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Original Research

Treatment and survival outcomes from epithelial ovarian caner in women aged 65 years or older

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Summary

Objective: To describe the clinical features associated with the treatment and survival outcomes of older women with epithelial ovarian cancer. *Materials and methods:* Fifty-five women aged $\geq$ 65 years and diagnosed with epithelial ovarian cancer were enrolled. The clinical characteristics, treatment procedure and survival outcomes were presented and analyzed. *Results:* The mean age at the time of epithelial ovarian cancer diagnosis was 69.9 $\pm$ 3.9 years, with most women presenting with advanced stage disease (83.6%). Thirty-five patients (63.6%) received optimal cytoreduction, of whom 23 underwent surgery with a low surgical complexity score Forty-two percent of patients presented with postoperative complications, while five patients presented with three or more postoperative complications simultaneously. The large majority (87.3%) of patients received chemotherapy, and more than half (42%) relapsed. The three-year overall survival rate was 52.8%, while three-year progression-free survival was 33.3%. Advanced FIGO stage and residual lesions were the factors associated with reduced overall survival ($p < 0.0001$, $p = 0.004$), FIGO stage was also associated with progression-free survival ($p = 0.001$). *Conclusions:* Aggressive surgical debulking and chemotherapy are feasible for older epithelial ovarian cancer patients. Advanced FIGO stage and residual lesions are associated with reduced survival.

Key words: Geriatric patients; Epithelial ovarian cancer; Cytoreduction; Chemotherapy; Survival.

Introduction

Ovarian cancer is the fifth leading cause of cancer-related death among women worldwide [1], with epithelial ovarian cancer (EOC) being the most common type of ovarian cancer. The median age of women diagnosed with EOC is 63 years [2] and approximately 70% of older patients (defined as > 65 years old) [3] are diagnosed as stage III ~ IV [4]. Thus, older patients often face complex treatment courses. Since older patients are often excluded from clinical trials, there is little information to guide physicians seeking the optimal strategy for such EOC patients. In addition, with increasing life expectancies many older patients can tolerate extensive surgery and challenging courses of chemotherapy. This leaves physicians facing a dilemma and lacking appropriate assessment protocols and criteria for surgery and chemotherapy.

Primary debulking surgery followed by adjuvant platinum-based chemotherapy is the standard treatment for advanced ovarian cancer. Removal of all gross residual disease is associated with improved survival of ovarian cancer patients, and the median survival is more than 50 months [5, 6]. Older patients may have problems often not present in the younger patient population. They more frequently have comorbidities, as well as impairments in personal aspects of daily living, cognitive impairments, and geriatric special syndromes [7]. These challenges have led to older women being treated less aggressively than younger patients even in the absence of co-morbidities. However, several studies have found that the poor prognosis of older women with EOC is mainly due to the suboptimal and less radical management, without consideration of their biological status [8-10]. Older patients usually receive delayed and dose-reduced chemotherapy [11,12]. With the development of appropriate anesthesiology, perioperative care, and surgical techniques, older patients without serious comorbid conditions can receive the standard treatments recommended for younger patients without increased postoperative complications and mortality [13]. Thus it is recommended that patients over 65 receive complete cytoreduction and routine chemotherapy whenever possible [14,15].

In this study, we conducted a retrospective analysis of the clinical features, treatment and survival outcomes of older

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patients with EOC in our clinical practice. We also sought to identify the factors associated with better prognosis and survival.

Table 1. — *Clinical and pathology characteristics of 55 geriatric patients with epithelial ovarian cancer received surgeries in our hospital.*

	No.	%
Total	55	
Age (Mean ± SD)	69.91 ± 3.96	
65-69	31	56.36
70-74	15	27.27
> 75	9	16.36
FIGO stage		
I	8	14.55
II	1	1.82
III	42	76.36
IV	4	7.27
Pathological type		
Serous	44	80
Mucinous	5	9.09
Endometriosis	0	0
Clear cell	6	10.91
Comorbid illnesses	29	52.73
Multiple comorbid	10	18.18
Disease type		
Primary	53	96.36
Recurrent	2	3.64
Adjuvant Chemotherapy	48	87.27
< 6	32	58.18
≥ 6	23	41.82
Resistance	7	14.58[a]
Relapse	23	41.82

a. 7(14.58%) patients developed resistance among the 48 patients receiving adjuvant chemotherapy, not among the 55 patients.

Table 2. — *Type of comorbid illnesses.*

	No. (%)
Hypertension	16 (29.09)
Coronary artery disease	8 (14.55)
Diabetes	8 (14.55)
Other cancer[a]	2 (3.64)
Other illnesses[b]	5 (9.09)

a. 1 case of breast cancer, 1case of gastric cancer. b. 1 case of old tuberculosis, 1 case of post-cholecystectomy, 1 case of kidney transplant (donor), 1 case of hepatic hemangioma, 1case of venous thrombosis.

Table 3. — *Surgical procedures and operative outcome in 55 geriatric patients with epithelial ovarian cancer.*

	No.	%
Surgery	55	100
Staging Surgery	4	7.27
PCS	39	70.91
ICS	7	12.73
Other	5	9.09
Residual disease		
R0[a]	29	52.73
R1[b]	6	10.91
RX[c]	20	36.36
ASA		
1	2	3.64
2	30	54.54
3	23	41.82
CSG		
Low	43	78.18
Intermediate	10	18.18
High	2	3.64
Postoperative complications	23	41.82
Estimated blood loss (EBL)	775.09 ± 758.31 (range 50∼3000)	
< 500	25	45.45
500-999	15	27.27
1000-1999	9	16.36
≥ 2000	6	10.91
Intraoperative Transfusion	26	47.27
Total hospital stay	20.38 ± 10.33 (range 11∼83)	
10-19	33	60
20-29	18	32.73
≥ 30	4	7.27
Postoperative hospital stay	12.93 ± 5.15 (range 6∼30)	
< 10	15	27.27
10-19	32	58.18
20-29	7	12.73
≥ 30	1	1.82
Postoperative interval of initial chemotherapy	15.84 ± 9.95 (range 4∼41)	
No chemotherapy	5	9.09
< 10	19	34.55
10-19	14	25.45
20-29	11	20
≥ 30	6	10.91

a. No residual tumor by the naked eye; b. Residual tumor of less than 1 cm in diameter; c. Residual tumor of more than 2 cm in diameter.

Materials and Methods

Data on all women (n = 55) diagnosed with EOC between January 2005 and June 2018 were extracted from the

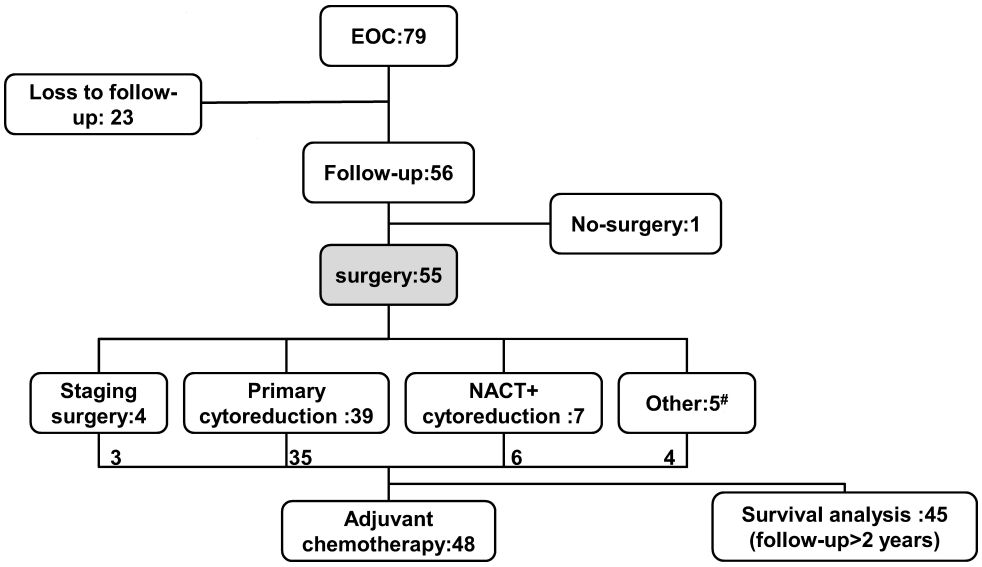

Figure 1. — The inclusion process and treatment process of patients recruited in this study. #: two cases of recurrent EOC underwent secondary cytoreduction, three cases of biopsy. EOC: Epithelial ovarian cancer; NACT: Neoadjuvant chemotherapy

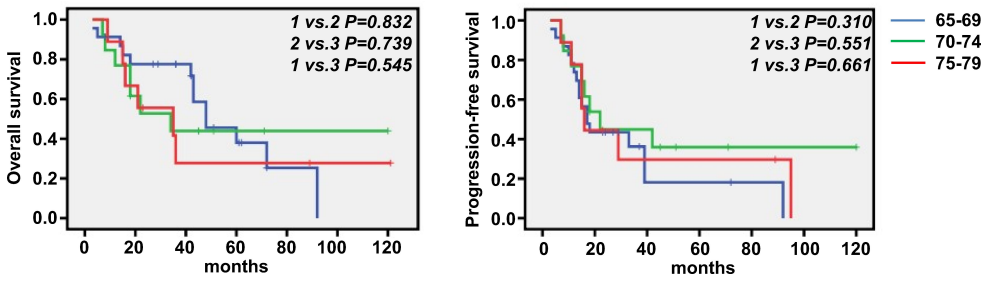

Figure 2. — A. Kaplan-Meier estimate of overall survival and progression-free survival by patients' age.

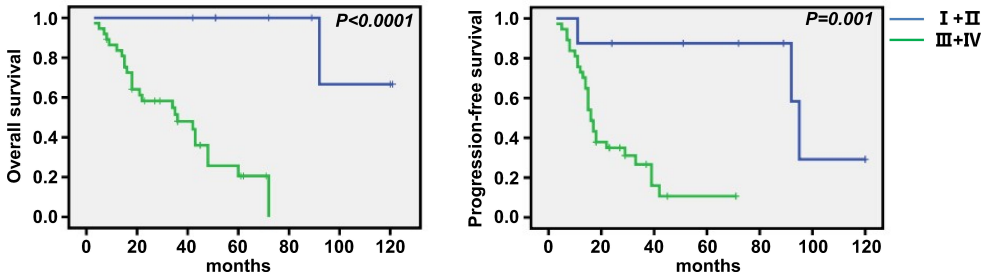

Figure 3. — Kaplan-Meier estimate of overall survival and progression-free survival by FIGO stage.

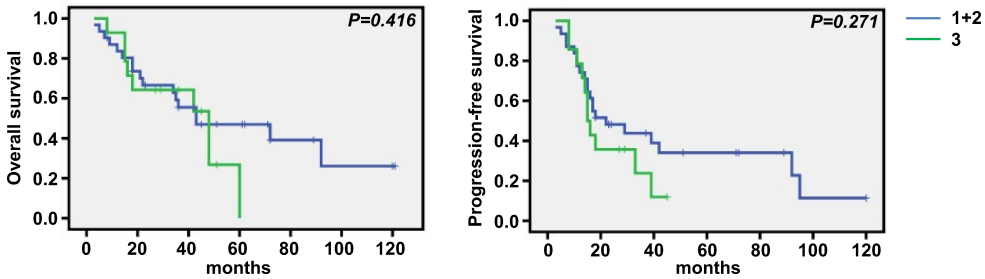

Figure 4. — Kaplan-Meier estimate of overall survival and progression-free survival by the score of ASA.

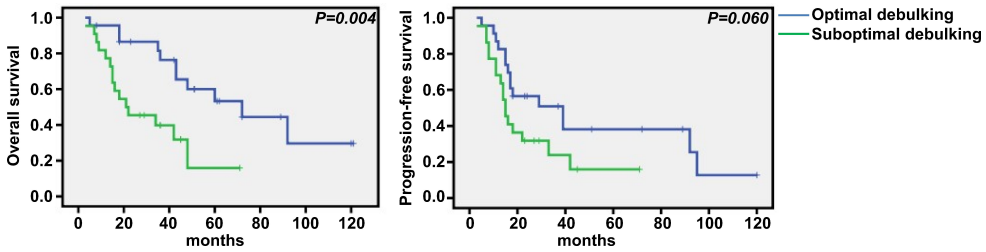

Figure 5. — Kaplan-Meier estimate of overall survival and progression-free survival by the residual lesions.

Table 4. — *Type of Postoperative complications.*

	No. (%)
Hypoproteinemia	10 (18.18)
Wound dehiscence	3 (5.45)
Anemia	3 (5.45)
Hypokalemia	3 (5.45)
Ascites	3 (5.45)
Ventosity	3 (5.45)
Pulmonary infection	2 (3.64)
Deep venous thrombosis	2 (3.64)
Renal dysfunction	2 (3.64)
Nausea and vomiting	2 (3.64)
Diarrhe	2 (3.64)
Ileus	1 (1.82)
arrhythmia	1 (1.82)
Ventosity	1 (1.82)

medical records of the First Affiliated Hospital of University of Science & Technology of China. Patients confirmed to have a diagnosis of EOC after surgery were eligible unless they had a prior ovarian cancer treatment, a history of oophorectomy, an unresectable mass, incomplete required data, or pregnancy at presentation. The inclusion process and treatment process of patients recruited in this study are presented in Figure 1. The clinical and pathology characteristics of the study patients are shown in Table 1. This study was approved by the ethics review board of Anhui Provincial Hospital, file # 2018KY52.

Data collected from patient records included clinical characteristics, surgical treatment details, post-operative treatment, and outcomes. Clinical characteristics included age, tumor histology and grade, FIGO stage, comorbidities, scores of American Society of Anesthesiologists (ASA) class, imaging, and laboratory test results. Surgical treatment details included the surgical procedure used, ascites volume, estimated blood loss, intraoperative transfusion, diameter of largest residual lesion, and surgical complexity score group (CSG). Post-operative treatment characteristics included postoperative complications, the length of total and postoperative hospital stay, the postoperative interval of initial chemotherapy, regimen of chemotherapy and number of cycles. Outcomes included platinum sensitivity, adverse events, time to progression, and date of last follow-up or death.

Tumor stage was based on pathological stage information and the International Federation of Gynecology and Obstetrics (FIGO) system, supplemented by clinical stage information if pathological stage was unavailable or unknown. In the case of neoadjuvant chemotherapy, tumor stage was recorded based on clinical stage information only. Histologic type was recorded based on the World Health Organization classification system. Optimal surgery was defined as no residual tumor (R0) or residual tumor of less than 1 cm in diameter (R1). Residual tumors of more than 1 cm in diameter (RX) were classified as suboptimal debulking.

Chemotherapy regimens were given as individual therapy with platinum and paclitaxel in different regimens. Complete blood cell counts and serum biochemistry tests were performed the day before administration of chemotherapy and after chemotherapy infusion. Response to primary chemotherapy was determined by imaging results and serum CA-125 levels.

For follow-up, patients generally visited every three months for the first two years and every six months thereafter. At each visit they received a pelvic examination and a serum CA-125 test. Abdominal ultrasound scans were performed every six months, while computed tomography of the whole abdomen and chest X-ray were performed annually unless a relapse was suspected. Progression of disease and ovarian cancer–related deaths were recorded at each follow-up visit.

Kaplan–Meier and log-rank tests were used to estimate progression-free (PFS) and overall survival (OS). These were calculated from the date of initial cytoreductive surgery to the date at which progression was recorded, or date of last progression-free follow-up visit or death. All statistical tests were two-sided, with p values < 0.05 considered statistically significant. Data analyses were performed with Graph Pad Prism 6.0 and SPSS 16.0.

Results

Patients and clinical characteristics

The clinical and pathological characteristics of the 55 EOC study patients are shown in Table 1. The women were all $\geq$ 65 years of age, with 43.6% being $>$ 70 years. Fifty-three patients were being treated for EOC as a primary diagnosis, and two for recurrent EOC. Most presented with ad-

Table 5. — *Simultaneous occurrence of three or more surgical complication.*

No	Age	Stage		Residual lesions	Surgery	Complications	Status	Overall survival
1	67	IIIc	Low	RX	PCS	Hypoproteinemia, hyponatremia, renal dysfunction, ventosity	Died	18
2	72	IIIc	Low	RX	PCS	Hypoproteinemia, ascites, Deep venous thrombosis	Died	22
3	67	IIIc	Low	RX	PCS	Ventosity, Nausea and vomiting, arrhythmia	Died	42
4	78	IIIc	Low	R0	ICS	Hypoproteinemia, ascites, Hypokalemia, Nausea and vomiting, Diarrhea	Died	35
5	67	IIIc	Low	R0	ICS	Wound dehiscence, Ileus, Pulmonary infection, Deep venous thrombosis	Survival	8

R0, optimal cytoreduction with no residual macroscopic disease; RX, suboptimal cytoreduction with residual macroscopic disease > 2 cm; PCS, primary cytoreductive surgery; ICS, interval cytoreductive surgery.

vanced stage disease (83.63%), with serous tumor being the most common pathological type (80%). Half the patients (52.7%) had at least one comorbid condition and 34.5% had multiple comorbid conditions. The frequency and types of comorbid conditions are presented in Table 2. Hypertension was the most common single condition (29.1%), followed by coronary artery disease (14.5%) and diabetes (14.5%). Two patients had prior non-ovarian cancer diagnoses. The first of these had been treated for clear cell carcinoma and breast cancer, while the second had been treated for high-grade serous carcinoma and also had a history of gastric cancer. In neither case was the prior cancer history thought to be related to the current diagnosis of EOC. In addition, one women had a history of tuberculosis, another cholecystectomy, another a prior kidney transplant (donor), another hepatic hemangioma, and another woman had a prior history of venous thrombosis.

Perioperative procedure

All patients received surgical treatment, the details of which are presented in Table 3. Three patients received pelvic peritoneal or omental biopsies as their only surgical treatment. Both of the recurrent EOC patients underwent surgeries allowing for optimal secondary cytoreduction.

The majority of patients (63.6%) received optimal cytoreduction, with 20 (36.3%) receiving conservative treatment or non-optimal debulking. Cases where optimal cytoreduction could not be achieved included one case of palliative interval cytoreductive surgery (tumor involved in the root of small bowel mesentery), three women who received biopsies only, and sixteen women who received primary palliative cytoreductive surgery. Fifteen of the 20 cases had an ASA score of three.

Among the 35 patients who received optimal cytoreduction at debulking surgery, 23 (65.7%) underwent surgery with a low CSG because of comorbid diseases (60.8%) or because of senile age (71.30 $\pm$ 4.23). Only two patients received optimal cytoreduction with high CSG. Both were 65 years old and diagnosed with high-grade serous ovarian cancer at stage IV and an ASA score of three. One underwent resection of uterus, bilateral adnexal, omentum, para-aortic lymph nodes, bladder retrograde peritoneum, pelvic floor peritoneum, partial rectum, and sigmoid colon, as well as sigmoid colorectal anastomosis. This patient received initial chemotherapy eight days after operation, then finished adjuvant chemotherapy for six times. After two courses of neoadjuvant chemotherapy, the other patient underwent resection of the uterus, bilateral adnexal, omentum, appendix, partial diaphragmatic surface, abdominal pelvic peritoneal, and a sigmoid colon resection as well as colorectal anastomosis. She completed four courses of adjuvant chemotherapy. Both these patients had no serious surgical complications, no disease progression was detected, and both were still alive at the conclusion of the study.

Twenty-three patients presented postoperative complications (Table 4), of which hypoproteinemia was the most common (18.18%). Five patients had three or more kinds of postoperative complications simultaneously (Table 5). All complications resolved with treatment, and there were no deaths due to serious complications. 49(89.09%) of the patients left hospital within 20 days of surgery, and 19 patients (34.5%) began an initial round of chemotherapy within 10 days of their initial surgical treatment.

Chemotherapy

Following surgery, 48 (87.3%) patients received chemotherapy. Among these, 7 developed resistance and 23 cases relapsed. Only 23 (41.8%) women completed all six prescribed rounds of chemotherapy. Eight patients received neoadjuvant chemotherapy and 7 underwent interval cytoreductive surgery followed by adjuvant chemotherapy. One patient underwent only a biopsy and received no postoperative chemotherapy. Among the 7 patients who received neoadjuvant chemotherapy in this study, 4 achieved R0 surgery, two presented with grade1 (G1) hematologic toxicity and the others reported no side effects. Side effects from chemotherapy were reported by 56.2% (27/48) of patients and included 21 cases of hema-

tologic toxicity and 10 cases of G3-G4 myelosuppression. No deaths were attributed to chemotherapy in this cohort.

Survival analysis

All patients were followed up in the clinic or by telephone. The survival analyses included only patients who had reached a follow-up period of more than two years at the end of our study. Ten patients who had been treated for less than two years prior to our analyses were not included in the survival analysis. Of the 45 EOC patients who follow-up lasting over two years and were included in the survival analyses, the median OS and PFS were 43.0 months (95% CI: 35.8-50.2 months) and 18 months (95% CI: 10.2-25.8 months) respectively. Kaplan–Meier curves showing OS and PFS for the 45 patients according to age, FIGO stage, score of ASA and residual lesions are presented in Figure 2, 3, 4 and 5. These analyses revealed that FIGO stage (Figure 3), and residual lesions (Figure 5) were significantly associated with OS. In addition, FIGO stage was associated with PFS (Figure 3). The diameter of residual lesions after surgery was not associated with PFS, but was related to OS (Figure 5). Sixty percent of women survived at least two years and 52.7% survived at least three years. The rate of two-year PFS was 35.56% and three-year PFS was 33.33%.

Discussion

Therapeutic management of elderly patients with EOC is challenging and requires a balance between complete cytoreduction to enhance survival, and the prevention of postoperative severe complications leading to death. According to The Surveillance, Epidemiology, and End Results (SEER) Program, rates of optimal surgery decrease with patient age ($<$ 60 years old: 43.7%; 60 to 79 years: 29.5%; $\geq$ 80 years old: 21.7%), and this results in increased mortality [8]. We found that postoperative residual tumors predict both OS and PFS among older patients with ovarian cancer. Older patients tolerate surgery well in our experience, with acceptable levels of complications and a mortality rate similar to that of younger patients [16]. Geriatric patients with ovarian cancer therefore deserve maximal surgical effort. In the present study, the majority of patients had a low or intermediate CSG, with only two patients having high CSG. Improvements in the fields of anesthesiology, perioperative care, and surgical techniques have increased the rate of operability and safety of surgery for older patients [17]. It has been reported that super upper abdominal surgery can be carried out even in older patients, however the complexity of surgery for older patients is greatly increased as well as the prognosis [18]. We also demonstrated that the association of stage with OS and PFS holds for older patients with ovarian cancer.

Sharma *et al.* showed that patients with comorbid conditions are able to tolerate radical procedures without an increase in postoperative complications[19]. In our study, although most patients (52.7%, 29/55) presented with at least one comorbid illness, no deaths occurred within 30 days of surgery. Among the 35 patients with optimal debulking, despite the presence of comorbid illness (18/38, 47.37%), they were able to achieve optimal debulking with a low postoperative mortality. The mean ASA score of patients that received conservative treatment or underwent non-optimal debulking was 2.6. ASA scores have previously been reported to influence survival [20], however in our study there were no significant associations between ASA and either OS ($p = 0.42$) or PFS ($p = 0.27$).

Prior studies have found the poor prognosis of older women with ovarian cancer was related to less use of chemotherapy [21]. Older patients can tolerate aggressive single agent and combination chemotherapy treatment [22], and paclitaxel plus platinum-based chemotherapy has been shown effective in the treatment of older patients with ovarian cancer [8,14,23]. Even though it has been demonstrated that completion of chemotherapy is associated with survival [24], just over half (51.2%; 32/48) of the patients treated with chemotherapy in the present study received less than the recommended six courses. Failure to complete six courses of chemotherapy was not associated with statistically significant differences in OS ($p = 0.770$) or PFS ($p = 0.548$) compared to those who completed therapy. We speculate this is probably due to the diversity of chemotherapy regimens included in this study. In addition, failure to complete courses was not the result of side effects due to treatment ($p > 0.05$) in this study population. Prior studies have demonstrated that toxicity does not significantly increase with age [21]. Villela *et al.* reported that older patients tolerate combination chemotherapy without increased rates of grade 3 and 4 toxicities when treated with paclitaxel and carboplatin [25]. As a result, we suspect the poor survival of older EOC patients is the result of inadequate chemotherapy rather than toxicity from this treatment.

Limitations of this study include the retrospective design, the relatively small number of patients, and the possibility of selection bias limiting the ability to generalize the findings. In principle, adequate treatment is possible in most cases even in the presence of comorbidities, hence advanced age should not be considered a contraindication for appropriate treatment. Adequate treatment for older patients with ovarian cancer is very important due to the aging world population, especially in China. In conclusion, this study suggests that older patients can achieve satisfactory outcomes with aggressive surgical debulking and optimal chemotherapy treatment.

Conclusion

Older EOC patients can achieve satisfactory prognosis provided that aggressive surgical debulking and chemotherapy are feasible. FIGO stage and residual lesions were both significantly associated with survival.

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Conflict of interest

The authors declare that there is no conflict of interest.

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