Surgical Outcome and Survival Analysis of Young Patients with Primary Epithelial Ovarian Cancer*

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Abstract. Objective: The mean age of diagnosis of epithelial ovarian cancer (EOC) is in the mid-fifties. Limited data exist about the clinical outcome of patients aged below 35 years. The aim of the present study was to evaluate the cancer-related characteristics, intraoperative findings, surgical outcome and survival in this group of young women. Patients and Methods: Within the period between 01/1989 and 06/2008, all consecutive patients younger than 35 years with histologically proven EOC were enrolled into this study. All patients' characteristics, intraoperative and histological findings, as well as survival data were systematically analyzed using a validated prospective documentation tool for the intraoperative and postoperative data collection. Results: Thirty-one patients younger than 35 years at primary diagnosis (mean age: 28.65 years; range: 15-35) were identified among 397 patients with primary EOC (7.8%). FIGO-stage III (45.2%) was the most common tumor stage and serous-papillary (54.8%) was the most frequent histological type. A complete tumor resection was achieved in 18 patients (58.1%) with only few postoperative complications. In a mean follow-up period of 44.65 months, 9 patients (29%) died. Mean progression-free survival was 74.72 months (95% CI: 34.22-115.22), whereas mean overall survival was 148.15 months (95% CI: 91.63-204.68) and hence longer than the equivalent survival data of the total patient collective. Conclusion: Primary EOC in young patients (≤35 years old) seems to be associated with a higher overall and progression-free survival, higher platinum-sensitivity rate and a rather better clinical outcome than older patients. Further multicenter studies are warranted to evaluate the underlying reasons for these observations.

Ovarian cancer is the second most common gynecological malignancy, but the most common cause of death among women who develop gynecologic cancer (1). The lifetime risk of ovarian cancer in the general population of women is 1.4% and the age-adjusted incidence rate is 13.5 cases per 100,000 women, whereas incidence rates appear to have slightly decreased over the past 30 years (2). The mean age of diagnosis of epithelial ovarian cancer is in the mid-fifties (3). The incidence increases with age up to 80 years old and then declines. The overall risk of malignancy of an adnexal mass in premenopausal and postmenopausal women is 6-11% and 29-35%, respectively (4).

The optimal primary treatment of epithelial ovarian cancer (EOC) is considered to be radical cytoreductive surgery followed by a combination chemotherapy regimen with paclitaxel and platinum (5). It has long been reported that an advanced patient age is associated with a reduced surgical radicality including lower rates of bowel resection, which may explain the poorer outcome in elderly patients with advanced ovarian cancer (6, 7). Limited data exist about the tumor dissemination pattern, histological type distribution, surgical treatment and overall survival of epithelial ovarian cancer in women aged below 35 years (8). The present study was conducted in order to further evaluate the clinical picture and course of EOC in this special group of patients.
Patients and Methods

The data of a total of 31 consecutive patients, who were primarily diagnosed and operated on due to histologically proven ovarian cancer during the period 01/1989 and 06/2008, were analyzed. All cytoreductive operations were performed by a gynecological oncologist (J.S., W.L.). The primary aim of each cytoreductive surgical intervention was maximal tumor resection. Standard procedures included midline laparotomy, peritoneal cytology, multiple peritoneal biopsies, hysterectomy, adnexitomy, infra-gastric omentectomy and systematic pelvic and paraaortic lymph node dissection. In order to achieve maximal tumor resection, additional multisurgical procedures had to be performed in more advanced cases such as peritoneectomy and bowel resections. Written informed consent of the patients was always obtained prior to surgery with special focus also on the fertility issue. When fertility preservation was desired, in cases of unilateral tumor affection, only unilateral adnexitomy, cytology, multiple biopsies of the peritoneum, infra-gastric omentectomy and systematic pelvic and paraaortic lymph node dissection were performed.

During primary surgery, sections from fresh frozen suspected ovarian cancer tissue were always taken. Resection specimens of all patients were examined at the Institute of Pathology, Charité University Hospital, Berlin, Germany. Histology and grade of differentiation were re-evaluated by a gynecopathologist (CD). Hematoxylin and eosin (H&E) stained sections were cut from paraffin-embedded blocks and used for histopathological evaluation; grading of tumors was assessed using Silverberg grading system. All relevant patients data including history, surgery data, histological documentation system (IMO), which was developed for ovarian neoplasms with special focus on the description of the tumor pattern, maximal tumor burden and postoperative residual tumor mass (11).

The FIGO stage was classified as follows: I: 28.8% ; II: 45.2% ; III: 12.9% ; IV: 12.9% . Most tumors (35.5% ) were of low differentiation. Twenty patients (64.5% ) had no ascites at initial presentation, whereas 6 patients (19.4% ) had ascites less than 500 mL and 5 patients (16.1% ) more than 500 mL.

CA-125 tumor marker was elevated (reference level <35 U/mL) in the vast majority of the patients (80.6% ) with a mean of 2252±7987.90 U/mL (range: 10-30,000 U/mL). No significant association with second malignancies could be observed; only one patient had a positive personal history of a second malignancy (uterine carcinoma). Data are presented in Tables I and II. Seven patients (22.6% ) had a second malignancy (uterine carcinoma). Data are presented in Tables I and II. Seven patients (22.6% ) had a
positive family history of ovarian (3) or breast (4) cancer, however without proven evidence of a hereditary pattern. Only one patient had a known \textit{BRCA-1} mutation.

\textbf{Surgical outcome.} All women in the present analysis underwent surgery per midline laparotomy as primary treatment. The mean operative time was 268±113.5 minutes (range: 62-596 min). A complete tumor resection was achieved in 18 patients (58.1%), one patient (3.2%) had tumor residuals less than 5 mm and 6 patients (19.4%) tumor residuals between 5 and 10 mm. In 4 patients (12.9%), tumor residuals larger than 1 cm maximal diameter were left. In patients with macroscopic tumor residuals, localization of the tumor was in the upper abdomen (omenta bursa, perihpatic and periiileal) in the vast majority of cases (98%). The postoperative complications were only minor: one patient experienced a wound infection with a subsequent delayed wound healing, another patient suffered from a postoperative lymph fistula due to systematic lymphadenectomy without a clinical consequence and only one patient developed an intestinal insufficiency/perforation and had to be reoperated. Data are presented in Table III.

In six patients (19.35%), a fertility-preserving operation with a unilateral ovariectomy was performed. In the majority of the patients (61.3%), the uterus was preserved. Otherwise, 51.6% of the patients were correctly staged in terms of the FIGO recommendations (10) with cytology, peritoneal biopsies, infragastric omentectomy and systematic pelvic and paraaortal lymphadenectomy when a complete tumor resection was accomplished. Appendectomy was performed mainly in mucinous EOC, when the appendix was affected by the tumor or if so desired by the patient (41.9%).

The surgical procedures performed are presented in Table IV. A systematic pelvic (median removed lymph nodes: 24; range: 3-60) and paraaortal lymphadenectomy (median removed lymph nodes: 8; range: 1-71) was performed in a total of 16 patients (51.6%). At this point it has to be noted that only a small number of the dissected lymph nodes was histologically proven to be affected by the tumor: mean number of positive pelvic lymph nodes was 1.00 (range: 0-11) and mean number of positive paraaortal lymph nodes was...
An extensive peritonectomy was performed in 21 patients (67.7%) mainly in the paracolic gutters and the small pelvis. A diaphragmatic resection or stripping was performed in 11 patients (35.5%) due to diffuse peritoneal carcinomatosis in the diaphragmatic region. None of the patients underwent a resection of the urinary bladder or the ureter. A total of 11 patients (35.5%) underwent a partial resection of the small intestine, whereas in 15 patients (48.4%) a partial resection of the large bowel had to be performed. In only two patients (6.5%) was a colostomy applied. A considerable number of patients underwent a multivisceral approach in terms of partial hepatectomy or partial gastrectomy (6.5% and 12.9% respectively) so that a maximal tumor debulking could be obtained. In 8 patients (25.8%), a tumor load in the omental bursa was described. A mesenterial carcinosis was noted in only 5 patients (16.1%). Extraperitoneal metastases were presented in 4 patients (12.9%), in terms of malignant pleural effusion. None of the patients presented distant metastases in solid parenchymatous organs. In the majority of the patients (87%), the highest tumor burden was localized in the pelvic region.

**Overall and progression free survival.** The mean follow-up period was 44.65±72.63 months (range: 0-267 months). The mean number of recurrences the patients experienced was 0.87 (range: 0-3). The mean progression-free survival time (PFS) was 74.72 months (range: 3-231) with a median of 220.00 months. The mean overall survival (OS) of the patient collective was 148.15 months (range: 1-267 months) with a median of 220.00 months. Fifteen patients (48.4%) experienced at least one relapse episode of the disease during the follow up period. Nine patients (29.0%) died during the same period due to cancer-related causes. Thirteen (86.7%) of the 15 patients with a relapse were initially classified as platinum-sensitive (i.e. relapse >6 months after platinum-based chemotherapy).

The mean number of chemotherapy lines administered was 1.87 (range: 0-5). All 31 patients showed a normalization of the tumor marker CA-125 after completion of the 1st-line chemotherapy (mean CA-125: 18 U/mL) regardless of whether they were initially operated without tumor residuals or not.

**Discussion**

The incidence of ovarian cancer increases with age, so that most women with EOCs are diagnosed between the ages of 40 and 65. In girls and younger women, non-epithelial histologies (germ cell tumors, sex cord stromal tumors and mixed cell tumors) are rather more common (12). The strongest known risk factor for ovarian cancer is a family history, which is present in about 10 to 15% of women who develop the disease. Based on a meta-analysis of pooled case-control studies, it was estimated that a family history of ovarian cancer in one relative increased the lifetime probability of ovarian cancer in a 35-year-old woman from 1.6 to 5% disorder. In contrast, hereditary syndromes are associated with a lifetime risk of ovarian cancer as high as 50% (13-15). In the present analysis it was possible to show that 22.6% of the patients had a positive family history of ovarian or breast cancer and herewith higher than the rate of 10-15% reported in the current
literature for the overall ovarian cancer patients collective (14, 15, 21, 22). Although there was awareness of only one patient having an established \textit{BRCA-1} mutation, it is assumed that even more patients were carriers of germline mutations in the \textit{BRCA} gene. Therefore, all young patients were informed about the possible genetical risk and the feasibility of a further genetical investigation and analysis.

Over the last 25 years, five-year survival rates for EOC patients have modestly improved from 36\% in the mid 1970s to 45\% by the year 2002 (16). However, this increasing trend is much less pronounced among elderly patients, leading to an increasing age gradient in prognosis, as shown by Gondos \textit{et al.} (23). Correlative to these findings, the present study reports considerably higher survival rates for young patients than those described in the current literature for the total EOC patient collective, with a 2-year and 5-year overall survival of 81\% and 62\% respectively compared to the five-year survival rates of 45\% (16). Since elderly patients (>65 years) with EOC seem to present a similar distribution of tumour stage, grading and histological type compared to younger patients (24), alternative reasons such as a lower complication rate, better physical resources, \textit{BRCA1}-related higher chemotherapy sensitivity and possibly an alternate attitude of the physician, should be discussed as reasons for the better outcome in the younger patient group and should further be evaluated in future studies.

Regarding the platinum-sensitivity and the initial FIGO stage, it is reported that only 3 out of all 31 patients (9.6\%) were classified as primary platinum-resistant; a clearly lower rate than described in the literature for the overall EOC patient collective (20). With all the patients presenting a complete normalization of the tumor marker CA-125 (mean value: 18 U/mL) after completion of 6 cycles of platinum-based chemotherapy, this can possibly be considered as an

<table>
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<th>Survival function</th>
<th>Mean</th>
<th>Std. Error</th>
<th>95% CI</th>
<th>Median</th>
<th>Range</th>
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<tr>
<td>Overall survival (months)</td>
<td>148.15</td>
<td>28.84</td>
<td>91.63-204.67</td>
<td>220.00</td>
<td>1-267</td>
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<tr>
<td>Progression-free survival (months)</td>
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<td>20.66</td>
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<td>3-231</td>
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Figure 1. Kaplan-Meier overall survival curve and data for overall and progression-free survival for young patients with primary epithelial ovarian cancer after primary tumor debulking surgery.
additional sign of a better chemotherapeutical response. This is consensual with the recent published results by Tan et al., that BRCA-positive EOC patients have better outcomes than non-hereditary EOC patients with higher response rates to first and subsequent lines of platinum-based treatment (25).

Only 58% of patients presented with an initial FIGO stage III or IV, contrary to over 75% equivalent rates reported in the literature for the overall EOC patient collective (16).

Regarding the histology and grade of differentiation, no relevant differences were noticed between young patients and the common ovarian cancer patients, since serous papillary histology and poor differentiation grade were in both cases most commonly diagnosed.

Similar results of a more favourable tumor stage, more advantageous survival rates and a rather higher differentiation grade are also reported by Chen et al. (17) and Tang et al. (8) in recent analyzes on EOC patients aged below 30 and 35 years, respectively.

Wimberger et al. reporting on the impact of age on surgical outcome in patients with advanced ovarian cancer, describes a reduced operative radicality associated with a poorer outcome in elderly patients (>65 years) (18). One would expect opposing results pertaining to younger patients. Indeed, almost 60% of patients could be operated on without any macroscopic tumor residuals, even if this was associated with a relative high rate of multisepcal upper abdomen-procedures such as hepatectomy (6.5%), gastroctomy (12.9%) and tumor resections in the omental bursa (25.8%). Significant lower rates (34%) of complete tumor resection are described elsewhere on over 2,700 EOC patients with a mean age of 57.5 years (19).

In conclusion, primary epithelial ovarian cancer in patients below 35 years of age is commonly unilateral and of serous-papillary histology. They have a better surgical outcome with improved survival rates, higher response to first-line platinum-based treatment, a lower relapse rate and better operative results regarding radical tumor resection associated with low perioperative complications in comparison to the common EOC patients target group aged in the mid-fifties at initial diagnosis. Further clinical studies incorporating translational research programs are warranted to investigate the underlying reasons for this observation.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest in regard to the present text.

References


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