RESEARCH COMMUNICATION

Outcome of Interval Debulking in Advanced Ovarian Cancer Patients

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Abstract

Interval debulking and neoadjuvant chemotherapy have been used in management of advanced epithelial ovarian cancer for many years in order to achieve optimal residual disease and reduce surgical morbidity. The present study was conducted to evaluate the outcomes of advanced ovarian cancer patients treated with these two approaches prior to cytoreductive surgery in Chiang Mai University Hospital between January 2001 and December 2006. The medical records of 29 patients who met the criteria were retrospectively reviewed. Most had stage IIIC serous cystadenocarcinomas. We found that the 5 year progression free survival and overall survival were 10% and 22% while the median values were 13 months and 34 months, respectively. Multivariate analysis showed that a suboptimal residual tumor volume was a statistically significant adverse prognostic factor for overall survival. In conclusion, interval debulking surgery and neoadjuvant chemotherapy before cytoreductive surgery lead to a more favorable outcome with advanced epithelial ovarian cancers.

Key Words: Interval debulking - neoadjuvant chemotherapy - advanced epithelial ovarian cancer

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Introduction

Most epithelial ovarian cancer patients were diagnosed at an advanced stage due to ineffective screening. The standard treatment includes aggressive initial tumor debulking surgery followed by adjuvant platinum-based chemotherapy (Griffiths, 1975; Hacker et al., 1983; Delgado et al., 1984; Bertelsen et al., 1990; Hoskins et al., 1994; Bristow et al., 2002). The amount of residual disease is the most important factors impacting survival (Griffiths, 1975; Chi et al., 2001,). Residual tumors larger than 1-2 cm have no meaningful impact on survival (Hoskins et al.,1994). In an effort to increase the proportion of optimal residual volume patients, the concept of interval debulking, defined as a surgical procedure with debulking intent following an initial suboptimal effort and several cycles of systemic chemotherapy, has been adopted in many centers (Pecorelli et al.,2003). Furthermore, for patients in whom initial cytoreduction is contraindicated due to widespread metastatic disease or poor performance status, neoadjuvant chemotherapy is given in order to reduce the extent of disease and improve the performance of the patients, after which surgery can proceed (Pecorelli et al., 2003).

The advantages of neoadjuvant chemotherapy include a risk reduction of peri-operative morbidity, a higher rate of optimal resection, and the fact that survival is not compromised by deferring the initial attempt at surgical debulking (Huober et al., 2002; Baekelandt et al., 2003).

In our center, both interval debulking and neoadjuvant chemotherapy have been frequently used in patients with advanced disease in whom the only initial surgery that can be done is biopsy or in whom the tumor was unresectable at diagnosis. The purpose of this study is to evaluate survival rates and the prognostic factors that impact on the survival of these patients.

Materials and Methods

Following Research Ethics Committee approval, the medical records were reviewed for all 29 advanced epithelial ovarian cancer patients (FIGO stage IIIC-IV) at Chiang Mai University Hospital between January 2001 and December 2006 who could not reach maximum primary surgery or in whom surgeons were unable to perform initial cytoreductive surgery due to non-optimized performance status with wide spread of disease and who were receiving at least three courses of chemotherapy before repeated surgical cytoreduction. The following data were extracted by chart reviewed: demographic data, symptoms presented, FIGO stage, histological cell type and grading, the details of chemotherapy, the type of surgery at first and second attempt, and the status at follow up.

The first surgery attempt was done in referral hospitals in some patients, but all secondary cytoreductive surgery was performed in our institute. Optimal debulking was defined as residual disease less than 1 cm, which is

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consistent with the Gynecologic Oncology Group definition (Gallo et al., 2003) . The chemotherapy regimen was either a platinum-based combination or single platinum, depending on the patient's performance status at initial diagnosis. Patients who received neoadjuvant chemotherapy were diagnosed as epithelial ovarian cancer by cytology or rising CA 125 plus imaging. The amount of chemotherapy before and after secondary cytoreductive surgery was determined by the attending doctors.

Patients were scheduled for follow up after completion of treatment every 3 months in the first year, every 4 months in the second year, every 6 months in the third to fifth years and then annually thereafter. During follow-up, progression of disease was defined either by physical examination, rising of tumor markers, or imaging study showing re-growth of the tumor.

Progression free survival and the overall survival were defined as the interval from the date of primary surgery or the date of first administration of chemotherapy to the date of tumor progression or the date of patients' death, respectively.

Statistical analysis of the data was carried out by the SPSS for Windows program (Version 10.0). Progression free survival and overall survival were estimated by the Kaplan-Meier Method. Multivariate analyses of the independent prognostic factors were performed using a Cox proportional hazards regression model.

Results

Patient/tumour characteristics

Patient/tumour characteristics are summarized in Table 1. Most complained of abdominal distension. About 70% of the patients were in FIGO stage IIIC and the rest were in stage IV. All of the studied patients demonstrated ascites. The most common histology was serous cystadenocarcinoma and the most common tumor grading was poor differentiation. The greater part of lesion was confined to the pelvis in 50% of the studied patients. The majority organ of distant metastasis site in stage IV was the lung, followed by the liver and the spleen parenchyma. The median level of initial CA 125 was 171 IU/ml. There were 11 patients (38%) with a CA 125 level greater than 1,000 IU/ml.

Surgery

Primary and secondary surgeries were carried out in 24 and 29 patients, respectively (see Table 2). About half of the studied patients underwent only tumor biopsy in the initial surgery. Five patients did not receive primary surgery because optimal cytoreduction was not possible at initial diagnosis. They were given neoadjuvant chemotherapy after being diagnosed as having epithelial ovarian cancer by cytology or imaging plus CA 125 as mentioned above. The secondary cytoreductive surgery was performed after at least 3 courses of chemotherapy. Optimal cytoreduction was achieved in 20 patients while 8 of these patients revealed no residual tumor after operation. The rest achieved only sub-optimal debulking. Severe complication with iatrogenic resection of the right external iliac artery was found in one patient. Her tumour was diagnosed as a stage IIIC clear cell carcinoma and she received 3 courses of carboplatin plus paclitaxel before secondary cytoreduction. However, only tumor debulking was conducted with suboptimal result. A femoro-femoral bypass graft was performed by a vascular surgeon to repair

Table 1. Patients' Characteristics (N=29)

Mean age (range: age)		54 (42-70)
Presenting symptom	Abdominal mass	10 (34.5)*
	Abdominal pain	10 (34.5)
	Abdominal distension	17 (58.6)
	Dyspnea	2 (6.9)
Stage	IIIC	20 (69.0)
	IV	9 (31.0)
Histology	Serous	20 (69.0)
	Endometrioid	3 (10.3)
	Clear cell	4 (13.8)
	Mixed serous/ clear cell	1 (3.4)
	Undiff carcinoma	1 (3.4)
Tumor grade	Well diff	1 (3.4)
	Moderately diff	6 (20.7)
	Poorly diff	17 (58.6)
	Unclassified	5 (17.2)
	Ascites	29 (100)
Greater part of lesion	Pelvis	15 (51.7)
	Abdomen	4 (13.8)
	Both pelvis & abdomen	10 (34.5)
Distant metastasis	Lung	6 (20.7)
	Liver	2 (6.9)
	Spleen	1 (3.4)
The median level of initial tumor marker (CA 125: range)		171(19-5000) IU/ml

*Number (%)

Table 2. Surgical Procedures (29 patients)

Timing	Type	No. (%)	Residual dis (%)		
			No	Opt	Subopt
Primary	Biopsy	16 (55.2)	-	-	16
	Unilateral SO	8 (27.6)	-	-	8
	Total	24 (82.7)	-	-	24
Secondary	Debulking tumor	3 (10.3)	-	2	1
	TAH+BSO	7 (24.1)	1	1	5
	TAH+BSO+App	7 (24.1)	2	4	1
	TAH+BSO+LN	3 (10.3)	2	1	-
	TAH+BSO+LN+App	8 (27.6)	3	3	2
	TAH+BSO+bowel*	1 (3.4)	-	1	-
	Total	29 (100)	8	12	9

No, none; Opt, optimal; Subopt, suboptimal; SO, salpingo-oophorectomy; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; App, appendectomy; LN, lymph node sampling; *, resection

Table 3. Chemotherapy Cycles Stratified by Regimen

Cycle	1	2	3	4	5	6
Initial regimen (N=29)						
Carboplatin			4	1		
Carboplatin + paclitaxel			12	7		1
Cisplatin + cyclophosphamide			2			
Cisplatin + gemcitabine			2			
Subsequent regimen (N =28)						
Carboplatin		1	5			
Carboplatin + paclitaxel		5	12	1		
Cisplatin + cyclophosphamide			2			
Cisplatin + gemcitabine			2			

Table 4. Number of Patients Receiving Chemotherapy Regimens Stratified by Timing

Initial\Subsequent	Carboplatin	PT	PC	PG	Total
Carboplatin	4	1	-	-	5
PT	2	17	-	-	19
PC	-	-	2	-	2
PG	-	-	-	2	2
Total	6	18	2	2	28

PT, paclitaxel & carboplatin; PC, cisplatin & cyclophosphamide; PG , cisplatin + gemcitabine

the transaction vessel. She developed deep vein thrombosis with acute renal failure due to progression of tumor and passed away after only one month of secondary cytoreduction.

Chemotherapy

The details of chemotherapy are summarized in Tables 3 and 4. Most patients received 3 courses of carboplatin plus paclitaxel before interval debulking surgery and were given 3 courses of chemotherapy after that. The mean number of total courses of chemotherapy was 3 cycles with a range of 3-9 cycles. The majority of the studied patients received the same regimen at initial and subsequent chemotherapy as shown in Table 4. Only 3 patients received the different regimens. Two of them were given 4 cycles of carboplatin plus paclitaxel followed by 2 and 3 cycles of carboplatin in each. Both of them remained free of disease progression. The other patient was given 2 cycles of carboplatin and was changed to carboplatin plus paclitaxel due to rising CA 125. After the second course of carboplatin plus paclitaxel, she underwent cytoreductive surgery and achieved suboptimal debulking. The same combination regimen was administered to her for 2 cycles after surgery. This patient died from progression of disease 5 months after the last course of chemotherapy.

Follow up and survival

With the mean follow-up time of 22 months (2-63 months), a total of 24 patients (82.8%) revealed progression of disease after treatment. Of these patients, 17 died from progressive disease. Figures 1 and 2 demonstrate their survival curve. The 5 years progression free survival and overall survival were 10% and 22% while the median progression free survival and overall survival were 13 months and 34 months, respectively. If we exclude 5 patients who received neoadjuvant chemotherapy, the median progression free survival and overall survival were 14 and 27 months (data not shown in the figure).

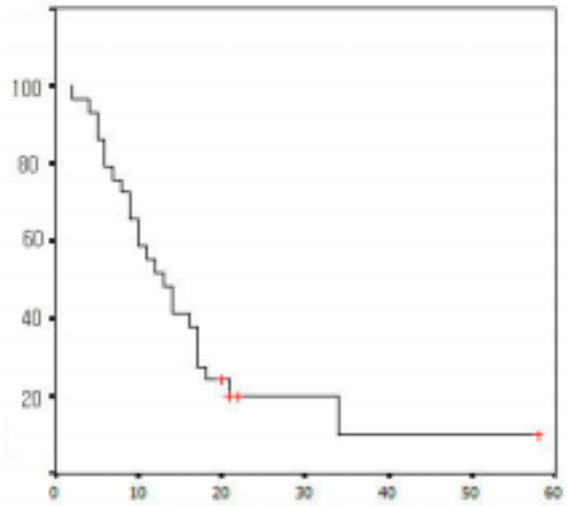

Figure 1. Progression-Free Survival

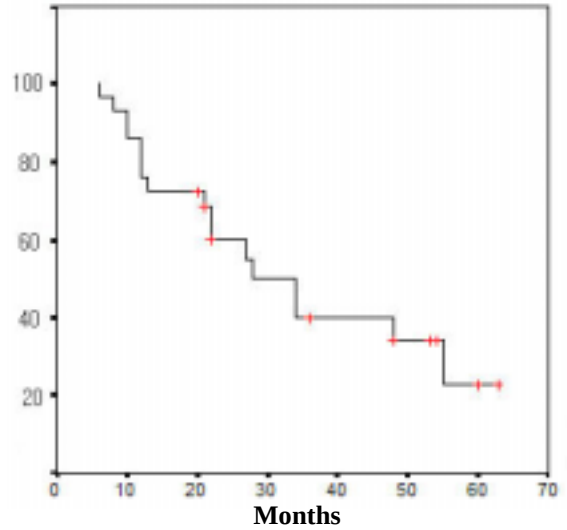

Figure 2. Overall Survival

Multivariate analysis revealed that the major distribution disease which spread in the whole abdomen and the suboptimal residual tumor volume were the independent prognostic factors for progression free survival. However, only the suboptimal residual tumor volume was the statistically significant adverse prognostic factor for overall survival as shown in Table 5.

Discussion

The benefit of interval debulking in increasing overall survival is controversial. In 6 non-randomized studies of interval cytoreduction following a primary suboptimal surgical effort, the feasibility of obtaining an optimal

Table 5. Multivariate Analysis of Prognostic Factors by the Cox Proportional Hazard Model

Prognostic factors	Progression Free Survival			Overall Survival		
	Relative risk	p value	95% CI	Relative risk	p value	95%CI
Age: < 60 vs. > 60 years	0.68	0.50	0.22-2.10	0.93	0.92	0.25-3.47
Tumor marker: < 1,000 vs. > 1,000	0.35	0.06	0.12-1.04	0.65	0.45	0.21-2.01
Histology Serous vs. non serous	0.85	1.12	0.35-3.58	2.29	0.26	0.55-9.56
Chemotherapy: Single vs. combination	0.26	0.08	0.06-1.18	0.78	0.76	0.14-4.19
Distribution site: Pelvis vs. abdomen + pelvis	3.03	0.03	1.13-8.08	2.66	0.08	0.87-8.07
Residual tumor: None & optimal vs. suboptimal	3.79	0.02	1.23-11.3	3.66	0.03	1.09-12.2
Stage: IIIC vs. IV	1.74	0.23	0.71-4.30	0.72	0.56	0.24-2.16

resection after induction chemotherapy has ranged from 24.1% to 77.3% (Wils et al., 1986; Neijt et al., 1987; Lawton et al., 1989; 1990; Redman et al.,1990; Jacob et al., 1991). Despite successful interval resection in a significant proportion of patients, these reports have consistently reported survival outcomes comparable to patients undergoing a suboptimal primary resection without interval surgery (Neijt et al., 1987; Redman et al., 1990; Jacob et al., 1991). In addition, with 3 prospective, randomized studies about the benefits of interval cytoreductive surgery in advanced ovarian cancer with bulky residual disease following an initial attempt at cytoreductive surgery, the results are inconclusive.

In 1994, Redman et al reported on 79 patients with advanced ovarian cancer and residual disease of more than 2 cm after initial surgery who were randomized to received chemotherapy alone (N=42) or chemotherapy with interval cytoreduction (N=37). All patients received a total of 8 cycles of platinum-based non-taxane chemotherapy, and half of the patients in interval cytoreductive surgery arm showed successful cytoreduction to residuals of less than 1 cm. Redman et al. also concluded there was no statistically significant difference in median overall survival time for patients undergoing interval surgery (15 months) compared to patients not undergoing interval surgery (12 months).

However, in the subsequent year, (van der Burg et al., 1995) reported results of a randomized phase III trial conducted by the European Organization for the Research and Treatment of Cancer (EORTC) to evaluate the benefits of interval surgery after suboptimal primary debulking by comparing 140 patients who received 3 cycles of cisplatin and cyclophosphamide chemotherapy followed by an interval attempt at cytoreduction and 3 additional cycles of chemotherapy to 138 similar patients receiving the same chemotherapy regimen without interval surgery. The interval surgery group had a statistically significant advantage in median survival time (26 months) compared to patients not undergoing interval surgery (20 months).

This finding was inconsistent with the report in 2004 from the Gynecologic Oncology Group (GOG); Rose et al. studied 550 patients with stage III & IV epithelial ovarian cancer left with a residual tumor of more than 1 cm following an initial attempt at primary cytoreductive surgery (Rose et al.,2004) . The design difference from the EORTC study was the chemotherapy regimen. All patients in the GOG study received cisplatin plus paclitaxel. They revealed no statistically significant difference in median survival time in patients who underwent interval surgery (33.9 months) and chemotherapy alone (33.7 months).

In the present study, 24 patients who received interval debulking surgery after at least 3 courses of chemotherapy showed median progression free survival and overall survival as 14 and 27 months, respectively. These findings are comparable to the study from the interval surgical arm of the EORTC study (van der Burg et al., 1995). The type of our initial surgery was similar to the EORTC study even though most of our patients received carboplatin plus paclitaxel instead of the cisplatin and cyclophosphamide which was used in the EORTC study.

Proposed advantages of neoadjuvant chemotherapy include an increased rate of optimal residual disease, less extensive surgery, reduced blood loss, lower morbidity, shortened hospital stay, improved quality of life, and acting as a mechanism to select out patients with platinum-resistant disease (Baekelandt et al., 2003, Lee et al.,2006). In our study, 5 patients received neoadjuvant and 3 of them (60%) achieved optimal cytoreductive surgery. This result is slightly higher than the previous reports which revealed the rate of optimal resection as 35%-50% of patients receiving neoadjuvant chemotherapy (Bristow et al., 2007, Huober et al., 2002, Inciura et al.,2006). This difference might be from the small number of our patients.

Four of 5 neoadjuvant chemotherapy patients in our study had progression of disease and 2 of them died of disease at 28 and 34 months after initial diagnosis. One patient still shows no evidence of disease at 22 months. The median overall survival in these 5 patients was 34 months. This outcome was slightly higher than the mean weighted median overall survival time of a meta-analysis study of platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer (Bristow et al., 2006).

The adverse prognostic factor for survival in the present study was suboptimal residual tumor. This finding was supported by the previous studies. They also mentioned the other independent adverse prognostic factors such as ascites, liver metastasis, poor performance status and age over 65 years (Kuhn et al., 2001,Rafii et al., 2007).

The morbidity of interval cytoreductive surgery in the previous report was reduced when compared with the patients who underwent primary surgery (Morice et al., 2003). In our study, we found only 1 patient with serious complication as external iliac artery resection.

The limitation of the present study was the small number of patients and the lack of comparison with data from advanced epithelial ovarian cancer patients without interval surgery. However, the outcome of this treatment was comparable to the well designed previous study.

In conclusion, interval debulking surgery and neoadjuvant chemotherapy before cytoreductive surgery revealed a favorable outcome in advanced epithelial ovarian cancer with a high rate of optimal residual tumor and minimal morbidity.

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