

Original Article

The clinical study of secondary cytoreductive surgery in the treatment of low grade serous ovarian cancer

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Abstract: Objective: To investigate the therapeutic effect of secondary cytoreductive surgery in the patients with low grade serous ovarian cancer and to analyze the influence of the postoperative quality of life. Method: We collected the clinical data of patients with low grade serous carcinoma who underwent secondary cytoreductive surgery in our hospital from January 2003 to January 2015, and performed a retrospective analysis. We collected the basic data of patients, survival information, chemotherapy and disease related characteristics. We recorded the patient's post-operative treatment, overall survival (OS), disease-free survival (DFS) and death situation, and evaluated the quality of life of patients before and after the secondary cytoreductive surgery according to European organization for research and treatment of cancer quality of life questionair (EORTC QLQ-C30). Results: A total of 50 patients with low grade ovarian cancer were enrolled in this study. There were 39 patients (78%) with gross residual disease (GRD) among the 50 patients. The median DFS was 57.4 months and 14.9 months respectively for patients without and with GRD. The median OS was 92.9 months and 70.4 months respectively for patients without and with GRD. The Cox multivariate regression analysis showed that the risks of survival with disease and death in patients with GRD were 3.27 and 2.04 times greater than who without GRD. The results were applied comparative t-test and showed that the postoperative quality of life was better than that preoperative in patients ($P < 0.05$). Conclusion: Whether the secondary cytoreductive surgery is performed thoroughly or not is closely related to the disease-free survival and overall survival of patients with low grade serous ovarian cancer. The implementation of secondary cytoreductive surgery is helpful to improve the quality of life of patients.

Keywords: Low-grade serous cancer, secondary cytoreductive surgery, gross residua, overall survival, disease-free survival

Introduction

Ovarian cancer is one of the most common cancers in female, which ranks the sixth in common female cancers in the world [1]. On a global scale, the newly diagnosed patients with ovarian cancers accounted for approximately 4% of all newly diagnosed female cancer patients each year [2, 3]. Statistics data demonstrated that, the incidence of ovarian cancer is approximately 6.6/100000 [4]. Generally, the patients are at the terminal stage of ovarian cancers when diagnosed, thereby leading to a low survival rate. How to effectively treat and prevent ovarian cancer is a key and difficult problem in the treatment of ovarian cancer at present.

In current clinical practices, the effects of tumor reduction surgery on the treatment of ovarian cancer have been confirmed by a number of studies [5-7]. Some studies concluded that, complete tumor reduction surgery could enhance the efficiency of chemotherapy by reducing the clones of resistant cells. In addition, tumor reduction surgery could contribute to enhancing the killing effect of chemotherapy on the small-volume and well-vascularized tumors [8]. Although it is common to apply the combination treatment of single tumor reduction surgery and systemic chemotherapy on ovarian cancer patients clinically, a significant proportion of patients (approximately 70%) will suffer from disease recurrence [9]. Therefore, it is necessary to apply secondary cytoreductive

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surgery in treatment. At present, the studies on the effects of secondary cytoreductive surgery mostly focused on the treatment for high-grade serous tumor [10, 11], while the therapeutic effect on low-grade serous tumors is still not clear. Therefore, it is necessary to conduct clinical studies to further clarify its therapeutic effect on low-grade serous ovarian cancer.

In this study, the clinical data of the patients who suffered from low-grade serous ovarian cancers and received secondary cytoreductive surgeries were retrospectively analyzed, in order to clarify the therapeutic effect of secondary cytoreductive surgery on low-grade serous ovarian cancer and to investigate its effect of on survival time. Results show that, secondary cytoreductive surgery is beneficial to the treatment of patients with low-grade serous ovarian cancer, which can effectively increase the disease-free survival and overall survival and the quality of life of patients.

Materials and methods

Materials

This study was conducted to collect women patients who were diagnosed with low grade serous ovarian cancer in our hospital from January 2003 to January 2015. The inclusion criteria of patients were as follows: the pathological diagnosis was low grade serous ovarian carcinoma, and they underwent secondary cytoreductive surgery; the patients with complete surgery and follow-up data; the patients who can meet the classification standard of the International Federation of gynecology and Obstetrics (FIGO) [13] and exhibit recurrence. Exclusion criteria were as follows: patients with secondary cytoreductive surgery clinical information is incomplete; pathologically diagnosed non-serous ovarian cancer; combined liver and other organ damage and other serious secondary complications which surgery cannot be performed. This study has been approved by the Ethics Committee of our hospital.

Data collection

Basic data of patients, including the stages, surgical resection and chemotherapy schemes, recurrence, progression-free duration, treatment schemes for recurrence, serum carbohydrate antigen 125 (CA125), CT image data dur-

ing recurrence, the presence of ascites and physical examination data, were acquired. In addition, during the secondary cytoreductive surgery, the nodule number, gross residua (the residual with the size smaller than 1 cm can be defined as no gross residua) [14] and postoperative complications were also recorded. Postoperative treatment methods, overall survival, disease-free survival and the occurrence of death were recorded during follow-ups.

Definition of overall survival and disease-free survival

overall survival was defined as the interval from the date of diagnosis to the date of death or failure of follow-up visit, or the interval from secondary cytoreductive surgery to the date of death or failure of follow-up visit. disease-free survival was defined as the interval from secondary cytoreductive surgery to the date of disease recurrence or death.

Quality of life assessment

EORTC QLQ-C30: including five functional scales-somatic function, role function, cognitive function, emotional function and social function; three symptoms scale-fatigue, pain and vomiting of the (EORTC QLQ-C30); six response-specific items and one overall quality of life scale. The score was linearly transformed to 0-100 points. The higher the functional scale and the overall quality of life scale, the better the function and health status. The higher the symptom scale and specific symptom score, the more severe the symptoms or problems.

Statistical analysis

Epidat3.1 was used for data entering, SPSS17.0 was used for statistical analysis, and Kaplan-Meier survival analysis was used to construct survival curves, and the log-rank method was used to compare differences between two groups of survival time. The Cox regression model was used for univariate analysis to determine the impact of different clinical variables (ascites, GRD, CA125 level, age, number of tumor nodules, and the use of drugs before and after secondary cytoreductive surgery) on OS and DFS. The univariate variables were included in the multivariate Cox regression analysis. Paired t test was used to analyze the difference of quality of life before and after the

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Table 1. Basic information of patients

Variable	Number (%)
Patient age at diagnosis (median, range)	45.6 (21-74)
FIGO classification at diagnosis	
I/II	4 (8%)
III/IV	42 (84%)
Unconfirmed	4 (8%)
Disease status after primary tumor reduction	
Without gross residua	8 (16%)
With gross residua	29 (58%)
Unconfirmed	13 (26%)
Adjuvant therapy	
Monitoring	5 (10%)
Chemotherapy	
Platinum drugs + paclitaxel	32 (64%)
Pure platinum drugs	6 (12%)
Platinum drugs + cyclophosphamide	4 (8%)
Platinum drugs + paclitaxel + bevacizumab	1 (2%)
Platinum drugs + hormone therapy	1 (2%)
Hormone therapy	
Etrozole	1 (2%)
Maintenance treatment	
Chemotherapy	
Platinum drugs	3 (6%)
Hormone therapy	
Letrozole	5 (10%)
Tamoxifen	6 (12%)
Leuprorelin acetate	1 (2%)

Table 2. Therapeutic regimens before secondary reduction surgery

Drugs used before secondary reduction surgery	Number
Chemotherapy	
Paclitaxel	5
Platinum drugs paclitaxel	5
Carboplatin	3
Liposomal doxorubicin	1
High-dose chemotherapy + biological therapy	1
Ifosfamide + etoposide	1
Vinorelbine	1
Hormone therapy	
Letrozole	1
Tamoxifen	1

two reduction. We further carried out a multivariate regression analysis for significant variables in univariate analysis. Paired t test was used to analyze the difference of quality of life before and after secondary cytoreductive sur-

gery. $P < 0.05$ is considered to be statistically significant.

Results

Basic information of included patients

50 patients with low-grade ovarian cancers were included in this study. The basic data were shown in detail in **Table 1**. The ages at which the patients were diagnosed with serous ovarian cancers range from 21 to 74 years old, with an average of 45.6 years old. Seven patients were identified with serous low malignant potential tumors before being diagnosed with low-grade serous cancers [12]; the other 43 patients were initially diagnosed with low-grade serous tumors. According to the classification standard of FIGO, 42 patients (84%) were grade III/IV, 4 patients (8%) were grade I/II, and 4 patients (8%) were not clearly classified. After the initial tumor reduction surgeries, 8 patients (16%) had no gross residua, 29 patients (58%) had gross residua, and the residual state of the remaining 13 patients (26%) was unknown due to unclear clinical data. After the initial tumor reduction, 44 patients (88%) received chemotherapy, with the median period of chemotherapy of six treatment course (ranging from 3~15 treatment courses), in which one of the most common chemotherapy regimens was platinum drugs combined with paclitaxel. Among the other six patients who did not undergo adjuvant chemotherapy, one patient underwent hormone therapy, and the remaining five patients were monitored.

Chemotherapy regimens before and after secondary cytoreductive surgery

The average medium interval between the first cytoreductive surgeries and secondary cytoreductive surgeries was 33.2 months (6.5~81.4 months). Before the secondary cytoreductive surgery, 19 patients (38%) underwent systemic treatments (As shown in **Table 2**), and 31 patients (62%) directly underwent secondary cytoreductive surgeries (As shown in **Table 3**). In addition, according to the data of physical examinations, four patients were detected with ascites. After

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Table 3. Therapeutic regimens after secondary reduction surgery

Drugs used after secondary reduction surgery	Number (%)
Chemotherapy	
Platinum drugs + paclitaxel	10 (20%)
Platinum drugs + liposome doxorubicin	3 (6%)
Liposome doxorubicin	3 (6%)
Paclitaxel	3 (6%)
Topotecan	3 (6%)
Platinum drugs + paclitaxel + bevacizumab	1 (2%)
Pure platinum drugs	1 (2%)
Ifosfamide + etoposide	1 (2%)
Altretamine	1 (2%)
Gemcitabine	1 (2%)
Others	1 (2%)
Hormone therapy	
Letrozole	6 (12%)
Tamoxifen	5 (10%)
Anastrozole	1 (2%)
Leuprolide acetate	1 (2%)

Table 4. Information of the patients undergoing secondary reduction surgeries

Variable	Number (%)
Treatment when progression/recurrence	
Chemotherapy	20 (40%)
Surgery	30 (60%)
Platinum drug status during secondary reduction surgery	
Tolerated	21 (42%)
Sensitive	23 (46%)
Not receiving platinum therapy	6 (12%)
Disease status during secondary reduction surgery	
Without gross residua	11 (22%)
With gross residua	39 (78%)
Complications	
Bleeding and need blood transfusion	13 (26%)
Pneumonia	3 (6%)
Abscess	1 (2%)
Anastomotic leak	1 (2%)
Bacteremia	1 (2%)
Bladder incision	3 (6%)
Enterotomy	1 (2%)
ICU	3 (6%)
Pancreatitis	1 (2%)
Urinary tract infections	1 (2%)
Wound infection	1 (2%)
Hospitalized due to intestinal obstruction	1 (2%)

secondary cytoreductive surgeries, 28 patients (56%) underwent chemotherapy, with the median period of chemotherapy of six treatment courses (2~19 treatment courses), and additionally, 13 patients (26%) received hormone therapy, with the median period of treatment of three treatment courses (3~6 treatment courses). As shown in **Table 3**.

Situations of patients during secondary cytoreductive surgery

The related situations of the patients who underwent secondary cytoreductive surgeries were shown in **Table 4**. Eleven patients (16%) had no gross residua, and 39 patients (78%) had gross residua. Moreover, the complications arose in 30 patients (60%).

Overall survival and disease-free survival

By calculation, the average median disease-free survival and overall survival of all patients were 14.9 and 64 months. At the 95% confidence interval, they were 8.98-20.82 and 36.51-91.49 months, respectively. In addition, based on the presence of gross residua, the disease-free survival and overall survival of patients were analyzed using survival curve (As shown in **Figures 1** and **2**). The DFS and OS of the patients with no GRD were longer than those with GRD, and the difference were statistically significant ($P < 0.001$).

The GRD is a prognostic factor for the survival of low grade serous ovarian cancer

We will conduct univariate analysis according to the following factors: ascites, GRD, CA125 level, age, number of tumor nod-

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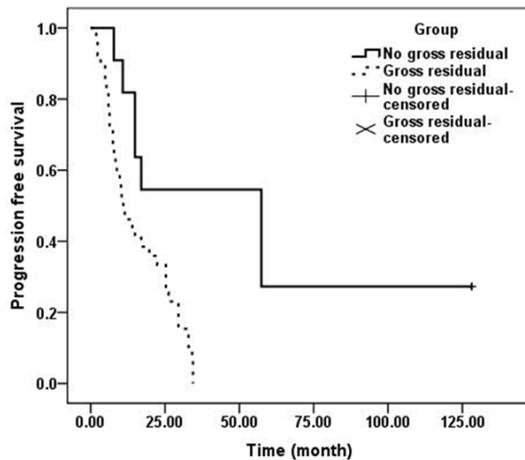


Figure 1. The disease-free survival. The median disease-free survival of patients without gross residua was 57.4 months, and the 95% confidence interval was 26.64-88.16 months; the median disease-free survival of patients with gross residua was 14.9 months, and the 95% confidence interval was 5.86-16.14 months ($P=0.001$).

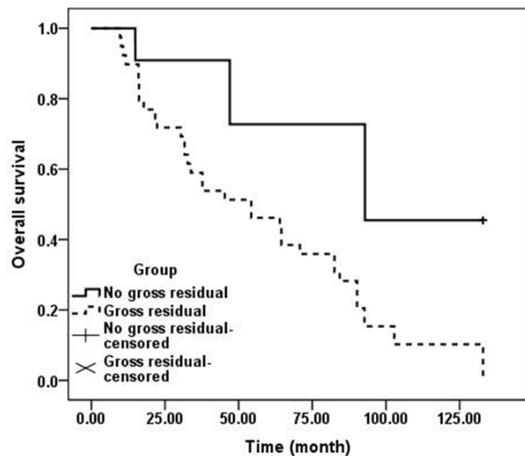


Figure 2. The overall survival. The median overall survival of patients without gross residua was 92.9 months, and the 95% confidence interval was 71.62-119.76 months; the median overall survival of patients with gross residua was 70.42 months, and the 95% confidence interval was 23.59-85.01 months ($P<0.001$).

ules, and the use of drugs before and after secondary cytoreductive surgery. The **Table 5** shows that GRD and more than 3 tumor nodules are the factors that influence the survival of low grade serous ovarian cancer. Multivariate Cox analysis of univariate variables was performed, and the results showed that the risk of survival and death was 3.27 and 2.04 times

higher than that of the remaining patients. We further carried out a Cox multivariate regression analysis for significant variables in univariate analysis, and the result showed that the risks of survival with disease and death in patients with GRD were 3.27 and 2.04 times greater than those without GRD. We further carried out a multivariate regression analysis for significant variables in univariate analysis, and analyzed the risk factors for overall survival and disease-free survival in patients with low grade serous ovarian cancer (**Table 6**).

The secondary cytoreductive surgery improves the quality of life of patients

Patients' physical function, role function, social function, pain, nausea and vomiting, dyspnea, diarrhea, loss of appetite and overall quality of life were significantly improved ($P<0.05$) compared with preoperative, as shown in **Table 7**.

Discussion

The present research results confirmed that, after secondary cytoreductive surgery, the disease-free survival and overall survival of the patients without gross residua were significantly prolonged, by 57.4 and 92.9 months, respectively. Postoperative quality of life was significantly better than preoperative; suggesting that secondary cytoreductive surgery significantly improved the quality of life of patients and reduced the symptoms and pain of patients.

At present, clinical studies on the effect of secondary cytoreductive surgery on the treatment for epithelial ovarian cancer, mainly focused on the treatment scheme of high-grade serous ovarian cancer. Most of patients with high-grade serous ovarian cancers require chemotherapy or hormone therapy, in which part of the patients can benefit from the treatment of secondary cytoreductive surgery. Retrospective studies results revealed that, secondary cytoreductive surgery could help prolong patient's survival time, and half of these patients were identified with recurrent epithelial cancer by pathological examination; furthermore, these patients had better sensitivity to platinum drug chemotherapy [5, 15]. Some ongoing prospective clinical trials are trying to define the exact effects of secondary cytoreductive sur-

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Table 5. The univariate analysis of survival of low grade serous ovarian cancer

Variables	Number	DFS			OS		
		β	RR (95% CI)	P	β	RR (95% CI)	P
Ascites							
Yes	4						
No	46	0.148	1.16 (0.46-2.95)	0.752	0.489	1.63 (0.61-4.34)	0.328
GRD							
Yes	11						
No	39	1.475	4.37 (1.69-11.24)	0.002	0.948	2.58 (1.27-5.25)	0.009
CA125 lever							
<57 U/mL	25						
\geq 57 U/mL	25	-0.274	0.76 (0.43-1.35)	0.352	-0.129	0.88 (0.39-1.97)	0.756
Age (year)							
<45.6	25						
\geq 45.6	25	-0.020	0.98 (0.55-1.73)	0.934	0.049	1.05 (0.40-2.79)	0.922
The number of tumor nodes							
<3	5						
\geq 3	45	1.966	7.14 (1.72-30.30)	0.007	1.247	3.48 (0.81-15.04)	0.095
The use of drugs before secondary cytoreductive surgery							
Systematic treatment	19						
No Systematic treatment	31	0.832	2.30 (0.31-17.11)	0.416	1.102	3.01 (0.50-18.06)	0.228
The use of drugs after secondary cytoreductive surgery							
No	9						
Chemotherapy* (1)	28	-0.580	0.56 (0.18-1.78)	0.325	-0.673	0.51 (0.11-0.34)	0.387
Hormone therapy* (2)	13	-0.315	0.73 (0.14-3.93)	0.714	-0.030	0.97 (0.85-1.11)	0.652

*Dummy variable.

Table 6. The multivariate analysis of survival of low grade serous ovarian cancer

Variables	Number	DFS			OS		
		β	RR (95% CI)	P	β	RR (95% CI)	P
GRD							
Yes	11						
No	39	1.185	3.27 (1.26-8.47)	0.015	0.713	2.04 (1.19-3.72)	0.020
The number of tumor nodes							
<3	5						
\geq 3	45	1.67	5.29 (1.24-22.70)	0.025	0.207	1.23 (0.90-1.67)	0.187

gery [16], in which low-grade serous cancers are also included in some studies. However, the effect of the secondary cytoreductive surgery on low-grade serous cancer has not yet been elucidated [17]. According to the results of a meta-analysis conducted by Al Rawahi *et al.*, female patients who underwent secondary cytoreductive surgery and without gross residual have longer survival times [5]. In 2009, Bristow *et al.* carried out studies on 2019 patients who underwent secondary cytoreductive surgery, and concluded that the volume of

reduced tumor was directly correlated with survival time [15]. When the number of patients in whom the residual tumors were removed using cytoreductive surgery increased, the survival time of all patients increased by three months with the increase of the number of patients by every 10%. In these studies, how to effectively define the best degree of cytoreductive surgery remained controversial. In addition, the selection bias of patients may also lead to exaggeration of the effectiveness of secondary cytoreductive surgery.

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Table 7. Comparison of quality of life scores between before and after secondary reduction surgery

	Preoperative	Postoperative	t	P
Functional Dimensions				
Physiological function	53.84 ± 14.27	76.52 ± 15.69	7.562	<0.001
Role function	62.91 ± 19.87	71.65 ± 23.45	2.011	0.024
Emotional function	63.57 ± 22.44	65.52 ± 25.48	0.406	0.343
Cognitive function				
Social function	59.21 ± 16.78	70.56 ± 22.45	2.863	0.003
The symptom dimension				
Tired	25.17 ± 8.45	23.22 ± 7.35	1.231	0.111
Pain	33.45 ± 14.56	27.92 ± 11.58	2.102	0.019
Nausea and vomiting	30.75 ± 13.64	25.74 ± 14.93	1.752	0.042
Specific symptoms				
Difficulty breathing	15.71 ± 10.68	11.67 ± 9.21	2.026	0.023
Sleep disorders	35.23 ± 22.65	31.55 ± 24.25	0.784	0.217
Constipation	40.16 ± 31.45	33.63 ± 29.58	1.069	0.144
Diarrhea	28.51 ± 13.37	23.35 ± 11.26	2.087	0.019
Loss of appetite	36.53 ± 24.48	27.76 ± 14.39	2.184	0.016
Economic difficulties	46.37 ± 33.64	42.65 ± 29.34	0.589	0.279
Overall quality of life	41.52 ± 20.58	65.39 ± 23.62	5.388	<0.001

In one study comprised of 1100 ovarian cancer patients who underwent secondary cytoreductive surgery, the researchers found that, after complete removal of the tumors using secondary cytoreductive surgery, the patients with tumors of 0.1-1.0 cm in size had significant increased overall survival times than the patients with tumors of larger than 1 cm [17]. Their study also confirmed that, compared to patients with tumors larger than 1 cm, patients tumors of 0.1-1.0 cm had increased disease-free survival time. They also found that, the patients who had no ascites and only local lesions at the time of recurrence were more suitable for surgery. Similar results were also observed in clinical trials of DESKTOP OVAR. The results of this trial revealed that physical condition, presence of ascites and FIGO classification were all effective predictive indicators of complete resection [18]. Therefore, it is generally considered that, ascites, the number and size of the tumors, the state of the body function and disease-free determines the survival time in later stage and whether the resection was completely [19-22]. The study conducted by Frederick confirmed that preoperative serum CA125 level could be used to predict the therapeutic efficiency of secondary cytoreductive surgery on tumors without gross residua [23]. However, in

this study, our results revealed that serum CA125 was not a significant predictor.

The study also has some limitations. Firstly, the number of samples is relatively small and it is necessary to conduct a study with a large number of samples to confirm the results of this study. Secondly, this study is a clinical prospective study and therefore it is impossible to confirm the actual situations of the patients. Thirdly, all patients in this study were from the our hospital and it may result in the selection and reference bias, thus affecting the accuracy of the results. Therefore, further research is needed to confirm the results of this study.

In summary, our results suggest that low-grade serous ovarian cancer patients can be treated by secondary cytoreductive surgery. In addition, the tumors should be removed as far as possible during secondary cytoreductive surgery, which can help the patients get a longer disease-free survival and overall survival.

Disclosure of conflict of interest

None.

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