Original Article
Evaluation of prognostic factors for secondary cytoreductive surgery in Chinese patients with recurrent epithelial ovarian carcinoma

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Abstract: Objective: Secondary cytoreductive surgery (SCS) is reported to be beneficial for patients with recurrent epithelial ovarian carcinoma (EOC). The current study is to evaluate risk factors that would affect the surgical optimal resection rate and prognosis of recurrent EOC after SCS in Chinese patients. Methods: In our study, 44 patients with recurrent EOC treated with SCS at Shandong Cancer Hospital were retrospectively reviewed. Patient characteristics were collected and multivariate logistic regression was used to analyze factors that affect the optimal surgical resection rate. The overall survival rate was calculated by the Kaplan-Meier method. Cox proportional-hazards regression was used to analyze risk factors that affect the overall survival of these patients. Results: 90.9% (40/44) patients achieved optimal cytoreductive surgery. Logistic regression did not find any factor that affects the optimal surgical resection rate. Among 24 cases that received chemotherapy before SCS, 18 cases achieved good response and thus had a better survival rate after SCS. Multivariate Cox proportional hazard regression analysis indicated that differentiation, the extent of surgical resection during the initial surgery, and course and efficacy of chemotherapy prior to SCS, and efficacy of chemotherapy after the first recurrence significantly correlated with survival of patients with recurrent cancer (P < 0.05; OR < 1). Conclusion: Selection of patients that are suitable to perform SCS will enhance the optimal surgical resection rate. The prognosis of Chinese patients with recurrent EOC after SCS is affected by histologic grade, the extent of residual disease and the effect of chemotherapy after first relapse.

Keywords: Ovarian carcinoma, recurrent, secondary cytoreductive surgery (SCS), overall survival

Introduction

Epithelial ovarian cancer (EOC) is the fifth most common cancer leads to death in women [1]. Tumor cytoreductive surgery combined with post-operative chemotherapy of paclitaxel and platinum-based agents is the current standard therapy for primary EOC [2]. Although this treatment is effective for early stage EOC, more than 60% women with advanced EOC will develop recurrent disease [3, 4]. There is no developed treatment strategy for recurrent EOC. The 5-year survival rate of recurrent EOC is still less than 30% [5]. Salvage chemotherapy and second cytoreductive surgery (SCS) are the two main therapeutic strategies for the recurrent EOC [6]. Despite the advance of chemotherapy, surgery is still the mainstay of recurrent patients' management.

SCS has been demonstrated to be beneficial for patients with recurrent EOC [7-16]. SCS can prolong survival in patients with platinum-sensitive and even some isolated platinum-resistant recurrent ovarian cancer [6, 17, 18]. However, the factors affect the prognosis after SCS has not been fully studied. Thus in the current manuscript, we retrospectively investigated the clinic characteristics of patients with recurrent EOC undergoing SCS in Shandong Cancer Hospital from 2004 Jan to 2012 Jun and determined risk factors that affect the overall survival of these patients.

Table 1. Clinical characteristic in patients with recurrent ovarian cancer

Clinical characteristics	Cases
Clinical stages	
Stage I	7
Stage II	7
Stage III	28
Stage IV	2
Pathological iypes	
Serous adenocarcinoma	28
Endometrial carcinoma	4
Other	12
Histological differentiation	
Low	34
Middle	9
High	1

Methods

Study design and data collection

We reviewed general patient information, clinical pathology, and follow-up data for patients with ovarian tumor who underwent surgery in our hospital from 2004 January to 2012 June. EOC was staged according to the International Federation of Gynecology and Obstetrics (FIGO) criteria. All cases were typed and graded according to a revised standard of the World Health Organization (WHO). General information (age, height, weight, and medical complications), operation-related information (operation date, operation methods, intraoperative ascites, hemorrhage, and blood transfusion) and pathological data (pathologic types, differentiation grades, and FIGO stages) were recorded. Patient follow-up was carried out at the outpatient department or by telephone.

The preoperative case selection standards were: (1) recurrent patients with disease free interval (DFI) > 6 months after first-line chemotherapy; (2) single recurrent tumor site or multiple recurrent sites that could be optimally resected (complete resection or maximal diameter of residual tumor size ≤ 2 cm); (3) otherwise healthy, with no obvious multiple diseases and durable to surgery; (4) informed consent from patients or their legal surrogates. The judgment for the feasibility of tumor site resection was based on the following conditions: (1) the boundary for pelvic and abdominal lesion sites was clear and there were gaps between pelvic tumor and the pelvic wall; (2) tumors were still shown as nodule with clear boundary, no invasion to the piriformis or other vital organs, or with only limited invasion defined by radiology.

Statistical analysis

All the data were analyzed with SPSS15.0. Patients who had complete remission (CR), partial remission (CR) or stable disease (SD) according to the WHO criteria were considered responders. Patients who had progressive disease (PD) were considered non-responders. Calculation of survival rates were plotted by the Kaplan-Meier method and compared using the log-rank test. The relationship between clinical and pathological variables and survival was examined with univariate analysis using the χ^2 and Fisher's exact probability tests test. Factors with statistically significant differences in univariate analysis were included in multiple logistic regression analysis. A multivariate Cox proportional hazard regression analysis was performed for each of the variables of interest. Odds ratio (OR), 95% confidence intervals (95% CI) and Wald statistic *P* values were reported for each model. P ≤ 0.05 was considered to be statistically significant.

Results

Clinical characteristics of patients

We reviewed clinical information for patients with ovarian tumor who had surgery in our hospital during 2004 January to 2012 June. The follow-ups were carried at September 2012, at least 3 months from surgery had passed for all patients. We successfully followed up 44 patients, among whom 14 had family history of malignant tumor. The age was ranged from 14-69, and the median age is 48. Their clinical characteristics were listed in **Table 1**. There were 28 cases of serous adenocarcinoma, 4 cases of endometrial carcinoma and 12 cases of other pathological types. There were 34 cases with low differentiation, 9 cases with middle differentiation, and 1 case with high differentiation. There were 7 cases of stage I, 7 cases of stage II, 28 cases of stage III and 2 cases of stage IV patients.

Among 24 cases that received chemotherapy before SCS, 13 cases were estimated to be hard to reach optimal surgical resection. After
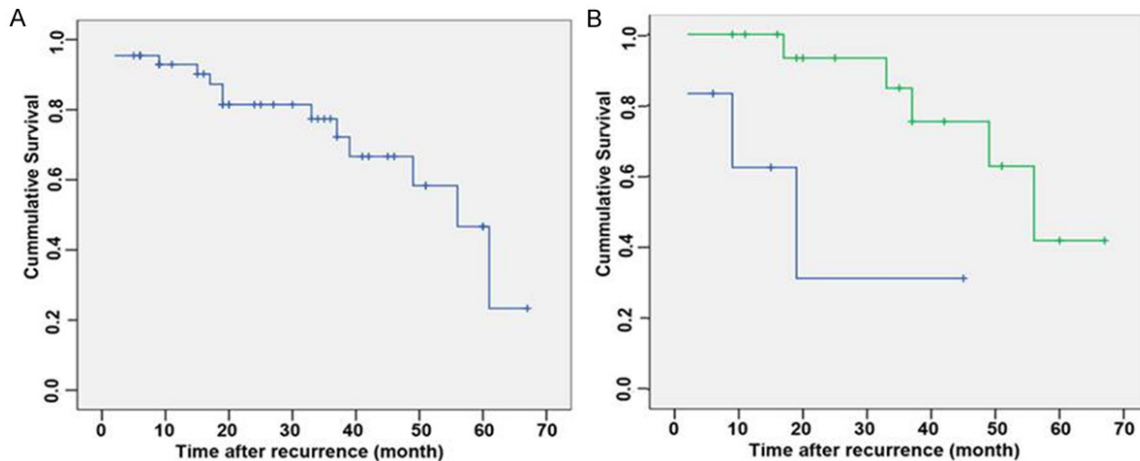
Figure 1. A. The Kaplan Meier survival curve of recurrent ovarian cancer patients following secondary cytoreductive surgery. Survival was defined as the time from recurrence to the death of a patient or the censoring or a patient. N = 44. B. The Kaplan Meier survival curve of patients with recurrent ovarian cancer stratified by response to preoperative neoadjuvant chemotherapy. N = 24; the green line indicates responders and the blue line indicates non-responders.
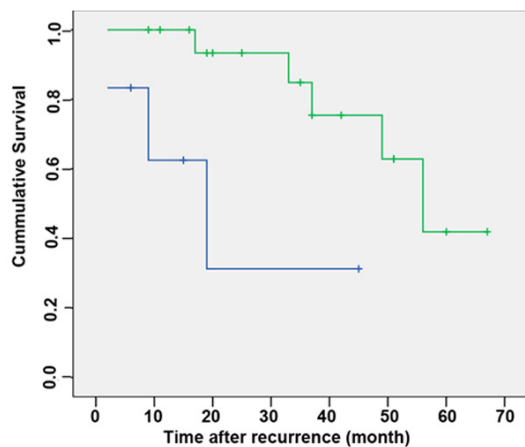

Figure 2. Comparison of survival rate in ovarian patients with effective and ineffective pre-operative chemotherapy. Green line indicates effective and blue line indicates ineffective pre-operative chemotherapy.

1 to 3 courses of adjunct chemotherapy, 7 cases were effective and reached partial remission and the other 6 cases without improvement. The other 11 cases received more than 6 courses of chemotherapy and reached remission, but there were still evidence showing tumor exist. There were 27 cases with isolated lesion site and/or limited to pelvic cavity, and 17 cases with extensive pelvic cavity metastatic lesion sites. There were 9 cases with ascites and among them 8 cases had extensive pelvic cavity metastatic lesion sites. There were 11

cases of patients with CA125 ≥ 500 U/mL and among them 8 cases had extensive pelvic cavity metastatic lesion sites. DFI was varied from 7 to 80 months, and medium was 15.5 months.

SCS operation extent and complications

Among the 44 cases of patients, 21 cases (47.7%) were resected with abdominal metastasis, including 5 cases of splenectomy, 4 cases of subcapsular metastasis of the liver, one case of diaphragm metastasis. 25 cases (56.8%) were resected with pelvic cavity. 17 cases (38.6%) had residual tumor in greater omentum and gastrocolic omentum primary cytoreductive surgery. 9 cases (20.5%) underwent pelvic lymphadenectomy or inguinal lymphadenectomy. 9 cases (20.5%) underwent partial ileectomy. 15 cases (34.1%) underwent partial excision of large intestine, including 11 cases of colectomy, 4 cases of presacral rectectomy. 2 cases underwent partial ureterectomy plus ureterocystotransplantation and 2 cases underwent partial cystectomy. 4 cases (9.1%) underwent abdominal wall metastasis resection. One case underwent adrenalectomy and another case underwent cholecystectomy. There were 8 cases had severe complications, including 3 cases of operational disruption, 5 cases of intestinal obstruction, all of which were caused by tumor. 4 cases of the intestinal obstruction were relieved by a second SCS and 1 case was relieved by conservative treatment.

Table 2. Univariate analysis of risk factors for survival of recurrent ovarian cancer patients

Variable	Regression coefficient	Standard deviation	Wald value	P value	Odds ratio
Tissue differentiation	-1.685	0.827	4.151	0.042	0.186
Primary operation extent	-1.132	0.593	5.039	0.025	0.264
Recurrent lesion status	1.326	0.647	4.198	0.040	3.764
Ascites	1.602	0.598	7.170	0.007	4.962
CA125 > 500 U/mL	1.910	0.61	9.674	0.002	6.750
Chemotherapy course before SCS	-0.951	0.406	5.483	0.019	0.386
Chemotherapy effect before SCS	-1.864	0.835	4.977	0.026	0.155
SCS optimal extent	1.008	0.435	5.377	0.020	2.741
Chemotherapy effect after recurrence	-2.049	0.516	15.781	0.000	0.129

Factors that affect satisfactory rate of SCS

All the patients received trans-abdominal hysterectomy plus bilateral salpingo-oophenrectomy, partial or complete omentectomy, debulking tumor surgery, pelvic lymphadenectomy or para-aortic lymphadenectomy. Among these patients, 90.9% (40/44) achieved optimal cytoreductive surgery, and complete resection was 13.6% (6/44). The maximal tumor residual diameter ≤ 0.5 cm, ≤ 1 cm and ≤ 2 cm was 13.6% (6/44), 75% (33/44) and 90.9% (40/44), respectively. After cytoreductive surgery, all patients received platinum-based chemotherapy for at least 6 courses. Logistic multivariate analysis did not show any factor significantly affect tumor resection rate. This could be due to a small number of unsatisfied SCS (4 cases).

Survival rate

The survival interval was defined as the time from recurrence to the death of patients or censored. There were 13 cases of death and 31 censored cases. The median survival interval was 26.0 months and the average was 28.7 months. The survival rate for 1, 2, 3, 4 and 5 year was 90.2%, 81.5%, 77.4%, 66.7% and 46.7%, respectively (**Figure 1**). The survival rate was significantly different between responder patients and non-responder patients (log-rank test, $P < 0.05$) (**Figure 2**).

Risk factors for survival interval after recurrence

The risk factors for survival rate in recurrent ovarian cancer were first analyzed with univariate logistic regression analysis. Eighteen risk factors were analyzed, including family history, diseased age, stage, pathological types and differentiation, primary operation extent and chemotherapy course and effect after operation, DFI, recurrent lesion status, ascites, CA125 levels, chemotherapy course and effect for SCS, ideal degree for SCS, chemotherapy course and effect after first recurrence and radiotherapy. The results demonstrated that 9 risk factors including tissue differentiation status, primary operation extent, recurrent lesion status, ascites, CA125 > 500 U/ml, chemotherapy course and effect for SCS, ideal degree for SCS, chemotherapy effect after first recurrence are significantly correlated with recurrent survival ($P < 0.05$, **Table 2**). Multivariate Cox proportional hazard regression analysis indicated that differentiation, the extent of surgical resection during the initial surgery, and course and efficacy of chemotherapy prior to SCS, and efficacy of chemotherapy after the first recurrence significantly correlated with survival of patients with recurrent cancer ($P < 0.05$; OR < 1). Among them, the odds ratio for tissue differentiation status was less than 1 (OR = 0.186), suggesting that low differentiation is beneficial for survival. Among 10 cases of patients with middle and high differentiation, there were 9 cases of low differentiation and 1 case of middle differentiation after SCS.

Discussion

The recurrence of EOC often suggests a poor prognosis and is often lethal. The general treatment principle for recurrent EOC is to palliate but not to cure the disease. The main considerations for the treatment of recurrent EOC are to increase the survival time, relieve symptoms and enhance life quality. Because there is still lacking of effective second-line chemotherapy, the 5-year survival rate for recurrent EOC is still less than 30% so far [19].

SCS has been demonstrated to be effective in treatment of recurrent EOC (16-18). Onda et al reported that SCS dramatically increases overall survival in recurrent ovarian cancer patients with DFI > 12 months, no liver metastasis, isolated tumor site and the diameter of metastatic tumor < 6 cm [20]. Zang et al found that optimal SCS (tumor residual ≤ 1 cm) is correlated with improved patient survival in 107 cases of recurrent EOC patients who received SCS [21]. This suggests that optimal SCS is beneficial for recurrent EOC. However, due to the extensive pelvic cavity implanting and adjoin in recurrent EOC, SCS is hard to perform. If optimal resection cannot be reached, SCS may not be beneficial for the patient survival, and even will increase body burden, decrease the immunity and promote the tumor development. Thus evaluation of the feasibility of recurrent tumor resection prior surgery is extremely important.

Many factors could affect the resection feasibility and efficacy such as numbers of recurrent lesion sites, ascites and the efficacy of preoperative chemotherapy [22]. In the current manuscript multivariate logistic analysis did not find any factors affected the resection efficacy, this could be due to the limited number (4 cases) of unsatisfied resection. However, among 24 cases of patients who received preoperative chemotherapy, the survival rates were significantly higher in effective cases compared to ineffective cases. Thus, the resection efficacy could be enhanced by comprehensive pre-operative evaluation and selection of suitable cases. Based on our previous surgery experience, we normally select patients with clear tumor border, no invasion to pelvic piriformis or other vital organs, or only limited invasion with gaps still exist between pelvic tumor and pelvic wall, no invasion to vascular by pelvic and abdominal lymphatic metastasis to perform SCS. In the current report, 70.5% patients had combined surgery with excision of vital organs such as gastrointestinal tract, urinary tract, liver, gall bladder, spleen and kidney. The tumor satisfactory resection rate was 90.9% (40/44), among which 13.6% (6/44) was complete tumor resection, 61.4% (27/44) had a maximal tumor residual ≤ 1 cm and 15.9% (7/44) had a maximal tumor residual ≤ 2 cm. This is obviously higher than previous reported rate of 53.7% [23]. Among 4 cases who had a maximal tumor residual > 2 cm, there were 3

cases with extensive pelvic and abdominal metastasis, one case with pelvic and abdominal lymph node metastasis. The reasons for big tumor residual were two cases had tightly adjoin between iliac lymph nodes and blood vessels, and the other two cases had tightly adjoin between pelvic tumor and pelvic wall.

The 5-year survival rate in the current report was 46.7%, which is higher than previous reported 32% [19]. We analyzed the risk factors for survival time in recurrent EOC patients underwent SCS and found that tissue differentiation status, primary surgery extent, recurrent lesion status, ascites, CA > 500 U/ml, chemotherapy course and effectiveness prior to SCS, the ideal degree of SCS, chemotherapy effectiveness after the first recurrence are all important to the survival time after recurrence. Among them, tissue differentiation status, the ideal degree of SCS and chemotherapy effectiveness after the first recurrence are most important factors.

The ideal degree of SCS relies on well-trained professional doctors and the effectiveness of chemotherapy is dependent on reasonable and effective second-line therapy. Performing SCS in patients who are sensitive to platinum agents is beneficial to the survival rate [24]. To be noted, though the difference is significant between platinum-resistant and platinum-sensitive patients, it is still possible that platinum-resistant patients are sensitive to other chemotherapeutic drugs such as paclitaxel or other second-line therapies [10]. The selection of second-line chemotherapy for recurrent EOC should be personalized and based on previous response, recurrent status and the efficacy of chemotherapy prior to SCS.

It is noteworthy that the OR for tissue differentiation was lower than 1 (OR = 0.186), indicating that prior to SCS the lower differentiation status the more beneficial for the recurrent survival. Among the 10 cases of high and middle differentiated patients, pathological examination defined nine cases as low differentiation and one case as middle differentiation after SCS. This suggested that recurrence in high and middle differentiated patients will lead to advances of the tumor and result in poor prognosis. Thus, for these recurrent patients, more attention should be paid to and selection of

second-line therapy needs to be more cautious.

In summary, the survival interval for recurrent EOC is closely related to the tissue differentiation status, ideal degree of SCS and the efficacy of chemotherapy after recurrence. There is still no standard for the selection of recurrent EOC patient to undergo SCS. Large prospective studies are needed to define the selection criteria for SCS. Based on the borderline of the tumor site, location, ascites, CA125 levels and the efficacy of chemotherapy prior to SCS, the optimal resection rate could be enhanced by selection of suitable patients for well-prepared SCS. In addition, the introduction of minimally invasive method would further increase the survival rate [25]. Together with effective second-line chemotherapy, the survival interval for recurrent EOC and life quality could be enhanced.

Disclosure of conflict of interest

None.

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