranted to evaluate the predictive value of these factors.*

Ovarian cancer is the fourth most common malignant disease among European women. It is the fifth most frequent cause of death in women (1) and in relation to the number of patients affected, the most common cause of death from gynecological malignancies (2). The majority of patients with epithelial ovarian cancer have advanced-stage disease at the time of diagnosis. Surgery with maximal cytoreduction before starting primary chemotherapy remains the standard of care for primary ovarian cancer (3). However, around 75% of advanced (stage III and IV) ovarian cancer patients will ultimately develop a recurrent tumor and will require further treatment (4).

The role and potential benefits of secondary cytoreductive 'surgery are currently one of the most debatable issues. Skepticism regarding secondary cytoreduction may arise because of less favorable prognosis of recurrent ovarian carcinoma, technical difficulty, development of chemotherapy and heterogeneous data concerning this surgical approach. Although several authors reported a survival benefit for patients who underwent secondary cytoreduction, it remains uncertain which patients with recurrent ovarian cancer are suitable for salvage surgery. In recent studies, only complete resection was associated with prolonged survival in recurrent ovarian cancer (5-7). The objective of the present study was to identify predictors of complete tumor resection in secondary cytoreductive surgery.

Patients and Methods

All women with histopathologically recurrent epithelial ovarian cancer (or peritoneal carcinoma) who underwent secondary tumor debulking surgery between September 2000 and April 2006 at the Department of Gynecology, Charité-Campus Virchow Klinikum were included in our systematic analysis.

For every patient, the detailed tumor pattern was intraoperatively assessed by an independent trained person as based on the surgical procedures performed and by systematic interview of the surgical

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team. Postoperatively, all histological findings and collected data were entered into a validated histopathological documentation system (Intraoperative Mapping of Ovarian Cancer, IMO), especially developed for ovarian neoplasms (8-11). Three IMO levels divided the abdomen into three spaces: level 1, lower; level 2, middle; and level 3, upper abdomen. Data were analyzed within Tumor Ovarian Cancer databank (www.TOC-Network.de), a clinical, multicentric and prospective tumor bank of ovarian cancer. In the databank, intraoperative data, histopathological and clinically relevant information for each patient were included. All relevant patient data including history, follow-up and survival data were abstracted from the patients' records. Survival data of the patients were updated based on patients' files and/or responses from their physicians or insurance company.

Age at first diagnosis was documented (≤ 60 vs. > 60 years). Tumor stage was according to the FIGO classification for epithelial ovarian carcinoma (1989) (12), tumor histology was documented by the Institute of Pathology from Charité University. Diffuse peritoneal carcinomatosis was defined as tumor nodules diffusely covering the majority of the surfaces of bowel serosa and the parietal peritoneum of the abdomen and pelvis. Diameter of residual tumor was assessed as macroscopic tumor free/ ≤ 0.5 cm/ ≤ 1.0 cm/ > 2.0 cm, and ascites as any ascites vs. ≤ 500 ml vs. > 500 ml. Sensitivity to platinum-containing cytotoxic agents was defined according to international criteria (clinical, radiographic, and serologic disease free interval of at least 6 months after primary adjuvant platinum-based chemotherapy, standard GOG criteria) (13). Postoperative survival was calculated in months from the date of surgery to the date of death or to the date of last follow-up.

Statistical analysis was performed using SPSS statistical software for Windows version 17.0 and 18.0 (SPSS Inc., Chicago, IL, USA).

Survival curves were estimated according to the Kaplan-Meier method. The multivariate Cox proportional hazards regression model was used to identify the relative importance of variables as independent predictors of complete tumor resection. Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for prognostic factors were estimated. Graphics were produced with SPSS program. All *p*-values less than or equal to 0.05 were considered as significant.

Results

A total of 177 operations on patients with first relapse of ovarian cancer were performed in the Virchow Clinic between September 2000 and April 2006. The median age at first diagnosis was 55 years (range, 23-83 years). The most prevalent histology was serous (88.2%), followed by endometrioid (4.7%), clear cell (2.4%) and mucinous histology (1.8%). The vast majority of the patients had tumor of an advanced FIGO stage III-IV (77.9%) at the time of primary diagnosis. Macroscopic tumor spread was present in 86.2% at level 1, in 79.9% at level 2 and in 64.9% at level 3. Eighty percent of patients had diffuse peritoneal carcinomatosis. Forty-six percent had no ascites at the time of surgery, 21.3% had \geq than 500 ml and 32.2% of patients < 500 ml. (98.9%). In 98.9% of patients, surgery for relapse was performed after treatment with chemotherapy. Among patients treated with previous chemotherapy, disease in 28.2% was considered

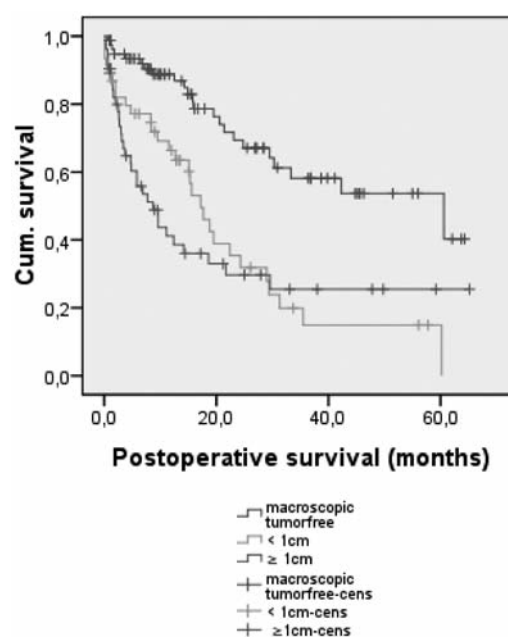


Figure 1. Overall survival according to tumor residual (tumor free, < 1 cm, ≥ 1 cm) in relapsed ovarian cancer.

platinum-resistant following GOG criteria and that in 67.8% of treated patients was platinum sensitive. In 7 (4%) patients, platinum sensitivity was not applicable because of non-platinum previous therapy or no therapy.

Secondary tumor debulking included the following procedures: hysterectomy (3.4%); bilateral salpingo-oophorectomy (4.0%); excision of retained omental tissue (33.3%); systematic lymphadenectomy (para-aortic and pelvic in 13.0%), pelvic lymph node dissection (5.6%) and para-aortic lymph node dissection (6.8%); small bowel resection (35.2%) and large bowel resection (42.4%). In 13.0% of patients, appendectomy was performed; in 56.1% a peritonectomy; 5.2% each underwent diaphragm resection and 4.6% partial stomach resection; 3.5% each underwent partial liver resection or splenectomy; 2.3% distal pancreatectomy; 2.9% partial bladder resection; 8.1% colostomy and 6.4% ileostomy.

The median operation time was 250 minutes (range, 23-719 minutes). It was possible to carry out complete tumor resection in a total of 79 patients (44.6%), while 46 patients (26.0%) had residual disease < 1 cm, and 52 (29.4%) had ≥ 1 cm intra-abdominal residual disease. A total of 37.2% of patients experienced non-surgical and surgical postoperative complications and 8.2% died within 30 days of surgery (perioperative mortality rate of 8.2%).

Impact on survival. The median disease free interval (PFS) was 8.4 months (range 0.0-55 months). At the time of last follow-up (available through December 2006), 51.4% of patients were alive, 47.5% had died and 1.1% had been lost

Table I. Prognostic factors of complete tumor resection in patients with ROC.

	<i>p</i> -value	HR	95% IC	
			Lower	Upper
Age >60 years (<i>vs.</i> age ≤60 years)	0.695	1.225	0.443	3.384
Ascites	0.077			
<500 ml	0.029	0.310	0.108	0.887
≥500 ml	0.178	0.383	0.095	1.549
Small bowel metastases	0.011	0.228	0.073	0.714
Large bowel metastases	0.424	1.667	0.476	5.835
Peritoneal carcinomatosis	0.680	0.710	0.139	3.619
Tumor in IMO-Level 1	0.592	0.660	0.145	3.010
Tumor in IMO- Level 2	0.167	0.338	0.072	1.577
Tumor in IMO- Level 3	0.048	0.337	0.115	0.992
Figo III-IV (<i>vs.</i> FIGO I-II)	0.683	1.341	0.328	5.486
Grade	0.182	0.234	0.028	1.975
Serous histology (<i>vs.</i> other histology)	0.026	5.891	1.235	28.101
Sensitivity	0.014			
Platinum-resistant (<i>vs.</i> Platinum sensitive)	0.004	0.188	0.060	0.587
Lymph node dissection performed (<i>vs.</i> no dissection)	0.128	2.274	0.789	6.556

to follow-up. The median overall survival (OS) of the entire cohort was 22.4 (95% CI=14.7-30.62) months. The median follow-up time was 10.8 (range 1.0-65.0).

When evaluating the impact of residual tumor on OS, highly significant differences ($p<0.001$) were seen: patients with complete tumor resection had an OS of 60.6 (21.3-99.8) months; patients with <1 cm residual tumor (optimal debulking) had an OS of 17.2 (13.0-21.3) months and those with ≥1 cm had an OS of 8.7 (4.1-13.2) months as illustrated in Figure 1. Classifying the patients according to their platinum sensitivity: the median OS of patients with platinum-sensitive disease at 30.3 (18.4-42.1) months was significantly longer than that of the patients with platinum-resistant disease, of 9.5 months (8.1-10.8, $p<0.001$). Other variables found in univariate analysis to have a statistically significant negative effect on postoperative survival in relapsed ovarian cancer were the presence of ascites, some tumor locations (tumor localization in level 2, mesentery, small bowel, abdominal wall and stomach), colostomy procedure and postoperative complications.

Factors predictive of complete tumor reduction. Variables examined as factors predictive of complete tumor reduction were: age, ascites, small bowel and large bowel metastasis, peritoneal carcinomatosis, tumor localization in levels 2 and 3, FIGO stage, grade, histological type, platinum-based chemotherapy response/sensitivity and systematic lymphadenectomy.

Multivariate analysis identified serous tumor histology as being the strongest independent prognostic factor for a complete tumor resection (HR=5.8 95% CI=1.2-28.1 $p<0.05$). Other independent predictors for not being macroscopic

tumor-free after surgery were ascites of less than 500 ml (OR=0.3; 95% CI=0.1-0.8, $p<0.05$), small bowel metastasis (OR=0.22; 95% CI=0.07-0.71, $p<0.05$), tumor spread in upper abdomen (OR=0.33 95% CI=0.1-0.9, $p<0.005$) and lack of platinum sensitivity (platinum-resistant OR=0.1 95% CI=0.06-0.5, $p<0.01$). No significant prognostic value was given by age >60 years, FIGO stadium (I/II *vs.* III/IV), grade (I, II *vs.* III), whether or not a lymph node dissection was performed. Data of the analysis are given in Table I.

Discussion

The role of primary cytoreduction in patients with epithelial ovarian cancer has been well studied and its impact on survival has been validated through various studies (3, 8).

Nevertheless, the role of secondary cytoreductive surgery is still not well defined. One of the first studies to systematically assess the value of secondary cytoreduction was published by Berek *et al.* more than 20 years ago. The authors demonstrated that patients who underwent optimaldebulking (defined as residual disease 1.5 cm) at the time of secondary cytoreduction had a median survival of 20 months compared to 5 months for patients who were debulked suboptimally (14). In a further study by Morris *et al.*, no survival benefit for secondary cytoreduction was found based on the analysis of 30 patients with recurrent ovarian cancer and a cut-off size of 2 cm for optimal debulking (15). In a follow-up study of 25 patients, Munkarah *et al.* also found no statistically significant benefit for secondary cytoreduction (16). The failure to demonstrate any prognostic impact on survival is most probably attributed

to the fact that in older studies 'optimal' tumor debulking was defined as residual disease less than 1 or 2 cm, and not as microscopic residuals. In all recent studies, secondary tumor debulking appears to have a significant effect on OS only in cases of complete macroscopic tumor resection (5, 8, 17 and 18).

In the present study, 44.6% of the women who underwent secondary cytoreduction were rendered visibly disease-free and reached a 5-year OS significantly longer than the patients with any microscopic tumor residuals.

As the value of cytoreductive surgery in patients with relapsed ovarian cancer is not yet clearly defined, patient selection remains arbitrary and depends on the individual center's preference, experience and attitude rather than on clearly established selection criteria. To date, few publications have focused on the selection criteria for cytoreductive surgery in recurrent ovarian cancer. In 1998, the II International Ovarian Cancer Consensus Conference suggested the following criteria for optimal candidates for secondary cytoreduction surgery: (i) disease-free interval >12 months, (ii) response to first-line platinum-based therapy, (iii) potential for complete resection based on preoperative evaluation, (iv) good performance status, and (v) younger age. However, this statement was based more on experts' opinions than on valid data (19).

The Descriptive Evaluation of Preoperative Selection Criteria for Operability in recurrent Ovarian cancer trial (DESKTOP OVAR) was undertaken to form a hypothesis for a panel of criteria to select patients who might benefit from surgery in relapsed ovarian cancer (5). The DESKTOP I trial was an exploratory study based on data from a retrospective analysis of hospital records. Twenty-five member institutions of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Committee (AGO OC) collected data on their patients who underwent cytoreductive surgery for relapsed invasive epithelial ovarian cancer performed between 2000 and 2003. A total of 267 patients were evaluated. The following variables were demonstrated to be associated with complete resection: FIGO stage at initial diagnosis (FIGO I/II vs. III/IV), performance status Eastern Cooperative Oncology Group (ECOG) 0 vs. >0, residual tumor after primary surgery (none vs. present) and absence of ascites >500 ml. These factors constituted the so-called 'AGO score', a predictive score for complete tumor resection in secondary tumor debulking. After a backward analysis, applied to the entire study population, the combination of performance status, early initial FIGO stage or no residual tumor after primary surgery, as well as absence of ascites was able to predict complete tumor resection in 79% of the patient collective.

The AGO score was subsequently prospectively evaluated in the DESKTOP II study (AGO-OVAR OP.2). The study collective consisted of patients with platinum-sensitive

recurrent ovarian cancer with a positive AGO score (PE ECOG 0, no residual tumor after primary surgery and ascites <500 ml), who underwent surgery with the aim of maximal cytoreduction. The goal of the study was to evaluate whether the retrospectively defined AGO score had predictive validity in a prospective multicentric setting. The DESKTOP II data were initially presented at the IGCS biennial meeting. In 412 platinum-sensitive patients screened, 193 patients were eligible for surgery, surgery with a positive AGO score. Of these, 127 patients underwent surgery and complete resection was achieved in 76%, undermining the validity of the retrospectively assessed AGO score in a prospective setting. In the subsequent, currently recruiting DESKTOP III trial, the AGO score will be tested in a randomized, multicenter setting.

The described OS in our study was, at 22.4 months, similar those previously described in the large prospective trials ICON4/AGO-OVAR 2.2 (20) and the Gynecologic Cancer Intergroup (GCIG) study AGO-OVAR 2.5 (21). These studies had median survival of 18 and 29 months, respectively. In most of the studies of cytoreductive surgery for recurrent ovarian cancer, median survival is not much higher than the ICON4/AGO-OVAR2.2 results (17, 22) but on average, series with more completely debulked patients exceed these results (5-6). The median postoperative survival of 60.6 months (95% CI=21.3-99.8) for patients left with no gross residual in our study is one of the longest reported for patients with recurrent ovarian cancer in the literature. In the recently published study by Benedetti Panici *et al.* median survival was also 61 months for patients who achieved optimal residual disease, defined as ≤ 1 cm maximal tumor diameter (18). However, the lack of randomized trials makes it impossible to conclude whether a more favorable outcome in series with high rates of complete debulking is attributed to biology (selection bias) or to surgical efforts.

Significant predictive factors identified in our study for complete tumor debulking in relapsed ovarian cancer were absence of ascites (<500 ml), no tumor in upper abdomen, no small bowel metastasis serous tumor histology and platinum sensitivity. A possible pitfall of our evaluation which should be referred to is the fact that we did not analyze the effect of patients' performance status and residual tumor after primary surgery. The fact that tumor dissemination in the upper abdomen and small bowel metastasis were associated with lower rates of complete tumor resection was possibly due to the wider tumor spread in this patient collective.

To conclude, we confirm that high complete tumor resection rates, associated with prolonged survival, are feasible in surgery for relapsed ovarian cancer. The aim of such surgery should be complete tumor resection, rendering optimal patient' selection criteria as being crucial in the field of secondary tumor debulking. According to our study,

patients with platinum-resistant disease with presence of ascites and/or wide tumor dissemination pattern in the relapsed setting do not appear to significantly benefit from secondary tumor debulking and may therefore be optimal candidates for others therapies, such as targeted agents. However, future prospective randomized trials are warranted to evaluate these findings.

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