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Prognostic factors for maximally or optimally cytoreduced stage III nonserous epithelial ovarian carcinoma treated with carboplatin/paclitaxel chemotherapy

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Abstract

Objective: To identify factors predictive of poor prognosis in women with stage III nonserous epithelial ovarian cancer (EOC) who had undergone maximal or optimal primary cytoreductive surgery (CRS) followed by six cycles of intravenous carboplatin/paclitaxel chemotherapy.

Methods: A multicenter, retrospective department database review was performed to identify patients with stage III nonserous EOC who had undergone maximal or optimal primary CRS followed by six cycles of carboplatin/paclitaxel chemotherapy at seven gynecological oncology centers in Turkey. Demographic, clinicopathological and survival data were collected.

Results: A total of 218 women met the inclusion criteria. Of these, 64 (29.4%) patients had endometrioid, 61 (28%) had mucinous, 54 (24.8%) had clear-cell and 39 (17.9%) had mixed epithelial tumors. Fifty-five (25.2%) patients underwent maximal CRS, whereas 163 (74.8%) had optimal debulking. With a median follow-up of 31.5 months, the 5-year progression-free survival (PFS) and overall survival (OS) rates were 34.8% and 44.2%, respectively. Bilaterality (hazard ratio [HR] 1.44, 95% CI 1.01–2.056; $P = 0.04$), age (HR 2.25, 95% CI 1.176–4.323; $P = 0.014$) and maximal cytoreduction (HR 0.34, 95% CI 0.202–0.58; $P < 0.001$) were found to be independent prognostic factors for PFS. However, age (HR 2.6, 95% CI 1.215–5.591; $P = 0.014$) and maximal cytoreduction (HR 0.31, 95% CI 0.166–0.615; $P < 0.001$) were defined as independent prognostic factors for OS.

Conclusion: The extent of CRS seems to be the only modifiable prognostic factor associated with stage III nonserous EOC. Complete cytoreduction to no gross residual disease should be the main goal of management in these women.

Key words: cytoreduction, epithelial ovarian cancer, non-serous histology, prognosis, stage III.

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Introduction

Nowadays, it is well known that epithelial ovarian cancer (EOC) is not a homogenous disease.[1] Rather, EOCs are represented by a number of molecularly distinct diseases broadly defined by histotype with different routes of spread, patterns of relapse, response to chemotherapy and prognosis.[2]

Primary cytoreductive surgery (CRS) and taxane-/platinum-based adjuvant chemotherapy are the cornerstones of the initial treatment for all histological subtypes of EOC.[3,4] Nevertheless, prognosis is variable, largely depending on the quality of primary CRS and the time of development of platinum resistance. Therefore, advanced EOC represents a heterogeneous group regarding the outcome after initial management.[5]

Established prognostic factors for stage III EOC include age,[6,7] performance status (PS),[6] extent of residual disease (RD)[6,7] and histology.[7] Nevertheless, previous studies investigating the prognostic factors for advanced EOC suffer from several limitations, such as heterogeneous study populations (inclusion of patients with stage III and IV disease together),[8–11] analyzing serous and nonserous malignant tumors simultaneously,[6–15] small number of patients with nonserous EOC[7,9–13] and the variation in adjuvant chemotherapy regimens.[9,11,12,14] Although it has been well known for a long time that the quality of primary CRS is the strongest predictor of outcome,[16,17] the extent of RD after primary CRS was not an inclusion criterion in most of the previous studies, and patients with maximal, optimal and suboptimal CRS were generally analyzed simultaneously.[6,8,10–12] It seems plausible to adjust the optimality of primary CRS and adjuvant chemotherapy for the evaluation of prognostic factors for stage III EOC. In addition, it is difficult to claim that older series do reflect the current practice in terms of primary CRS and adjuvant chemotherapy.[12,13,15]

Previous studies investigating the prognostic factors for stage III EOC consistently analyzed serous and nonserous tumors together and included patients mostly with serous EOC.[6,7,12,13] Therefore, prognostic factors for stage III nonserous EOC have not been delineated clearly. From the current perspective that different histotypes in EOC probably represent different disease entities,[18] we wondered whether the established prognostic factors for all histotypes[6,7,12,13] are also valid when nonserous malignant tumors are analyzed as a separate group. Given the low frequency of nonserous histotypes, we designed this multicenter retrospective study in order to shed some light on this issue with the aid of a well-defined homogenous study population. The purpose of the current study was to identify factors predictive of poor prognosis in women with stage III nonserous EOC who had undergone maximal or optimal primary CRS followed by six cycles of intravenous (IV) carboplatin/paclitaxel chemotherapy.

Materials and Methods

Study design and eligibility

Medical records of women who underwent primary surgical treatment for EOC between January 2007 and December 2016 at seven gynecological oncology centers in Turkey were retrospectively reviewed. The study protocol was approved by the local institutional review boards. All patients provided informed consent regarding research use of their medical information at admission.

The study population included women who had nonserous EOC (i.e., endometrioid, clear-cell, mucinous and mixed subtypes) with histopathologically proven stage III[19]disease. Women were included if they had undergone primary surgical treatment, including total hysterectomy plus bilateral salpingo-oopherectomy, with bilateral pelvic and para-aortic lymphadenectomy and other surgical procedures, resulting in maximal or optimal CRS. All patients had to have RD of 1 cm or less in order to be eligible. Patients who were cytoreduced to greater than 1 cm of RD were excluded. Because this study focused only on women with nonserous EOC, women with high- and low-grade serous carcinoma were excluded, as well as patients having no lymphadenectomy. We also excluded patients who received neoadjuvant chemotherapy, women with synchronous malignancies and those with incomplete medical records. A PS of 0 (normal activity) or 1 (symptomatic and fully ambulatory) was also an eligibility criterion. Women with a PS ≥ 2 were excluded. Patients with coexisting medical comorbidities were excluded as this undoubtedly influences the decision-making process of a surgeon regarding whether to undertake an aggressive CRS.

Clinical information

Patient data were extracted from seven institutions with maintained EOC databases. After selecting the eligible cases, the following information was

abstracted from medical records: demographic characteristics, preoperative serum cancer antigen 125 (CA 125) level, date and type of surgical procedure, presence or absence of ascites, the status of peritoneal cytology examination (negative, or positive), bilaterality, size of RD after surgery, stage of disease, time to recurrence, length of follow-up and survival. Tumor characteristics were abstracted from original pathology reports. Data were collected from centers with an online standardized form. All operations were performed by gynecological oncologists with the intent to achieve optimal cytoreduction. RD after primary CRS was recorded according to the assessment by the surgeon. Lymphadenectomy was performed after completion of other cytoreductive procedures. All patients underwent detailed preoperative and surgical exploration to exclude primary colorectal and appendiceal carcinomas.

All pathological specimens from primary surgery were examined and interpreted by gynecological pathologists of the participating institutions who had experience in gynecological malignancies. Nonserous EOC was diagnosed after examination of permanent sections. Histological classification was performed with the criteria defined by the World Health Organization (WHO).[20,21] Architectural grading was defined by standard International Federation of Gynecology and Obstetrics (FIGO) criteria. Clear-cell carcinomas were neither graded nor assigned as grade 3 in this study. Cases diagnosed as high-grade endometrioid were not removed from the endometrioid group.

The current study investigated cases with mixed nonserous histologies (including mucinous, clear-cell, endometrioid and transitional cell types) as a separate group and did not assign mixed tumors according to the dominant component. Mixed tumors were diagnosed according to the WHO definition, in that more than one cell type was present, and the minority component accounted for at least 10% of the tumor. Mixed tumors containing serous component were excluded. For the purposes of this study, only pure tumors were classified as endometrioid, clear-cell or mucinous, whereas tumors with more than one cell type were classified as mixed. All tumors were staged according to the 2014 FIGO staging system.[19] In patients treated before 2014, stage was determined retrospectively on the basis of surgical and pathological assessment.

The treatment policies were decided by the attending physician or by the multidisciplinary tumor board at each participating institution. Adjuvant chemotherapy was administered to all patients. The standard primary chemotherapy regimen included paclitaxel 175 mg/m^2 plus carboplatin dosed at an area under curve of 5 or 6 every 21 days for six cycles. Targeted agents were not used to treat any of the patients during primary treatment.

Patients returned for follow-up evaluation every 3 months for the first 2 years, every 6 months for the next 3 years and annually thereafter. Computed tomography or magnetic resonance imaging was performed annually. Survival data were last calculated on 31st December 2016. The survival status of the patients was determined as alive or dead at the time of the last follow-up. For all study subjects with a recorded death, this was confirmed by performing a social security death index search.

Definitions

Baseline PS was defined according to the Gynecologic Oncology Group (GOG) criteria, and only patients with a PS of 0 (normal activity) and 1 (symptomatic and fully ambulatory) were included in the current study in order to overcome the confounding effect of PS on the measured outcome.

Maximal cytoreduction was defined as no gross RD (microscopic RD) after primary CRS. Optimal cytoreduction was defined as less than or equal to 1 cm maximal diameter of the largest residual tumor nodule at the completion of the primary operation. Suboptimal cytoreduction was defined as >1 cm of RD. Lymphadenectomy was defined as the performance of pelvic and para-aortic LN dissection at the same time. We defined pelvic lymphadenectomy as the removal of lymphatic tissue in the external, internal and common iliac and obturator regions. Para-aortic lymphadenectomy was defined as removal of the lymphatic tissue over the inferior vena cava and aorta, beginning at the level of aortic bifurcation up to the left renal vessels.

Progression-free survival (PFS) was defined as the time, in months, from the date of primary surgery until the date of documented recurrence on the basis of clinical examination or radiological imaging; death from any cause, whichever occurred first; or the date of last contact for patients remaining alive without recurrent disease. Patients who had no active ovarian cancer at the last contact were censored in the PFS analysis. Overall survival (OS) was calculated as the time period, in moths, between the date of primary surgery to the date of death or the last contact. Surviving patients were censored at their last known

follow-up. As treatment after relapse was not uniform and varied among institutions that participated in the current study, the primary end-point was chosen as PFS.

Statistical analysis

Statistical analyses were performed using the statistical software package SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The data were expressed as median and range for continuous variables. Binary variables were reported as counts and percentages.

Survival analysis was based on the Kaplan–Meier method, and the results were compared using a log-rank test. Cox regression analysis was used to determine factors affecting PFS and OS, presented as hazard ratios (HRs) and 95% confidence intervals (CI), unadjusted or adjusted for all factors. All variables with a P value <0.05 in the univariate analysis were included in the multivariate analysis. A P value <0.05 was considered to indicate statistical significance.

Results

During the study period, 367 women with stage III nonserous EOC were treated at seven participating centers. We excluded 23 patients who had no lymphadenectomy, 17 women who received neoadjuvant chemotherapy and 9 women with incomplete medical records. One hundred patients who received suboptimal debulking were also excluded. Therefore, the present analysis addresses the remaining 218 women. The rate of suboptimal CRS was found to be 31.4% (100/318) in the entire cohort. The inclusion process of the patients and the suboptimal CRS rates with regard to the histotypes are demonstrated in Table 1.

Of 218 women who met the inclusion criteria, 64 (29.4%) patients had endometrioid, 61 (28%) had mucinous, 54 (24.8%) had clear-cell and 39 (17.9%) had mixed epithelial tumors. The median age of the patients was 54 (range, 18–78) years, and the median duration of follow-up was 31.5 (range, 1–120) months. There were 55 (25.2%) women with stage IIIA1, 14 (6.4%) with stage IIIA2, 34 (15.6%) with stage IIIB and 115 (52.8%) with stage IIIC disease. Fifty-five (25.2%) patients underwent maximal CRS, whereas 163 (74.8%) had optimal debulking. Table 2 summarizes the clinicopathological characteristics of the study population.

For the entire cohort, the 5-year PFS was 34.8%, with a median PFS of 28 months (95% confidence interval [CI] 20.58–35.42, Standard Error [SE]: 3.785). The median PFS for endometrioid, clear-cell, mixed epithelial and mucinous histotypes were 38, 24, 22 and 20 months, respectively (Fig. 1a).

For 55 (25.2%) women undergoing maximal CRS, the median PFS was not reached yet, whereas the corresponding figure was found to be 22 months (95% CI 16.3–27.7 months) for 163 (74.8%) patients who received optimal debulking ($P < 0.001$) (Fig. 2). The median OS for women with maximal CRS was significantly longer than that of women undergoing optimal CRS (not reached yet vs 39 months [95% CI 30.6–47.4 months], respectively; $P < 0.001$) (Fig. 3).

Univariate analysis demonstrated age (≤ 50 vs ≥70 years) ($P = 0.039$), bilaterality ($P = 0.001$), stage (stage IIIA1 vs others) ($P = 0.002$), omental

Table 1 The inclusion process of the patients and the suboptimal cytoreductive surgery rates with regard to the histotypes

	Clear-cell	Endometrioid	Mixed	Mucinous	Total
Total number of cases identified	93	94	71	109	367
Number of cases with incomplete medical records	2	2	3	2	9
Number of cases who received neoadjuvant chemotherapy	5	3	6	3	17
Number of cases who received no lymphadenectomy	5	3	3	12	23
Number of cases who received suboptimal debulking	27	22	20	31	100
Number of cases excluded	39	30	32	48	149
Suboptimal CRS rate	27/81 (33.3%)	22/86 (25.6%)	20/59 (33.9%)	31/92 (33.7%)	100/318 (31.4%)
Number of patients included	54	64	39	61	218

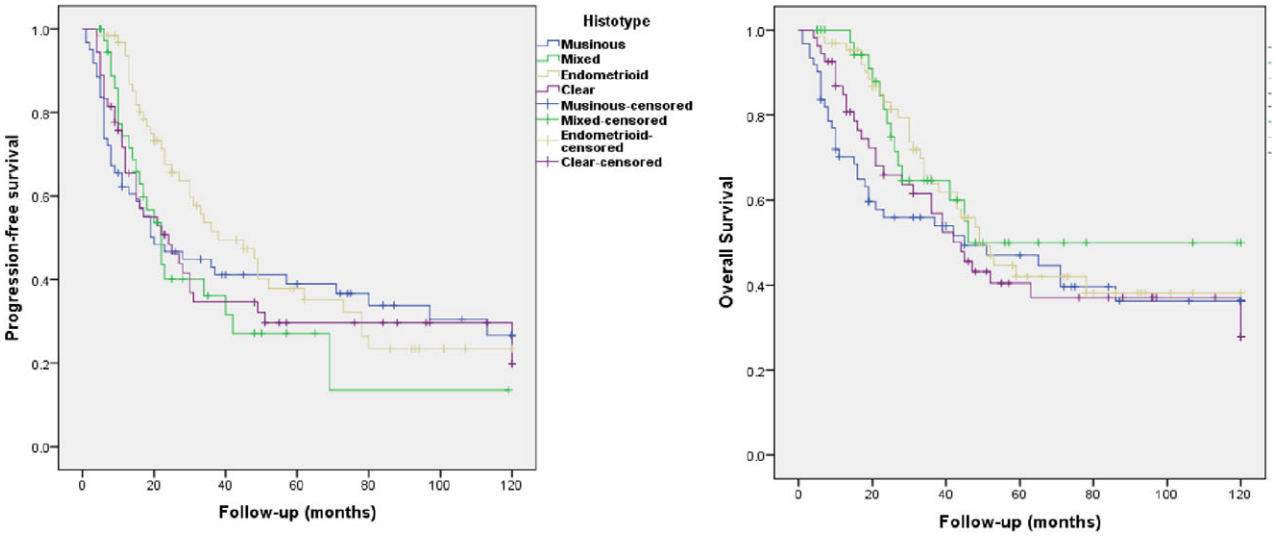

Figure 1 The progression-free survival and overall survival curves of women with endometrioid, clear cell, mixed epithelial and mucinous histotypes in stage III nonserous epithelial ovarian cancer.

involvement ($P < 0.001$), peritoneal involvement ($P = 0.001$) and gross RD ≤ 1 cm ($P < 0.001$) to be significant factors for decreased PFS (Table 2). At the end of multivariate analysis, bilaterality (HR 1.44, 95% CI 1.01–2.056; $P = 0.04$), age (≤ 50 vs ≥70 years) (HR 2.25, 95% CI 1.176–4.323; $P = 0.014$) and maximal cytoreduction (HR 0.34, 95% CI 0.202–0.58; $P < 0.001$) remained independent prognostic factors for PFS (Table 3).

The 5-year OS of the entire cohort was 44.2%, with a median overall survival of 47 months (95% CI 36.12–57.88, SE: 5.55). The median OS for endometrioid, clear-cell, mixed epithelial and mucinous histotypes were 49 months, 44 months, not reached yet and 45 months, respectively (Fig. 1b).

Univariate analysis demonstrated age ($P = 0.007$), bilaterality ($P = 0.008$), stage (stage IIIA1 vs others) ($P = 0.001$), omental involvement ($P < 0.001$), peritoneal involvement ($P = 0.001$) and gross RD ≤ 1 cm ($P < 0.001$) to be significant factors for decreased OS (Table 3). At the end of multivariate analysis, age (51–69 years vs ≤50 years (HR 1.73, 95% CI 1.23–2.66; $P = 0.013$), (≤ 50 vs ≥70 years) (HR 2.6, 95% CI 1.215–5.591; $P = 0.014$) and maximal cytoreduction (HR 0.31, 95% CI 0.166–0.615; $P < 0.001$) remained independent prognostic factors for OS (Table 4). At the time of reporting, of 218 women with stage III nonserous EOC, 109 (50%) were dead, whereas 109 (50%) were alive.

Discussion

This study represents a retrospective analysis of 218 patients with stage III nonserous EOC who have undergone maximal or optimal CRS followed by six cycles of IV carboplatin/paclitaxel chemotherapy. Our results indicated age ≤ 50 years, achievement of maximal cytoreduction and unilaterality of the tumor as independent prognostic factors for prolonged PFS. Although the number of patients is relatively limited, to the best of our knowledge, this is the first study reporting on the prognostic factors for stage III nonserous EOC.

A large GOG study identified factors of poor prognosis in a similarly treated population of women with stage III EOC.[6] This study included 1895 patients with stage III EOC who had undergone primary CRS followed by platinum/paclitaxel chemotherapy. Age, PS, tumor histology and residual tumor volume were independent predictors of outcome in patients with stage III EOC.[6] However, non-serous histologies constituted 21.3% ($n = 404$) of their study population, whereas 35% of patients ($n = 667$) underwent suboptimal CRS in that study.[6]

Landrum *et al.*[7] have reported that histology, age and extent of RD are identified as statistically significant variables for OS in a cohort of 428 patients with stage III EOC undergoing optimal CRS followed by intraperitoneal paclitaxel/ platinum chemotherapy. It

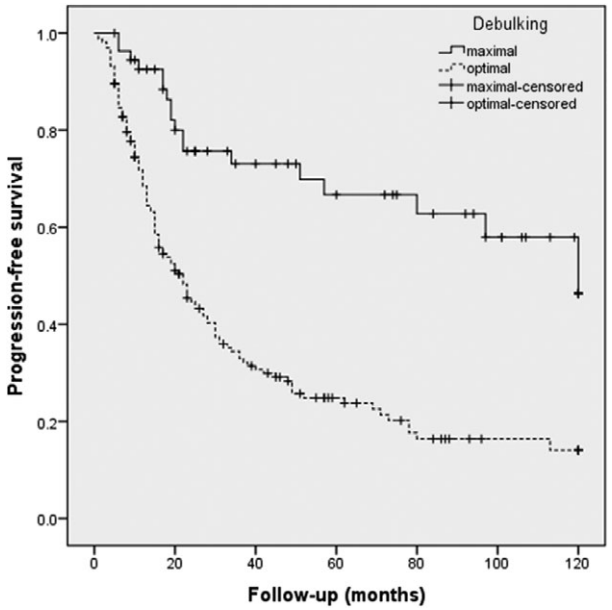

Figure 2 The progression-free survival curves of women who have undergone maximal and optimal cytoreduction in stage III nonserous epithelial ovarian cancer.

should be noted that patients with clear-cell and mucinous histology comprised only 6.3% (n = 27) of their study population. However, our findings pointing out age and extent of RD as independent prognostic factors for OS are in agreement with those of Landrum *et al*.[7]

Extent of RD, PS and adjuvant chemotherapy regimen were adjusted, and the confounding effects of these variables were minimized for the evaluation of

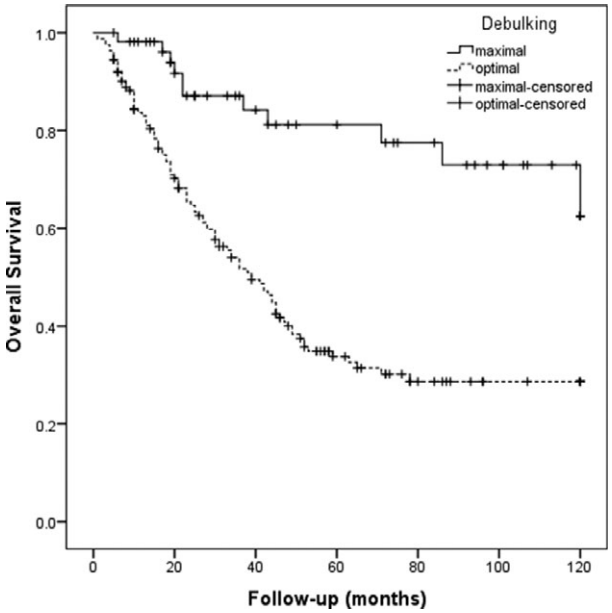

Figure 3 The overall survival curves of women who have undergone maximal and optimal cytoreduction in stage III nonserous epithelial ovarian cancer.

Table 2 Baseline characteristics of the patients

Characteristic	Values
Age, years (median)	54 (18–78)
Menopausal status, *n* (%)	
Postmenopausal	138 (63.3%)
Premenopausal	80 (36.7%)
Histopathology, *n* (%)	
Endometrioid	64 (29.4%)
Mucinous	61 (28%)
Mixed	39 (17.9%)
Clear	54 (24.8%)
Serum CA 125 (median, IU/ml)	240 (5–9523)
≥240 IU/mL	109 (50%)
<240 IU/mL	109 (50%)
Bilaterality, *n* (%)	
Present	107 (49.1%)
Absent	111 (50.9%)
Ascites, *n* (%)	
Present	122 (56%)
Absent	96 (44%)
Peritoneal cytology, *n* (%)	
Positive	148 (67.9%)
Negative	70 (32.1%)
Grade, *n* (%)	
1	31 (14.2%)
2	57 (26.1%)
3	76 (34.9%)
Number of LNs removed (median)	
Number of pelvic LNs removed	25 (10–93)
Number of para-aortic LNs removed	12 (5–66)
Retroperitoneal LN metastases, *n* (%)	
Present	121 (55.5%)
Absent	97 (44.5%)
Peritoneal involvement, *n* (%)	
Yes	141 (64.7%)
No	77 (35.3%)
Omental involvement, *n* (%)	
Yes	131 (60.1%)
No	87 (39.9%)
Debulking surgery, *n* (%)	
Optimal	163 (74.8%)
Maximal	55 (25.2%)
Stage, *n* (%)	
IIIA1	55 (25.2%)
IIIA2	14 (6.4%)
IIIB	34 (15.6%)
IIIC	115 (52.8%)
Status, *n* (%)	
Alive	109 (50%)
Dead	109 (50%)

LN, lymph node; *n*, number.

Table 3 Univariate and multivariate analyses for prognostic factors for progression-free survival

Variable	Univariate analysis		Multivariate analysis		
	PFS† (%)	*P*	HR	95% CI	*P*
Grade					
1	43.9	0.39			
2–3	34.9				
Stage					
$IIIA_1$	54.1	0.002	0.96	0.55–1.69	NS
IIIA2-IIIB-IIIC	28.7				
Serum CA 125 (median, IU/mL)					
≥240 IU/mL	33.6	0.75			
<240 IU/mL	35.9				
Ascites					
Present	36.4	0.32			
Absent	32.6				
Retroperitoneal LN metastases					
Present	40.1	0.12			
Absent	28.4				
Peritoneal cytology					
Positive	35.0	0.4			
Negative	34.7				
Omental involvement					
Yes	25.7	<0.001	1.36	0.87–2.10	NS
No	48.6				
Peritoneal involvement					
Yes	26.9	0.001	1.28	0.81–2.02	NS
No	49.0				
Histopathology					
Mucinous	39.0				
Endometriod	27.1				
Clear	37.9	0.4			
Mixed	29.6				
Age, y					
≤ 50	27.6	0.03			
51–69	25.0		1.42	0.98–2.05	0.062
≥70			2.25	1.17–4.32	0.014
Bilaterality					
Present	22.7	0.001	1.44	1.01–2.05	0.044
Absent	46.6				
Debulking					
Optimal	24.8				
Maximal	66.7	< 0.001	0.34	0.202–0.580	<0.001

†5-year progression free survival rate. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

prognostic factors for stage III nonserous EOC in the current study. However, age appeared to be an independent prognostic factor for PFS and OS in multivariate analysis, demonstrating that those patients≥ 70 years were 2.2 times more likely to have decreased PFS when compared to those ≤ 50 years. Landrum *et al*.[7] have stated that patient age stands as a prognostic factor for survival independent of RD, PS, grade and stage. The authors suggested that better understanding of the changes in tumor biology or immune response in older patients may lead to new insights into the best treatment methods for the rapidly increasing population.[7] It should be noted that age at the time of diagnosis for patients with EOC has been consistently recognized as an independent prognostic factor in previous studies.[7,8,12,22–24]

It is increasingly appreciated that tumor cell type correlates with epidemiological risk factors, "*BRCA 1 or 2*" mutation status, differences in gene expression profile and genetic events during oncogenesis and response to chemotherapy.[14]Nevertheless, information on the prognostic significance of histology in the context of changing therapeutic standards is limited.[5] The

Table 4 Univariate and multivariate analyses for prognostic factors for overall survival

Variable	Univariate analysis		Multivariate analysis		
	OS† (%)	*P*	HR	95% CI	*P*
Grade					
1	55.5	0.32			
2–3	43.6				
Stage					
IIIA1	66.7	0.001	0.88	0.45–1.72	NS
IIIA2-IIIB-IIIC	37.5				
Bilaterality					
Present	31.4	0.008	1.29	0.87–1.93	NS
Absent	57.5				
Serum CA 125 (median, IU/ml)					
≥240 IU/mL	38.8	0.558			
<240 IU/mL	49.6				
Ascites					
Present	39.4	0.17			
Absent	50.3				
Retroperitoneal LN metastases					
Present	47.4	0.17			
Absent	40.4				
Peritoneal cytology					
Positive	41.7	0.33			
Negative	49.3				
Omental involvement					
Yes	32.9	<0.001	1.47	0.90–2.42	NS
No	61.9				
Peritoneal involvement					
Yes	35.7	0.001	1.21	0.72–2.01	NS
No	59.7				
Histological subtypes					
Mucinous	47				
Endometriod	42	0.38			
Clear	40				
Mixed	50				
Age, y					
≤ 50	57				
51–69	36.1		1.73	1.23–2.667	0.013
≥70	42	0.007	2.6	1.215–5.59	0.014
Debulking					
Optimal	33.8				
Maximal	81.2	<0.001	0.31	0.166–0.615	0.001

†5-year overall survival. CI, confidence interval; HR: hazard ratio.

prognostic significance of histotype is controversial in stage III EOC given the relative rarity of histological subtypes other than serous.[25] Most studies describing the role of tumor histology in prognosis have focused on mucinous and clear-cell tumors.[5,26–30] However, histological subtype has been reported as an independent prognostic factor for stage III–IV EOC.[9,10] In contrast, Chi *et al*.[11]and Bristow *et al*.[31] showed that histological subtype was not a significant prognostic factor in earlier studies.

Winter *et al*.[6] reported that mucinous or clear-cell histology was associated with a worse PFS and OS compared with serous carcinomas. In a meta-analysis of 8704 women with stage III–IV EOC, it has been shown that the prognoses of women with mucinous tumors are worse than those with serous tumors, and the prognoses of patients with the clear-cell carcinomas are unlikely to be better.[8] Nevertheless, histotype did not seem to have prognostic significance in women with stage III nonserous EOC in the current study. Our findings do not agree with previous reports showing the prognostic significance of histological subtype in advanced EOC.[6–10,12] The prognostic significance of the tumor histology seems to be consistent when serous malignant tumors are compared with nonserous malignant tumors, whereas its

prognostic significance disappears when nonserous malignant tumors are studied as a separate group.

The volume of RD after primary CRS depends on the number and the size of tumor elements.[12] In this retrospective study, RD status after primary CRS was recorded according to the assessment of the attending surgeon. We were not able to define the number of lesions left after primary CRS. However, the maximum diameter of the greatest residual tumor nodule is a very crude estimate of RD, but it still provided valuable prognostic information in our study as it did in previous studies.[7,12,17] There was a statistically significant PFS and OS advantage for patients with no gross RD compared to those with macroscopic RD ≤1 cm in the current study. Our study has provided further information that the prognostic significance of the extent of RD stands even within a population of patients with ≤ 1 cm of RD.

Our analysis has shown that the extent of RD is an independent predictor of OS, whereas the substage of the disease is not. Our finding are in line with that of Landrum *et al*.[7] who suggested that efforts to reduce the tumor burden to no gross RD might mitigate the impact of stage. In addition, it has been reported that residual tumor size was associated with an increased risk of death for advanced nonserous EOC, whereas taxane-based chemotherapy was not a prognostic factor.[9]

Several potential limitations of our study warrant consideration. First, the retrospective nature of the study cannot exclude any bias. Second, treatment after recurrence was not uniform and varied among institutions that participated in the study. Therefore, our findings associated with OS should be met cautiously. Third, our study was restricted by the lack of a central pathology review. Although a comprehensive central pathology review would be ideal, patients with nonserous EOC included in the current study do reflect the 'real-world' diagnosis and practice in our country. We used information from routine practice in order to assess prognoses of women with stage III nonserous EOC. These women were homogeneously diagnosed and treated in tertiary referral centers, and histopathological evaluation was performed by highly experienced gynecological pathologists. Despite the abovementioned limitations, our findings provide additional information to the body of knowledge on this topic.

The strength of the current study, compared with previous reports, is mainly the homogeneity of the patient population and the treatment, which provides a precise estimation of the magnitude of the effect while controlling for confounder influences. The homogenous structure of our study seems to reduce the possibility of confounding and enhances the reliability of the prognostic effects of those have been estimated.

Our findings indicate that maximal cytoreduction is the only modifiable prognostic factor associated with stage III nonserous EOC. Maximal surgical effort seems to currently be the best option for the initial treatment of these women as PFS and OS seem to be superior whenever maximal cytoreduction has been achieved. We have to emphasize that women with no gross RD following primary CRS had survival rates that exceed any rates previously reported in stage III nonserous EOC treated with the current standard chemotherapy.

At any rate, the retrospective nature of our study does not permit us to draw definitive conclusions as similar previous studies. It should be noted that the results of the current study are limited only to patients who can be cytoreduced to 1 cm or less of RD.

We conclude that complete cytoreduction to no gross RD should be the main goal of management in women with stage III nonserous EOC, and it seems reasonable to perform maximal CRS whenever possible in those patients. However, further exploration of molecular markers and biologic pathways to better characterize the behavior of these rare histotypes is warranted.

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Disclosure

None declared.

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