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ORIGINAL ARTICLE

Ovarian cancer: 20-year experience with cytoreductive surgery and perioperative intraperitoneal chemotherapy

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Summary

Purpose: *Complete cytoreduction has been established as the most significant factor of long-term survival in epithelial ovarian cancer. Perioperative intraperitoneal chemotherapy has been added in the treatment of ovarian cancer the last 20 years. The purpose of the study was to determine the outcome of women with ovarian cancer using the data of one surgical team.*

Methods: *Women with ovarian cancer treated from 2000 to 2019 by the same surgical team were enrolled in the study. The patients underwent cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Clinical and histopathological variables were correlated to hospital mortality, morbidity, survival and recurrences.*

Results: *The mean age of 350 women was 59.5+11.7 years. The hospital mortality and morbidity rate were 2.0% and 28.3%, respectively. Complete cytoreduction was possible in 60% of the cases. The overall 5- and 10-year survival rate was 47% and 39%, respectively. The prognostic variables of survival were the extent of peritoneal malignancy, the extent of previous surgery, the grade of differentiation, the use of adjuvant chemotherapy, the lymphadenectomy of the resected large bowel, and the postoperative morbidity. The recurrence rate was 45.7%. The extent of peritoneal carcinomatosis, the extent of previous surgery, and the grade of differentiation were the prognostic variables of recurrence.*

Conclusions: *The limited extent of peritoneal carcinomatosis in women with well differentiated ovarian cancer that do not have history of previous surgery, who undergo standard pelvic peritonectomy procedure, and receive adjuvant chemotherapy are expected to be long-term survivors.*

Key words: *ovarian cancer, cytoreductive surgery, HIPEC*

Introduction

The optimal treatment of primary and recurrent epithelial ovarian cancer still remains an open and critical issue. Epithelial ovarian cancer is usually diagnosed when the tumor has already spread at the peritoneal surfaces. Cytoreductive surgery followed by systemic chemotherapy is the standard treatment [1]. Ovarian cancer is one of the most chemosensitive tumors. Despite complete response that is possible in 80% of the cases after cytoreduction and systemic chemotherapy the majority of patients develop recurrence, long-term survival is poor and does not exceed 25% [2-5]. The most significant prognostic variable of survival has been shown to be the maximal diameter of the residual tumor [6]. Even if a complete cytoreduction has been performed with no macroscopically visible tumor, microscopic emboli will always remain at the peritoneal surfaces. These neoplastic emboli confined at the traumatized peritoneal surfaces will give rise to recurrent tumors in 2-3 years despite the administration of systemic chemotherapy. Systemic chemotherapy cannot reach these emboli

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because they are devascularized. Intraperitoneal chemotherapy is effective in eradicating cancer emboli with maximal diameter less than 2-3 mm.

In practice, hyperthermic intraperitoneal intraoperative chemotherapy (HIPEC) has been used in locally advanced epithelial ovarian cancer as an adjuvant treatment after cytoreductive surgery with promising results [7-11].

The purpose of this study was to determine the long-term outcome of women with ovarian cancer.

Methods

The records of women with epithelial ovarian cancer treated by one surgical team from 2000 until 2019 were retrospectively reviewed. The diagnosis of the disease was possible with physical examination, complete hematological-biochemical examinations, tumor markers, abdominal and thoracic CT scans or MRI, and bone scanning. The performance status of the patients was assessed with the use of the Karnofsky scale. The extent of the disease was assessed using the peritoneal carcinomatosis index (PCI). The extent of previous surgery was assessed using the prior surgical score (PSS), and the completeness of cytoreduction (CC) using the CC score [12]. The volume of the disease was considered large if the lesion size of the largest implant was > 0.5cm or if there was confluence of lesions of various sizes.

Patients with acceptable performance status (Karnofsky performance scale > 50%), capable to undergo major surgery were included in the study. The patients were treatment-refractory, or were diagnosed at the time of initial diagnosis, or at recurrence. Patients with newly diagnosed ovarian cancer were selected for surgery if complete or near complete cytoreduction seemed to be possible. Otherwise they were considered candidates for neoadjuvant chemotherapy. Patients with evidence of distant and unresectable metastatic disease or those with gross small bowel infiltration were excluded from surgery. Additionally, patients younger than 16 years and older than 80 years, with recent myocardial or pulmonary disease, with WBC < 4.000, platelets < 100.000, blood urea level > 50 mg/dl, creatinine > 1.5mg/dl, and abnormal liver function other than bile duct obstruction were also excluded from surgery.

Treatments

All patients underwent surgery with midline incision from the xiphoid process to the symphysis pubis for maximal abdominal exposure. In a small number of patients, resection of the xiphoid process was considered necessary. After lysis of the adhesions the PCI was calculated. Standard peritonectomy procedures that were used with the intent of resecting the entire macroscopically visible tumor were pelvic peritonectomy, greater omentectomy+splenectomy, lesser omentectomy, right and left subdiaphragmatic, right and left lateral, cholecystectomy+resection of the omental bursa. Resection of other organs (small and large bowel, stomach, pancreas) was also performed if it was necessary to achieve complete or near complete cytoreduction.

Complete abdominopelvic lymph node resection was incidentally performed but after 2010 all patients with ovarian cancer underwent this type of lymph node resection.

From 2000 until 2005 early postoperative intraperitoneal chemotherapy (EPIC) was used in patients that underwent CC-0 or CC-1 surgery. The administration of EPIC was possible through a Tenckhoff catheter during the first five postoperative days. From 2005 until 2019 patients undergoing CC-0 or CC-1 surgery were given hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) with the Coliseum technique (open abdomen). HIPEC was possible with a continuous closed circuit of four drains (two inlet and two outlet), one heat exchanger and two roller pumps connected to the inlet and the outlet drains (Sun-Chip, Gamida-Tech, France) at 42.5-43°C for 90 min.

Those patients that received HIPEC remained in the ICU for at least 24 h postoperatively. The patients that received EPIC remained in the ICU for 5 days. All patients were recommended to receive systemic adjuvant chemotherapy.

Postoperative complications were recorded in detail. The uncomplicated patients were assessed as Grade 0. Patients with complications that required minor intervention, bowel rest, oral antibiotics, or monitoring were assessed as Grade 1. Patients with complications that required IV antibiotics, bowel rest, or chest tube drainage were assessed as Grade 2, those that required hospital re-admission, or surgical or radiological intervention were assessed as Grade 3, those that produced chronic disability, or organ resection, or bowel diversion as Grade 4, and those that resulted to death as Grade 5. Grade 1 and 2 complications were considered as minor complications and Grade 3 and 4 as major complications.

Histopathology

All resected specimens were examined in detail. The type of tumor, the grade of differentiation, the number of the resected and infiltrated lymph nodes were recorded. The lymph nodes of the retroperitoneal area were defined as RLN. The lymph nodes of the resected large bowel or rectum were defined as LBLN. The lymph nodes of the resected small bowel were defined as SBLN. Positive lymph nodes from any other site were considered as distant lymph nodes.

Follow-up

All patients that survived surgery were followed-up every 4 months during the first year, every 6 months until the completion of the 5th year, and once annually later, with physical examination, hematological-biochemical examinations, abdominal and thoracic CT scan, and tumor markers (CEA, CA-125). The recurrences and the sites of recurrence were recorded.

Statistics

Quantitative variables were expressed as mean values (±SD), while qualitative variables were expressed as absolute and relative frequencies. Life table analyses were used to calculate cumulative survival rate (standard errors) for specific time intervals. Univariate and multivariate Cox regression analyses were used in order to

Table 1. Patient general characteristics

Characteristics	*n (%)*
Karnofsky performance status	
90-100%	246 (70.3)
50-80%	104 (29.7)
Tumor volume	
Large volume	324 (98.5)
Small volume	5 (1.5)
Tumor grade	
High grade	325 (98.8)
Low grade	4 (1.2)
Peritoneal cancer index, mean (SD)	13.2 (9.8)
Completeness of cytoreduction	
CC-0	210 (60.0)
CC-1	99 (28.3)
CC-2	9 (2.6)
CC-3	32 (9.1)
Prior surgery score	
PSS-0	169 (48.3)
PSS-1	34 (9.7)
PSS-2	109 (31.1)
PSS-3	38 (10.9)
Neoadjuvant chemotherapy	143 (40.9)
Intraperitoneal chemotherapy	231 (66.0)
Adjuvant chemotherapy	263 (75.1)
Histopathologic type	
Serous	285 (81.4)
Endometrioid	27 (7.7)
Carcinosarcoma	0 (0.0)
Borderline	12 (3.4)
Mucinous	6 (1.7)
Others	16 (4.6)
Clear-cell	4 (1.1)
Grade of differentiation	
G1	37 (10.6)
G2	66 (18.9)
G3	246 (70.5)
Abdomino-pelvic lymph node resection	
Yes	85 (84.2)
No	11 (10.9)
Had been performed in the past	5 (5.0)
Positive abdomino-pelvic lymph nodes	48 (51.1)
Large bowel lymph nodes positive	124 (46.4)
Days of hospitalization, mean (SD)	13.8 (6.5)
Morbidity	
Uncomplicated	251 (71.7)
Complicated	99 (28.3)
Hospital mortality	7 (2.0)
Pattern of recurrence	
Distant	97 (62.2)
Local-regional	59 (37.8)

determine the independent predictors for disease-free and overall survival. The assumption of proportional hazards was evaluated by testing for interaction with a continuous time variable. Adjusted hazard ratios (HR) with 95% confidence intervals (95% CI) were computed from the results of the Cox regression analyses. Kaplan-Meier survival estimates for events were graphed over the follow-up period. All reported p values were two-tailed. Statistical significance was set at $p<0.05$ and analyses were conducted using SPSS statistical software (version 22.0).

Results

The records of 350 patients (mean age 59.5+11.7 years) were retrospectively analyzed. The general characteristics of the patients are listed in Table 1. The mean and median progression-free survival time were 7.0 and 1.9 years, respectively. The cu-

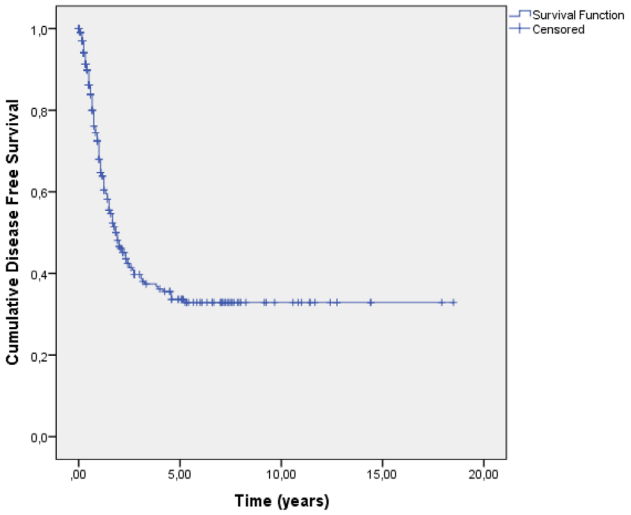

Figure 1. Disease-free survival of 350 women with ovarian cancer.

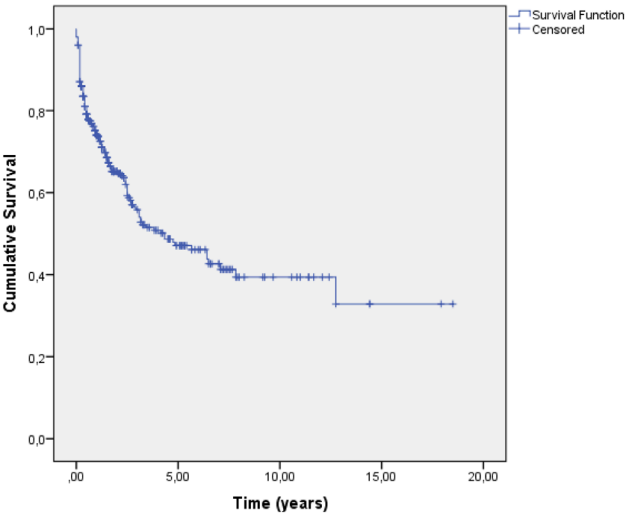

Figure 2. Overall survival of 350 women with ovarian cancer.

Table 2. Univariate and multivariate analysis of overall survival

	HR (95% CI)+	*p*	*Adjusted HR (95% CI)*+	*p*
Age (years)	1.03 (1.01 - 1.04)	<0.001	1.02 (1.00 - 1.04)	0.049
Karnofsky performance status				
90-100% (reference)				
50-80%	2.27 (1.62 - 3.17)	<0.001	1.11 (0.72 - 1.71)	0.635
Tumor volume				
Large volume (reference)				
Small volume	0.62 (0.09 - 4.44)	0.635	1.73 (0.23 - 12.79)	0.591
Tumor grade				
High-grade (reference)				
Low-grade	0.05 (0.00 - 5.84)	0.214	0.81 (0.11 - 5.82)	0.834
Peritoneal cancer index	1.08 (1.06 - 1.10)	<0.001	1.05 (1.02 - 1.08)	<0.001
Completeness of cytoreduction	1.78 (1.54 - 2.06)	<0.001	1.12 (0.86 - 1.46)	0.407
Prior surgery score	1.22 (1.05 - 1.41)	0.009	1.14 (0.94 - 1.38)	0.192
Neo-adjuvant chemotherapy				
No (reference)				
Yes	1.33 (0.95 - 1.86)	0.100	1.23 (0.78 - 1.94)	0.362
Intraperitoneal chemotherapy				
No (reference)				
Yes	0.82 (0.59 - 1.14)	0.241	0.72 (0.46 - 1.12)	0.145
Adjuvant chemotherapy				
No (reference)				
Yes	0.53 (0.37 - 0.75)	<0.001	0.17 (0.11 - 0.28)	<0.001
Histopathologic type				
Serous (reference)				
Endometrioid	0.64 (0.33 - 1.22)	0.173	0.79 (0.39 - 1.63)	0.529
Borderline	0.12 (0.02 - 0.85)	0.034	0.72(0.09-5.86)	0.757
Mucinous	0.64 (0.16 - 2.59)	0.532	3.31 (0.75 - 14.65)	0.115
Others	0.77 (0.34 - 1.74)	0.522	0.65 (0.25 - 1.72)	0.390
Clear-cell	1.53 (0.38 - 6.20)	0.552	1.12 (0.15 - 8.32)	0.913
Grade of differentiation				
G1 (reference)				
G2	3.25 (1.11 - 9.50)	0.032	3.42 (1.16 - 10.04)	0.025
G3	8.59 (3.15 - 23.43)	<0.001	8.06 (2.93 - 22.17)	<0.001
Abdomino-pelvic lymph node resection				
No (reference)				
Yes	0.86 (0.25 - 2.96)	0.808		
Positive abdomino-pelvic lymph nodes				
No (reference)				
Yes	1.12 (0.44 - 2.86)	0.807		
Large bowel lymph nodes positive				
No (reference)				
Yes	1.93 (1.31 - 2.83)	0.001		
Morbidity status				
Uncomplicated (reference)				
Complicated	3.16 (2.27 - 4.41)	<0.001	2.49 (1.66 - 3.74)	<0.001

+Hazard Ratio (95% Confidence Interval)

Table 3. Univariate (Left column) and multivariate (Right column) analysis of recurrence

	HR (95% CI)[+]	*p*	*Adjusted HR (95% CI)*[+]	*p*
Age (years)	0.99 (0.98 - 1.01)	0.392	0.99 (0.97 - 1.01)	0.397
Karnofsky performance status				
90-100% (reference)				
50-80%	1.21 (0.84 - 1.73)	0.307	1.22 (0.8 - 1.85)	0.356
Tumor volume				
Large volume (reference)				
Small volume	0.41 (0.06 - 2.94)	0.377	0.38 (0.05 - 2.8)	0.345
Tumor grade				
High-grade (reference)				
Low-grade	0.05 (0.00 - 3.00)	0.149	0.42 (0.06 - 3.02)	0.390
Peritoneal cancer index	1.07 (1.05 - 1.08)	<0.001	1.03 (1.01 - 1.05)	0.034
Completeness of cytoreduction	1.85 (1.61 - 2.13)	<0.001	1.24 (0.96 - 1.6)	0.096
Prior surgery score	1.55 (1.34 - 1.79)	<0.001	1.28 (1.05 - 1.56)	0.015
Neoadjuvant chemotherapy				
No (reference)				
Yes	2.39 (1.74 - 3.29)	<0.001	1.1 (0.72 - 1.67)	0.666
Intraperitoneal chemotherapy				
No (reference)				
Yes	1.01 (0.73 - 1.40)	0.932	0.91 (0.59 - 1.42)	0.687
Adjuvant chemotherapy				
No (reference)				
Yes	3.41 (1.92 - 6.03)	<0.001	1.04 (0.52 - 2.09)	0.906
Histopathologic type				
Serous (reference)				
Endometrioid	0.60 (0.33 - 1.09)	0.093	0.92 (0.47 - 1.79)	0.803
Borderline	-	-[++]	-	-[++]
Mucinous	0.46 (0.11 - 1.88)	0.282	1.51 (0.33 - 6.82)	0.591
Others	0.60 (0.27 - 1.36)	0.224	0.63 (0.25 - 1.59)	0.329
Clear-cell	1.35 (0.33 - 5.46)	0.674	1.4 (0.33 - 5.97)	0.648
Grade of differentiation				
G1 (reference)				
G2	2.99 (1.13 - 7.90)	0.027	1.94 (0.63 - 6.03)	0.249
G3	8.86 (3.61 - 21.73)	<0.001	3.55 (1.18 - 10.74)	0.025
Abdomino-pelvic lymph node resection				
No (reference)				
Yes	1.26 (0.44 - 3.60)	0.660		
Positive abdomino-pelvic lymph nodes				
No (reference)				
Yes	1.66 (0.83 - 3.31)	0.153		
Large bowel lymph nodes positive				
No (reference)				
Yes	2.18 (1.51 - 3.15)	<0.001		
Morbidity status				
Uncomplicated (reference)				
Complicated	1.29 (0.88 - 1.89)	0.191	0.93 (0.61 - 1.42)	0.744

[+]Hazard Ratio (95% Confidence Interval); [++]not computed due to no distribution

mulative progression-free rate for one, three, five and ten years was 50% (SE=3%), 41% (SE=3%), 35% (SE=3%) and 34% (SE=3%) (Figure 1). The mean and median survival time were 8.2 and 4.3 years, respectively. The cumulative survival rate for one, three, five and ten years were 74% (SE=2%), 56% (SE=3%), 47% (SE=3%) and 39% (SE=4%) (Figure 2).

Univariate analysis showed that low performance status and serious morbidity were associated with worse survival. In contrast, those patients that received adjuvant chemotherapy, or those with borderline cancer had significantly better survival compared to patients with serous ovarian cancer. In addition, the performance of abdominopelvic lymph node resection even with positive RLN had no impact on long-term survival. In contrast, patients with positive LBLN were associated with greater hazard (HR=1.93, 95% CI: 1.31-2.83, p=0.001). Multiple Cox regression analysis (Table 2) showed that age, peritoneal cancer index and grade of differentiation, adjuvant chemotherapy and complications were independently associated with survival in the final model.

Extensive peritoneal dissemination, extensive prior surgery, incomplete cytoreduction, and low differentiated ovarian tumors were associated with greater hazard for recurrence. Abdominopelvic lymph node resection and positive RLN had no significant relation to recurrence. In contrast, patients with positive LBLN had greater hazard for recurrence (HR=2.18, 95% CI: 1.51-3.15, p<0.001). When multiple Cox regression analysis was conducted (Table 3) it was found that extensive peritoneal dissemination, extensive prior surgery, and the grade of differentiation were prognostic variables of recurrence.

Discussion

Optimal cytoreductive surgery followed by systemic adjuvant chemotherapy still remains the standard treatment of advanced epithelial ovarian cancer [13,14]. Despite improvements in systemic chemotherapy the long-term survival does not exceed 20-25% [15]. Intraperitoneal chemotherapy has been shown to be effective in peritoneally disseminated diseases such as pseudomyxoma peritonei and peritoneal mesothelioma [16,17]. In the last two decades perioperative intraperitoneal chemotherapy has been extensively used in the treatment of recurrent ovarian cancer with favourable results [7-11,18]. One prospective randomized trial has shown that intraperitoneal chemotherapy is very effective in the treatment of recurrent epithelial ovarian cancer [19]. In another trial, HIPEC has been used as upfront treatment in newly diagnosed locally advanced ovarian cancer and has shown that there is significant survival benefit [20]. Cytoreductive surgery in combination with HIPEC has been criticized for high morbidity which delays the administration of systemic chemotherapy and results in high recurrence rate. This hypothesis has not been proved. It has been shown that surgical manipulations are responsible for high morbidity. However, intraperitoneal chemotherapy adds an insignificant percentage of complications [20]. The majority of complications are due to extensive peritoneal dissemination which requires extensive surgery [21,22]. The extent of prior surgery has not been sufficiently studied. There is a limited number of publications reporting the relation of prior surgery to survival and recurrences [7,15,23,24]. In our study extensive peritoneal dissemination was found to be a prognostic variable of recurrence, in addition to the grade of differentiation and the extent of previous surgery.

The extent of previous surgery has been found to be related to survival [7,15,24], although it was not indicated as a prognostic variable of survival. Paradoxically, the completeness of cytoreduction has not been found to be a prognostic indicator of survival, although it was strongly related to survival. In contrast, the extent of peritoneal dissemination, the use of adjuvant chemotherapy and the grade of differentiation were indicated as prognostic variables of survival.

The need for extensive retroperitoneal lymph node resection has been widely disputed in the literature. The LION study has not shown any survival benefit in women undergoing retroperitoneal lymph node resection [25]. In our study retroperitoneal lymph node resection has not been found to be related to survival. In contrast, the LBLN were found to be of critical importance. In peritoneal carcinomatosis the first line of defence is the peritoneum. Exceptions to this rule are the lymphoid aggregates that are abundant at the omentum and at the junction of the small bowel and its mesentery. At these sites the implanted invasive cancer emboli may penetrate the underlying tissues. As a consequence, metastatic nodules can be frequently found at unusual sites from which cancer disseminates easily at the surrounding lymphatic network. The same can be found when the peritoneal surfaces are mechanically disrupted by surgical manipulations. Therefore, positive LBLN may be found in ovarian cancer, and the disease may follow the dissemination as if the primary site were a large bowel carcinoma [26-28]. Thus, pelvic peritonectomy procedure may be required in almost every case of ovarian cancer even with limited peritoneal extent. This type of standard peritonectomy procedure in-

cludes the *en bloc* resection of the internal female genitalia with low anterior resection of the rectum and the mesorectum [28]. By this procedure the lymphatic network of the mesorectum is resected and appears to be beneficial for the patients with ovarian cancer [29].

Conclusions

There is an emerging body of evidence that supports the use of HIPEC with CRS and adjuvant chemotherapy for advanced epithelial ovarian cancer.

The limited extent of peritoneal carcinomatosis in women with well differentiated ovarian cancer that do not have history of previous surgery, who undergo standard pelvic peritonectomy procedure and receive adjuvant chemotherapy are expected to be long-term survivors.

Future randomized controlled trials are expected to further clarify the role of HIPEC for patients with ovarian cancer.

Conflict of interests

The authors declare no conflict of interests.

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