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ADVANCED EPITHELIAL OVARIAN CANCER: THE PROGNOSTIC SIGNIFICANCE OF RESIDUAL DISEASE AFTER CYTOREDUCTIVE SURGERY

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Surgery remains the cornerstone of the treatment for epithelial ovarian cancer. For patients with advanced disease, the initial cytoreductive operation reduces tumor bulk and produces increased sensitivity to chemotherapy for the remaining tumor. The purpose of our study is to report the benefit of cytoreductive surgery by comparing patients with optimal residual disease ≤2cm, with those with suboptimal residual tumor >2cm. To assess the risk of operative complications and to identify determinants of survival.

Patients and Methods*: Between January 1998 and March 2002, 37 patients with FIGO stage II-IV underwent cytoreductive surgery followed by postoperative adjuvant cisplatin-based chemotherapy. A second-look laparotomy was performed in 15 patients (40.5%). The median follow-up was 18 months (range, 7-54).*

Results: *Optimal cytoreduction to ≤2cm tumor deposits was performed in 16 cases (43.2%) and suboptimal cytoreduction to > 2cm residual tumors was performed in 21 cases (56.8%). The majority of patients had stage III disease (56.8%), serous epithelial ovarian cancer (67.6%), and moderately differentiated tumors (67.6%). Lymph nodes were positive in 15 cases (40.5%). Sixteen patients (43.2%) had positive cytology for ascites. CA-125 serum level was raised pre-operatively in 29 cases (78.4%). Postoperative complications occurred in 17 patients (45.9%). In our study population, advanced FIGO stage and high grade tumors acted as high-risk biologic markers in predicting suboptimal debulking. The overall median survival was 29 months, with overall 3-year survival of 40%. By multivariate analysis, only advanced FIGO stage, positive lymph nodes, and residual tumor deposits > 2cm remained significant for poor survival.*

Conclusion: *Optimal cytoreduction in women with advanced epithelial ovarian cancer is associated with a more favorable outcome survival.*

Key words: Epithelial ovarian cancer, cytoreductive surgery, residual disease, survival.

INTRODUCTION

Epithelial ovarian carcinoma is the leading cause of death from gynecological malignancies in the great majority of developed countries[1]. The high mortality attributable to ovarian cancer is in large part due to the advanced stage of disease commonly present at the time of diagnosis, because early stage ovarian cancer is often asymptomatic[2]. About three-quarters of all patients with invasive ovarian carcinoma will have intra-peritoneal metastasis at the time of exploratory laporatomy[3].

Tremendous advances have been made in chemotherapy for ovarian cancer over the past 20 years, but surgery remains the cornerstone of effective management of the disease[4]. Repeated investigations have shown that cancer of the ovary is unusual among solid tumors in that surgical reduction of tumor volume is highly correlated with a prolongation of patient survival[5]. Patients who are left with little or no visible residual cancer at the end of their initial surgery enjoy a dramatically improved survival over women who have bulky residual tumor at the end of initial surgery or who are treated by chemotherapy alone[4,6,7].

Clearly, aggressive surgery can be accomplished with

minimal morbidity by some surgeons in some patients, morbidity can be substantial, with serious operative and postoperative complications approaching 70%[8,9]. To date no randomized study of initial cytoreductive surgery prior to chemotherapy has been performed[10].

The aim of this study was to define the benefit of cytoreductive surgery in patients with advanced ovarian carcinoma by comparing patients with optimal cytoreductive surgery (≤ 2cm residuals) with those with suboptimal debulking (> 2cm residuals). To determine the type and frequency of complications for the surgical procedure and to assess patient, tumor, and treatment-related factors which have an impact on overall survival.

PATIENTS AND METHODS

Between January 1998 and March 2002, 37 consecutive women with advanced ovarian cancer (FIGO stage II-III-IV) were prospectively treated in the Department of General Surgery and the Department of Gynecology and Obstetrics, Minoufiya University Hospital, and the Department of General Surgery, Menya University Hospital. All operations in this series were performed by the surgeon authors.

The primary operation consisted of total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), and omentectomy (OM). Additional surgical procedures such as resection of portion of the small or large bowel, or splenectomy, were performed when considered necessary to achieve optimal debulking. Since the aim of surgery was to remove as much tumor as possible, sampling or systematic pelvic and para-aortic lymphadenectomy was performed after completion of cytoreductive surgery. Optimal cytoreduction was defined as no gross residual tumor greater than 2cm in diameter, whereas suboptimal cytoreduction was defined as any gross residual disease remaining greater than 2cm in diameter. Patients who were left with extraperitoneal metastases measuring >2cm in diameter were included in the suboptimal cytoreduction group.

Eligibility criteria were histologically confirmed diagnosis of advanced ovarian cancer (FIGO stage II-III-IV)[11] age < 75 years performance status 0,1,2 or 3 defined according to WHO criteria[12] no history of other malignant diseases, no previous chemotherapy or radiotherapy. Criteria of exclusion were early ovarian cancer (FIGO stage I and IIA), border line tumors with low malignant potential, surgery less than the standard operative procedure (TAH + BSO + OM) and/or less than sampling or systematic pelvic and para-aortic lymphadenectomy. Ascites when present, was sent for cytologic examination. CA-125 was used as tumor marker, with cutoff value of 35U/ml. A decrease in the tumor marker below the cutoff value was considered a remission of the tumor marker.

Postoperatively, all patients were treated by the CAP regimen, which consisted of 200mg/m² cyclophosphamide on day 1, 25mg/m² adriamycin on day 1 and 3, and 10mg/m² cisplatin on days 1-5, repeated every 3 weeks. If responses to the CAP regimen were judged to be satisfactory, we continued that regimen. If patients exhibited unsatisfactory responses to 2-4 cycles of the CAP regimen, they were switched to second-line chemotherapy which consisted of cisplatin 75 mg/m² on day 1 and paclitaxel 175 mg/m² on day 1. Responses to chemotherapy were assessed by ultrasonography, computed tomography and tumor marker CA-125 levels after 2 and 4 cycles of chemotherapy. Second-look laparotomy was performed on patients in whom residual tumors >2cm were left after initial surgery and for whom tumor markers were within normal ranges after 2-4 cycles of chemotherapy.

Data were collected regarding age, performance status FIGO stage, tumor histologic subtype, tumor grade, presence of ascites, pre-operative CA-125, residual disease after cytoreductive surgery, response to primary chemotherapy, and clinical status after primary treatment. Histology was determined according to FIGO criteria[11]. Response to primary chemotherapy was assessed according to WHO criteria[12]. Patients were followed up every 3 weeks during chemotherapy, every 6 weeks for the first 6 months after completing the treatment program, and every 2 months thereafter. Any death, regardless of cause, during the operation and within the first 30 postoperative days was classified as operative mortality.

Data collected and analyzed by SPSS statistical package (SPSS Inc. Chicago, IL, USA). Quantitative data expressed as mean and standard deviation (x ± SD) and analyzed by student t-test for comparison of groups. Qualitative data expressed as number and proportions and analyzed by X^2-test. Survival curves were estimated using the Kaplan-Meier methods[13]. Survival differences and associations of overall survival with treatment and other patient characteristics were analyzed by the log-rank test[14]. P value was set as <0.05 for significant. The Cox proportion hazards model was used to identify independent prognostic factors, with adjustments for various prognostic factors[15].

RESULTS

Patients' median age was 56 years (range, 31-72). Nine patients (24.3%) were nullipara and 25 (67.5%) were menopausal. (Table 1) shows clinical and histopathological characteristics of 37 patients with advanced ovarian carcinoma.

Operative characteristics are listed in (Table 2). of the

37 patients who underwent surgical debulking, 16(43.2%) were optimally cytoreduced to ≤ 2cm residual tumors, and suboptimal cytoreductive surgery to >2cm residual tumors was performed in 21(56.8%) of cases. Operative complications are listed in (Table 3). There were 17 complications in 37 patients (45.9%) undergoing cytoreductive surgery, almost 27% had more than one postoperative complication. There were two operative deaths (5.4%); one due to hypovolaemic shock and the other due to severe intra-abdominal sepsis.

The demographic, pathologic, and treatment characteristics in relation to residual tumors after cytoreductive surgery are shown in (Table 4). The frequency of residual tumors > 2cm in diameter was significantly higher in advanced FIGO stage (P=<0.01) and poorly differentiated tumors (P=<0.05). No clear relationship emerged between age, performance status, tumor histology, lymph node status, cytology of ascites, pre-operative CA-125 levels and the size of residual tumors.

Postsurgical chemotherapy was given to all patients using the CAP regimen. Paclitaxel was given as a second-line chemotherapy in 19 patients (51.3%) in case of failure of primary chemotherapy or progressive disease. A second-look laparotomy was performed in 15 patients (40.5%), macroscopic residuals >2cm was found in 6 patients (40%), and no tumor was found in 9 patients (60%).

Variables found to be statistically significant predictors of overall survival on univariate analysis are shown in table (5). Significant differences were observed with FIGO stage, histologic subtype, histologic grade, cytology of ascites, lymph node status and residual tumors. To find out the relative importance of these factors with an available significant prognostic value, they were entered into the Cox proportional hazard model (Table 6). The most important independent factors associated with a better prognosis were the FIGO stage II, negative lymph node status and cytoreductive surgery to ≤2cm residual tumors.

Patient follow-up ranged from 7 to 54 months (median, 18 months). (Fig 1) shows the Kaplan-Meier survival analysis for all 37 patients. The median survival for all patients was 29 months, with an estimated 3-year survival rate of 40%. Survival according to FIGO stage is shown in (Fig 2). The three-year median/survival rates were as follows: stage II 42 months/60%, stage III 30 months/38%, and stage IV 11 months/14% (P= <0.001). (Fig 3) shows survival curves for negative and positive lymph nodes. The three-year median/survival rates were as follows: node negative 40 months/58%, node positive 16 months/36% (P= <0.001). (Fig 4) shows survival curves for residual tumors left in the abdomen after primary cytoreductive surgery. Three-year median/survival rates were as follow: residuals ≤2cm: 42 months/55% versus 15 months/21% for residuals >2cm (P= <0.001).

Table (1)*: Clinical and histopathologic characteristics*

Variables	*No*	*%*
Age (years), median (range)	56	(31-72)
≤ 60	17	45.9
> 60	20	54.1
Performance status		
0+1	11	(29.7)
2+3	26	(70.3)
FIGO stage		
II	8	(21.6)
III	21	(56.8)
IV	8	(21.6)
Tumor histology		
Serous	25	(67.6)
Endometrioid	5	(13.5)
Mucinous	3	(8.1)
Undifferentiated	4	(10.8)
Histologic grade		
Well	5	(13.5)
Moderate	25	(67.6)
Poor	7	(18.9)
Lymph node status		
Negative	22	(59.5)
Positive	15	(40.5)
Cytology of ascites		
Negative	13	(35.2)
Positive	16	(43.3)
No ascites	8	(21.6)
Pre-operative CA-125		
Median (range)	644μ/ml	(8-35,000)
≤ 1000	16	(43.3)
> 1000	15	(40.5)
unknown	6	(16.2)
Size of residual disease		
Optimal ≤ 2cm	16	(43.2)
Suboptimal > 2cm	21	(56.8)

Table (2): *Operative characteristics*

Characteristics	*No*	*%*
TAH+BSO+OM*	37	(100)
Appendicectomy	21	(56.7)
Small bowel resecion	3	(8.1)
Large bowel resection	2	(5.4)
Bowel bypass procedures	2	(5.4)
Colostomy	1	(2.7)
Splenectomy	2	(5.4)
Pelvic and para-aortic lymphadenectomy		
Sampling	23	(62.2)
Systematic	14	(37.8)
Median estimated blood loss (range)	740ml	(400-3000)
Median operative time (range)	220min	(180-390)
Median No. of hospital days (range)	12	(11-45)

* TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; OM: omentectomy.

Table (3): *Operative complications of primary cytoreductive surgery*

Complications	*No.*	*%*
Visceral injury	5	(13.5)
Wound complications	4	(10.8)
Pneumonia	2	(5.4)
Thromboembolism	1	(2.7)
Fistula	1	(2.7)
Lymphocyst	4	(10.8)
In-hospital mortality	2	(5.4)

Table (4): *Clinical and histopathologic characteristics in relation to size of residual disease after cytoreductive surgery*

Variables	*Size of residual disease*		*P value*
	Optimal ≤2cm (n= 16)	*Suboptimal >2cm (n= 21)*	
Age (years), median (range)	45(31-72)	58(40-69)	> 0.05
Performance status			
0+1	7(43.8)	4(19)	>0.05
2+3	9(56.2)	17(81)	
FIGO stage			
II	7(43.8)	1(4.8)	<0.01
III	9(56.2)	12(57.1)	
IV	0(0)	8(38.1)	
Tumor histology			
Serous	10(62.5)	15(71.4)	
Endometrioid	3(18.7)	2(9.5)	>0.05
Mucinous	2(12.5)	1(4.8)	
Undifferentiated	1(6.3)	3(14.3)	
Histologic grade			
Well	5(31.2)	0(0)	<0.05
Moderate	10(62.5)	15(71.4)	
Poor	1(6.3)	6(28.6)	
Lymph node status			
Negative	12(75)	10(47.6)	>0.05
Positive	4(25)	11(52.4)	
Cytology of ascites			
Negative	8(50)	5(23.8)	>0.05
Positive	4(25)	12(57.1)	
Pre-operative CA-125			
Median (range)	7(43.7)	9(42.8)	
≤ 1000	6(37.5)	9(42.8)	>0.05
> 1000			

Table (5): Relation of survival with clinical, pathologic, and operative variables

Variables	3-year survival (%)	P value
Age (years), median (range)		
≤ 60	69	>0.05
> 60	62	
Performance status		
0+1	58	>0.05
2+3	51	
FIGO stage		
II	60	<0.001
III	38	
IV	14	
Tumor histology		
Serous	51	
Endometrioid	55	<0.05
Mucinous	67	
Undifferentiated	10	
Histologic grade		
Well	61	<0.05
Moderate	49	
Poor	32	
Lymph node status		
Negative	58	<0.05
Positive	36	
Cytology of ascites		
Negative	73	<0.001
Positive	14	
No ascites		
Pre-operative CA-125		
≤ 1000	61	>0.05
> 1000	53	
Size of residual disease		
Optimal ≤ 2cm	55	<0.05
Suboptimal > 2cm	21	

Table (6): ***Multivariate analysis of significant prognostic factors in relation to survival***

Prognostic factors	*Relative risk*	*95% confidence interval*	*P value*
FIGO stage	27.50	1.20-34.2	<0.001
Lymph node status	20.43	13.1-38.6	<0.01
Size of residual disease	2.1	1.15-4.39	<0.01

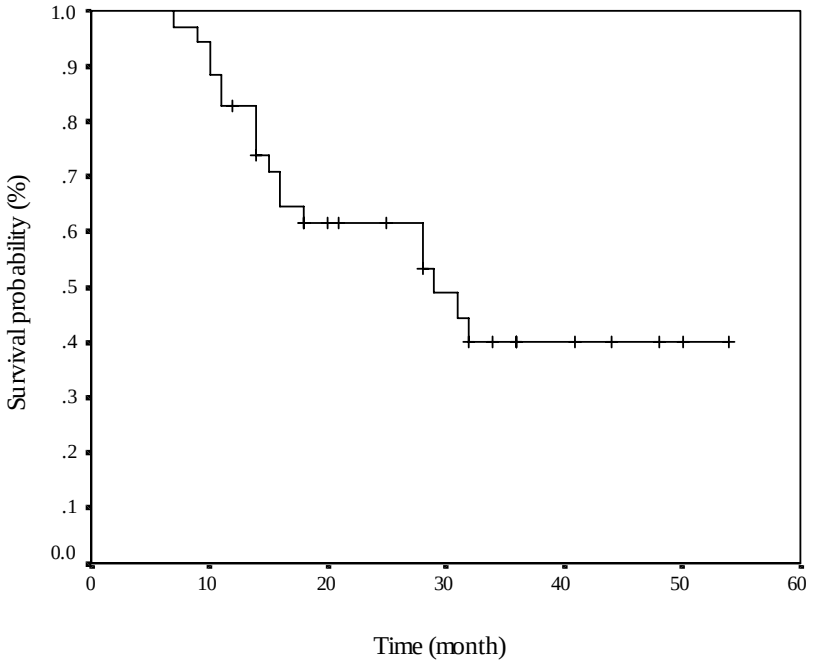

Fig. (1): Overall survival of the whole series

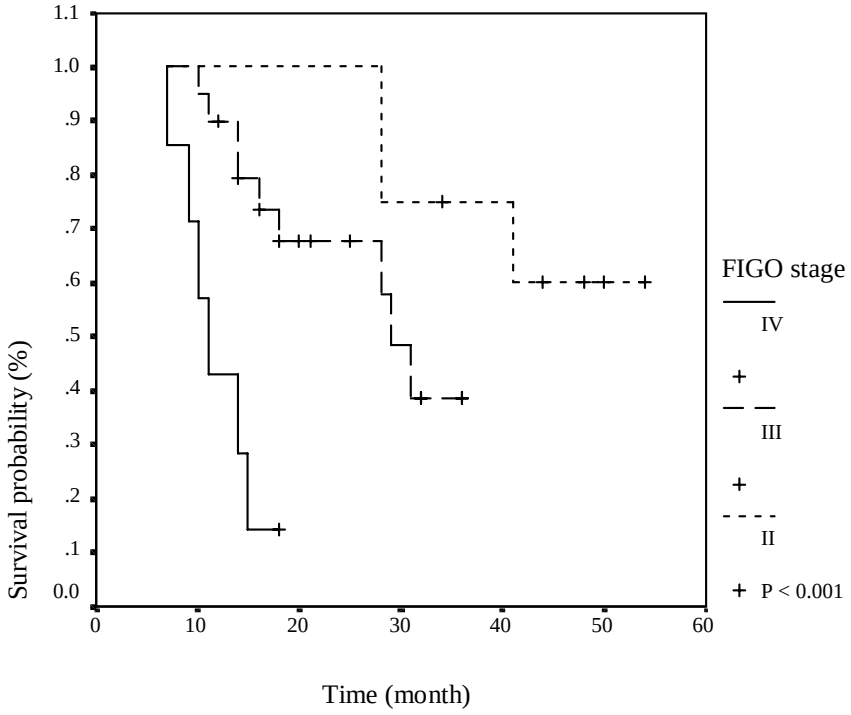

Fig. (2): *Survival probability of ovarian cancer patients according to FIGO stage*

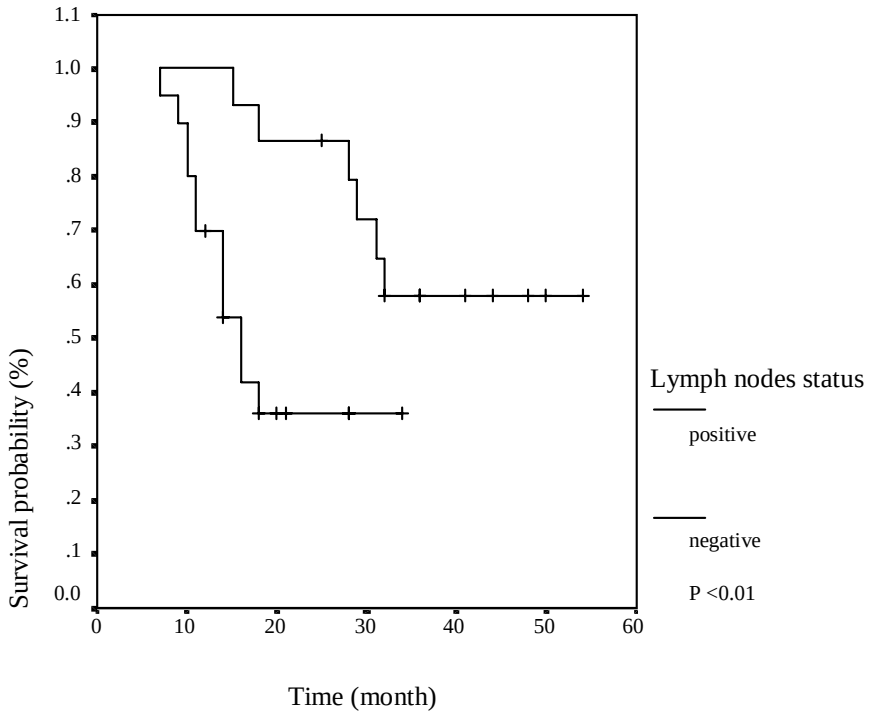

Fig. (3): Survival probability of ovarian cancer patients according to lymph node status

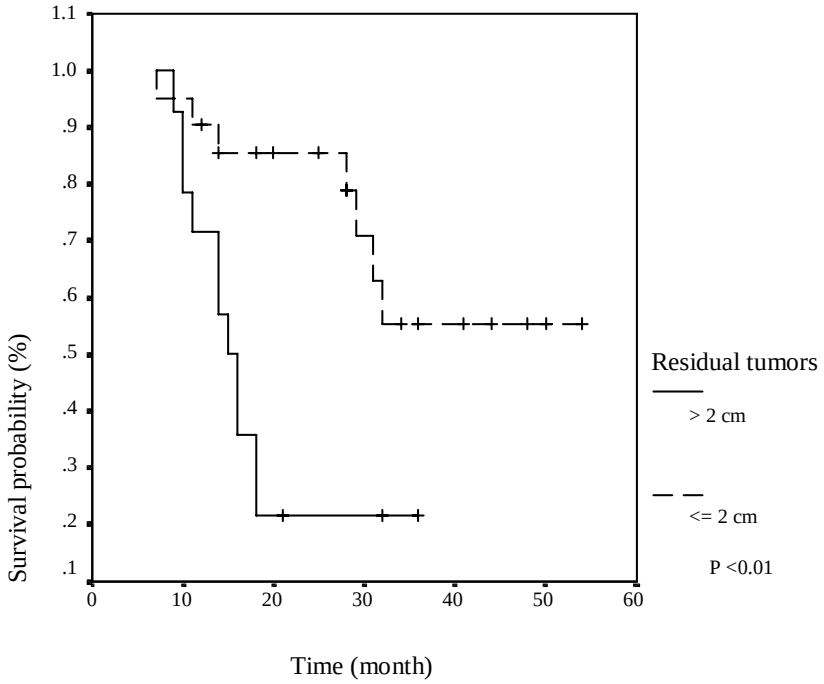

Fig. (4): Survival probability of ovarian cancer patients according to residual tumors

DISCUSSION

Various definitions of "optimal residual disease" exist, but it is now generally accepted as the presence of no tumor nodules that are more than 2 cm in diameter after surgery[3,4]. Using this definition, about one-third of patients with advanced epithelial ovarian carcinoma could be debulked to optimal status [16] . This was the case in our study. Our results confirm that cytoreduction at primary surgery can be associated with improved long-term survival. The larger the tumor residual at primary surgery, the poorer the prognosis. Others[10,17] suggest that it is important to achieve as close to no visible tumor as possible at the completion of primary surgery to obtain significant long-term survival benefits.

In this paper, we compare the outcomes of similarly treated patients with different initial disease volumes and residual status. Patients with residuals less than or equal to 2cm presumably have the most favorable tumor characteristics and prognosis when compared to those with gross diseases more than 2cm, as predicted by many other reports(18,3). In our study population, advanced FIGO stage and high grade tumors acted as high-risk biologic markers in predicting suboptimal debulking, in accordance with other reports [4,7] .

Of the numerous studies published over the past 15 years many had relatively short follow-up and included patients which employed a variety of surgical approaches and adjuvant treatments. The current study was limited to patients who were uniformaly managed with classical cytoreductive surgery and same regimens of chemotherapy. In our study the age of patients was not a significant prognostic factor for survival, in agreement with some reports[5]. This was not the case in certain other studies[18]. FIGO stage is a prognostic indicator recognized by most authors, sometimes independent from the results of surgery and type of chemotherapy[19]. This was in agreement with our results. Most studies report a low prognostic value for histologic subtype, probably because of bias in analysis due to small samples and/or difficulties in diagnosis. However, serous and undifferentiated carcinoma tend classically to decrease survival in agreement with other reports[20]. Endometrioid carcinoma (13.5%) was observed in our study in comparison with the 15% rate usually expected[5]. The prognostic significance of grade was demonstrated by several clinical studies in the 1980s[21,22]. However, grading has not been accepted enthusiastically by pathologists, because no standardized, easily reproducible, and objective classification exists[5]. Furthermore, after adjustment for FIGO stage and histologic type, grade does not appear to be an independent factor in some recent multivariate analyses[5,19], in accordance with our results. The adverse effect of ascites on outcome has been sporadically reported for epithelial ovarian cancers[16,23]. In the current study the presence of ascites per se was correlated with poorer outcome only in univariate analysis. In patients with cytology-positive ascites survival was markedly decreased, whereas patients with negative cytology had a favorable outcome. Preoperative CA-125 was not an independent risk factor for survival in univariate and multivariate analysis in our study, in agreement with some reports[2], although contradicting others[24]. In addition, CA-125 was not a reliable predictor of optimal cytoreduction in this study[24]. In the current study, a significant difference in survival curve was observed between the lymph node positive and lymph node negative patients, in accordance with most recent reports in the literature[25,26].

Debulking operation including lymphadenectomy causes serious complications, such as injuries of the inferior vena vaca, bowel, ureter, serious blood loss and lymphocyst[27]. Previous studies have reported at least one complication accompanying 30-67% of primary surgery for ovarian cancer[10], comparable to the 45.9% complication rate in our study. This suggests that surgeons must be skilled in the repair of vascular, gastrointestinal and genitourinary injuries when performing cytoreductive surgery.

Progress in chemotherapy certainly explains the increased survival rate observed during the past 20 years[5]. However, the improvement in the survival is probably explained by more extensive cytoreductive surgery and a cisplatin-based chemotherapy[3]. Favorable results of second-line paclitaxel-based chemotherapy have led us as in other reports[28] to incorporate paclitaxel into first-line therapy since 2002 whenever possible.

Although primary cytoreductive surgery is generally accepted as having a significant benefit for patients with ovarian cancer, less literature is available to indicate the benefit of secondary cytoreductive surgery. Approximately 50% of patients who undergo second-look surgical reassessment are found to have disease, and in 80% of these patients, the disease is macroscopic[29]. In our study 40.5% of patients underwent second-look laparotomy, macroscopic residuals >2cm was found in 40%. Similar results were found in other reports[30,31].

The median overall survival (29 months) and estimated 3-year survival (40%) in this study are comparable with previous studies ranging from 22.4 to 43 months, and from 28% to 65%, respectively[4,32,3]. Several independent prognostic factors predicting survival including FIGO stage, histologic subtype, tumor grade, lymph node status, cytology of ascites and size of residual disease have been reported[32,33]. A multivariate analysis of prognostic factors

has been conducted and only FIGO stage[5], lymph node involvement[25], and size of residual disease[16] were consistently recognized as independent prognostic factors for overall survival.

CONCLUSION

Our study confirms the benefit of cytoreductive surgery. Optimal surgical debulking, FIGO stage, and lymph node status appear to be important prognostic factors for survival in patients with advanced epithelial ovarian cancer.

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