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Effect of tumor type on response to adjuvant platinum-based chemotherapy and prognosis in patients with stage II–IV epithelial ovarian carcinoma

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ABSTRACT

Objectives: To evaluate the effect of histological subtype on oncological outcome and adjuvant platinum-based chemotherapy response in patients with epithelial ovarian cancer (EOC).

Material and methods: The study group was created with stage II–IV EOC patients. Progression-free survival (PFS) and disease-specific survival (DSS) estimates were determined by using the Kaplan–Meier method. The log-rank test and cox proportional hazards model were performed.

Results: A total 396 patients were included the study. Tumor type was serous in 332 (83.8%). Two hundred and thirty-one patients (58.3%) had maximal cytoreduction. Three hundred and twenty-seven (82.6%) patients received complete clinical response. Refractory disease was present in 69 (17.4%) patients. In patients with complete clinical response, 183 (56%) patients recurred. Five-year PFS was 32% in serous group and 31% in non-serous group (p = 0.755). Five-year DSS was 78% in serous group and 87% in non-serous group (p = 0.084). On multivariate analysis, recurrence rates 1.959 times (95% CI: 1.224–3.085; p = 0.004), death rates 2.624 times (95% CI: 1.328–5.185; p = 0.005) higher in patients with optimal cytoreduction than patients with maximal cytoreduction, respectively.

Conclusions: Although the rate of maximal cytoreduction was higher in patients with non-serous tumor type, the rate of refractory disease was higher after adjuvant chemotherapy. However, the recurrence rate was higher in serous tumor type. Survival rates were similar in serous and non-serous tumor types. Maximal cytoreduction was an independent predictor factor for survival. Maximal cytoreduction should be the main target in EOC.

Keywords: epithelial ovarian carcinoma; recurrence; refractory; serous ovarian carcinoma; survival

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INTRODUCTION

Epithelial ovarian carcinomas (EOCs) are considered as the second most common gynecologic malignancy and fifth most common malignancy of all types among women worldwide [1]. EOCs have the highest mortality rates in gynecologic malignancies; over 225,000 women are diagnosed and over 140,000 deaths occur per year globally [2]. Primary ovarian carcinomas originate from germ cells, sex-cord stromal cells or epithelial cells which constitute 90–95% of all histologic types [3]. The symptoms are usually nonspecific and most of the patients are at advanced stages at the time of diagnosis [1]. Only 20% of patients are at early stages with a 90% 5-year survival rate. However, most cases are diagnosed at advanced stages which causes poor prognosis with 20% 5-year survival.

Malignant epithelial ovarian carcinomas include approximately 70% of serous subtype, 10–15% of endometrioid subtype, 5–10% of clear cell subtype and 3–4% of mucinous

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subtype [4]. Maximal cytoreductive surgery combined with platinum-based chemotherapy is the standard treatment modality for advanced stage disease. During debulking surgery, reaching maximal cytoreduction and leaving no visible tumoral tissue are the main targets. Patients with ≤ 1 cm residual tumoral tissue have better survival rates than those with > 1 cm residual tumor after cytoreduction [5, 6]. The presence and proportion of residual disease are admitted as significant prognostic predictors for response to platinum-based chemotherapy and survival in advanced stage EOC independently of histologic subtypes.

Serous epithelial ovarian carcinoma has the highest response rate to platinum-based chemotherapy among all histologic subtypes. However, mucinous subtypes especially those with advanced cases have lower response rates to platinum-based chemotherapy [7, 8]. Also, different studies reported that clear cell subtype has a restricted response to platinum-based chemotherapy and poor 5-year survival [7–9].

The primary endpoint of this study is the association between histological subtypes and survival among patients with FIGO (International Federation of Gynecology and Obstetrics) stage II–IV EOC. The secondary end point is to define the effectiveness of histological subtypes in response to platinum-based adjuvant chemotherapy.

MATERIAL AND METHODS

A total of 396 patients were enrolled in the study group. The entire cohort included patients who underwent cytoreductive surgery with FIGO stage II–IV EOC between January 1993 and December 2017 in our gynecologic oncology clinic. Sixty-four patients were non-serous subtype, and 332 patients were serous subtype who had ≤ 1 cm residual tumoral tissue after debulking surgery. Data related to patients were retrieved from patients' files, gynecologic oncology electronic database system and pathology reports. All patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytologic sampling, total omentectomy ± systematic lymphadenectomy and cytoreductive surgery. All pathological specimens were evaluated by experienced gynecologic pathologists. All patients received platinum-based adjuvant chemotherapy. Adjuvant chemotherapy decision was made by the tumor board.

Patients with synchronized tumors and non-epithelial tumoral components were excluded from the study group. In addition, low-grade serous carcinoma, although one of the histological subtypes of epithelial ovarian carcinoma, was excluded because it is considered a distinct group from other epithelial subtypes. Also, patients who had secondary malignancies, who received neoadjuvant chemotherapy, who received nonplatinum-based adjuvant chemotherapy, who were operated in other institutions and who did not undergo maximal-optimal cytoreduction were excluded, too. Maximal cytoreduction was defined as leaving no visible residual tumor and optimal cytoreduction was defined as leaving ≤ 1 cm residual tumoral tissue after debulking surgery. This study was approved by the local ethical committee by the file number of 90057706-900.

Assessment of stages of entire cohort was based on 2014 FIGO staging system for EOC. A re-evaluation was carried out for procedures performed before that date and standardization was obtained according to original pathology reports. Endometrioid, mucinous and clear cell histologic subtypes were admitted as non-serous tumor type. Serous tumor type referred only to high-grade serous ovarian carcinomas in this study.

Platinum-based storage regimens used in our clinic are (i) Paclitaxel (175 mg/m^2) + Carboplatin (AUC = 6), (ii) Paclitaxel (175 mg/m^2) + Cisplatin (75 mg/m^2), (iii) Docetaxel (75 mg/m^2) + Carboplatin (AUC = 6), (iv) Docetaxel (175 mg/m^2) + Cisplatin (75 mg/m^2), (v) Paclitaxel (175 mg/m^2) + Epirubicin (60 mg/m^2) or Adriamycin (50 mg/m^2) + Carboplatin (AUC = 6), (vi) Cyclophosphamide (500 mg/m^2) + Epirubicin (60 mg/m^2) or Adriamycin (50 mg/m^2) + Cisplatin (50 mg/m^2). Response to adjuvant chemotherapy was defined according to World Health Organization (WHO) criteria [10]. The response to chemotherapy in patients with measurable lesions was evaluated using clinical, biochemical (CA125) and imaging methods (computed tomography or magnetic resonance imaging) one month after the end of adjuvant chemotherapy. Complete clinical response (1) was accepted as no visible macroscopic tumor, and partial clinical response (2) was accepted as > 50% reduction in macroscopic tumor size. Stable disease (3) was accepted as < 50% reduction or < 25% increase in macroscopic tumor size and progressive disease (4), as > 25% increase in macroscopic tumor size and/or detection of a new macroscopic tumor focus.

Patients with complete clinical response entered routine follow-up programme. Adjuvant chemotherapy scheme was switched in patients with progressive disease. When partial clinical response or stable disease was detected after six cycles of chemotherapy, the same adjuvant chemotherapy scheme was continued. During this adjuvant chemotherapy protocol, a re-evaluation of patients was carried out and they were classified as complete clinical response or 'refractory disease'. Also, disease progression during first-line adjuvant chemotherapy was defined as 'refractory disease'. Radiological (detection of new lesions with advanced imaging techniques) and laboratory (increase in CA125 levels) recurrence in patients with complete clinical response was considered as 'recurrent disease'. Two main criteria are used in the definition of isolated laboratory recurrence in our

clinic. The first of these is (i) an increase of ≥ 2 times the upper limit of normal (35 IU/mL) in at least two measurements in the patient group whose CA125 value is in the normal range after primary treatment. The second is (ii) the increase in CA125 value to two times or more than the nadir value in at least two measurements in patients whose CA125 value is not within the normal range after primary treatment. Refractory disease and recurrent disease were defined as 'disease failure'.

Disease-specific survival (DSS) was accepted as time from initial surgery to death because of disease or the period from initial surgery to last follow-up visit. Progression-free survival (PFS) was defined as the period from initial surgery to proven recurrence or refractory disease with clinical examination and/or radiological imaging or the period from initial surgery to last follow-up visit in whom refractory disease/recurrence did not occur.

Patients who had complete clinical response after adjuvant therapy were followed up with 3-month intervals in first 2 years, 6-month intervals up to 5 years and 1 year intervals later on with pelvic examination, abdominal-pelvic ultrasonography, complete blood count, blood chemistry and serum tumor markers. Chest X-ray was utilized yearly. In case of suspicion, thoracic and/or abdominal computerized tomography was used.

Statistical analysis

SPSS 21.0 (SPSS Inc., Chicago, IL, USA) was used for data management and statistical analysis. Comparisons between groups were performed using the x2 test, the Mann–Whitney U test, or Kruskal–Wallis test where appropriate. In case of significance between groups, Bonferroni and post-hoc tests were used. Descriptive statistics were expressed as mean ± standard deviation or median (min–max) for continuous variables and number/percentage for categorical variables. Survival outcomes were calculated with the use of Kaplan–Meier method. Survival curves were compared using the log-rank test. All variables with a p value < 0.250 in the univariate analysis were included in the multivariate analysis. Multivariate analysis was performed using the Cox proportional hazards model to evaluate independent factors affecting survival. P values less than 0.05 were considered significant.

RESULTS

This study included 396 FIGO 2014 stage II–IV EOC patients who underwent surgery and received adjuvant chemotherapy. The median age was 51 years (range 20––80) at the time of diagnosis. Tumor type was serous in 332 (83.8%), endometrioid in 39 (9.8%), clear cell in 22 (5.2%) and mucinous in 3 (0.8%) patients. Ascites was present in 257 (68%) patients. Two hundred and thirty-one patients (58.3%) had maximal; 165 (41.7%) patients had optimal cytoreduction. Median serum CA125 level was 462.5 IU/mL (range 1–25,000). Lymphadenectomy was performed on 335 (84.6%) patients. The median number of total removed lymph node count was 57 (range 1–160). Peritoneal cytology was positive in 250 (72.6%) patients and omental involvement was positive in 291 (75%) patients. According to FIGO 2014 criteria; 16 (4.1%) patients were stage IIB, 25 (6.5%) were stage IIIA1, 11 (2.8%) were stage IIIA2, 49 (12.6%) were stage IIIB, 255 (65.6%) were stage IIIC and 8 (2.1%) were stage IVB. Clinical and surgico-pathological features of the main study group were shown in Table 1.

Paclitaxel + carboplatin was administered as adjuvant chemotherapy regimen to 268 (67.7%) patients, paclitaxel + cisplatin to 10 (2.5%), docetaxel + carboplatin to 35 (8.8%), docetaxel + cisplatin to 5 (1.3%), paclitaxel + epirubicin/adriamycin + cisplatin to 25 (6.3%) and cyclophosphamide + epirubicin/adriamycin + cisplatin to 39 (9.8%) patients. In addition to these, other platinum-based chemotherapies were administered to 14 (3.5%) patients. Three hundred and twenty-seven (82.6%) patients received complete clinical response. Refractory disease was present in 69 (17.4%) patients. In patients with complete clinical response, 183 (56%) patients recurred. Finally, 252 (63.6%) patients had disease failure (Tab. 1).

Patients in serous group had disseminated disease and low maximal cytoreduction rate when compared to non-serous group. On the other hand, refractory disease was 28.1% in non-serous tumor group and 15.4% in serous tumor group (p = 0.014). Also, in patients with complete clinical response after adjuvant chemotherapy, recurrence rate was 58.4% in serous group and 41.3% in non-serous group (p = 0.031). Eventually, disease failure was similar in the two groups. Disease failure was 64.8% in serous group and 57.8% in non-serous group (p = 0.290). Details of comparison between the two groups were summarized in Table 2.

Survival

Median follow-up time was 46 months (range, 1–253). Five-year PFS was 32% and five-year DSS was 79% in entire cohort. Ascites presence, type of cytoreduction, preoperative serum CA125 level, lymph node metastasis and FIGO 2014 stage were prognostic factors for PFS and DSS in entire cohort. Ascites presence, high preoperative serum CA125 level, optimal cytoreduction, presence of lymph node metastasis and advanced stage were prognostic factors related to poor survival. In addition, ascites volume > 1500 cc and not performing lymphadenectomy were related to poor PFS, but they had no impact on DSS. Tumor type was not a predictor for either PFS or DSS. Five-year PFS was 32% in serous group and 31% in non-serous group (p = 0.755). Five-year DSS was 78% in serous group and 87% in non-serous group (p = 0.084) (Tab. 3).

Table 1. Clinical and surgico-pathological features

Features		Mean	Median (range)
Age at diagnosis [year]		51.9	51 (20–80)
Body mass index [kg/m^2]		29.3	28.9 (17.5–72)
Removed lymph node count		57.8	57 (1–160)
Preoperative CA125 [IU/mL]		1068.7	462.5 (1–25000)
Follow-up time [months]		60.94	46.0 (1–253)
Ascites [cc]		2718	1500 (50–18000)
		n	%
Tumor type	Serous	332	83.8
	Endometrioid	39	9.8
	Clear cell	22	5.6
	Mucinous	3	0.8
FIGO 2014 stage	IIA	25	6.4
	IIB	16	4.1
	IIIA1	25	6.5
	IIIA2	11	2.8
	IIIB	49	12.6
	IIIC	255	65.6
	IVB	8	2.1
Lymphadenectomy	Not performed	61	15.4
	Performed	335	84.6
Lymph node metastasis a	Negative	103	30.8
	Positive	229	68.4
	Not reported	3	0.8
Ovarian tumor laterality	Right ovary	68	17.3
	Left ovary	56	14.2
	Bilateral	269	68.4
Omental involvement	Negative	97	25
	Positive	291	75
Ascites presence	Negative	121	32.0
	Positive	257	68.0
Cytoreductive surgery	Optimal cytoreduction	165	41.7
	Maximal cytoreduction	231	58.3
Peritoneal cytology	Negative	94	23.7
	Positive	250	63.1
	Not reported	52	13.1
Response to adjuvant chemotherapy	Complete clinical response	327	82.6
	Refractory disease	69	17.4
Recurrence b	Negative	144	44
	Positive	183	56
Disease failure	Negative	144	36.4
	Positive	252	63.6

a — Three hundred-thirty five patients underwent lymphadenectomy; b — Three hundred-twenty seven patients with complete clinical response

Table 2. Comparison of serous and non-serous tumor types

Factors	Serous tumor type (n: 332)	Non-serous tumor types (n: 64)	p value
	Median (range)	Median (range)	
Age [years]	50 (20–80)	52 (30–77)	0.933
Body mass index [kg/m^2]	29 (17.5–44.2)	29 (20–72)	0.103
Removed lymph node count	55 (1–160)	58 (9–142)	0.368
Preoperative Ca125 [IU/mL]	493 (1–25.000)	293 (3–7250)	0.289
Ascites volume [cc]	1800 (50–18.000)	1000 (100–10.000)	0.392
	n [%]	n [%]	
Stage III & IV	304 (91.6)	43 (79.6)	0.007
Lymphadenectomy	287 (85.7)	48 (75.0)	0.020
Lymph node metastasis a	206 (72.5)	23 (47.9)	0.001
Cytology positivity	221 (67)	29 (48.3)	0.020
Ascites presence	229 (73.1)	17 (39.7)	< 0.001
Maximal cytoreduction	173 (52.1)	58 (90.6)	< 0.001
Refractory disease	51 (15.4)	18 (28.1)	0.014
Recurrence b	164 (58.4)	19 (41.3)	0.031
Disease failure c	215 (64.8)	37 (57.8)	0.290

a — three hundred-thirty five patients underwent lymphadenectomy; b — three hundred-twenty seven patients with complete clinical response; c — refractory disease + recurrent disease

Table 3. Prognostic factors effecting progression-free survival and disease-specific survival in main cohort (n: 396)

Prognostic factors		5-year progression-free survival		5-year disease-specific survival	
		[%]	p value	[%]	p value
Age [years] [a]	≤ 51	35	0.200	82	0.111
	> 51	28		75	
Preoperative Ca 125 [IU/mL]	≤ 35	59	0.004	89	0.036
	> 35	28		77	
Tumor type	Serous	32	0.755	78	0.084
	Non-serous	31		87	
Lymphadenectomy	Not performed	16	0.001	71	0.244
	Performed	35		80	
Lymph node metastasis	Negative	44	0.007	90	0.005
	Positive	29		77	
Total removed lymph node count [a]	≤ 57	38	0.377	82	0.768
	> 57	31		82	
FIGO 2014 stage	Stage II	65	< 0.001	97	0.001
	Stage III & IV	27		76	
Ascites presence	Negative	44	0.002	88	0.001
	Positive	24		73	
Ascites volume [cc] [a]	≤ 1500	34	0.001	81	0.173
	> 1500	12		68	
Type of cytoreduction	Optimal	23	< 0.001	64	< 0.001
	Maximal	38		88	

[a] — median value

Table 4. Prognostic factors affecting recurrence (multivariate analysis)

Factors	OR	95% CI	p value
Age (> 51 vs ≤ 51) [a]	1.274	0.826–1.965	0.274
Preoperative Ca125 (> 35 IU/mL vs ≤ 35 IU/mL)	1.387	0.802–2.399	0.241
Lymphadenectomy (not performed vs performed)	1.318	0.675–2.575	0.418
Stage (III&IV vs II)	1.043	0.413–2.705	0.930
Type of cytoreduction (optimal vs maximal)	1.959	1.244–3.085	0.004
Ascites volume (> 1500 vs ≤ 1500) [a]	1.717	1.089–2.706	0.020

[a] — median value; CI — confidence interval; OR — odds ratio

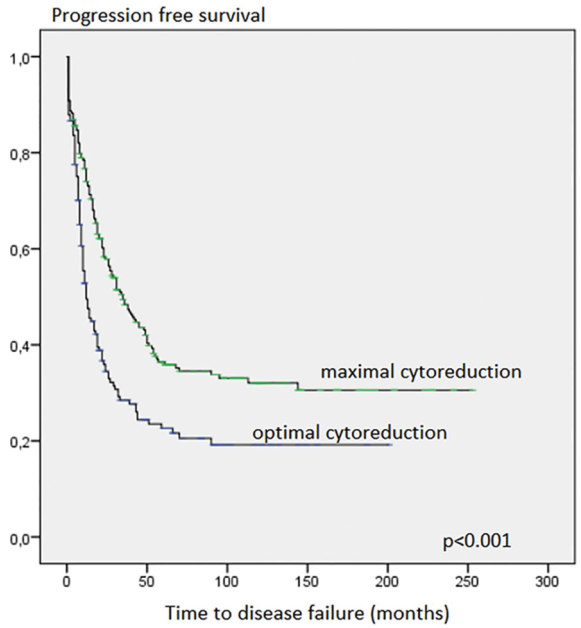

Figure 1. The relationship between type of cytoreduction and progression-free survival

In the univariate analysis, the correlation of those with a p value < 0.250 was analyzed. The presence of ascites was not included in the model for PFS, as the presence of ascites was highly correlated with the volume of it. In addition, because lymph node metastasis highly correlated with lymphadenectomy and FIGO stage, it wasn't included. Therefore, a model was created for PFS using age, preoperative CA125 level, lymphadenectomy, FIGO stage, cytoreduction type, and ascites volume. On multivariate analysis, type of cytoreduction and ascites volume > 1500 cc were independent predictors for recurrence in main cohort (Tab. 4). Performing optimal cytoreduction increased recurrence rate 1.959 times than performing maximal cytoreduction [95% confidence interval (CI): 1.244–3.085; p = 0.004] (Fig. 1). Ascites volume > 1500 cc also increased recurrence rate 1.717 times (95% CI: 1.809–2.706; p = 0.020).

In the univariate analysis, FIGO stage, presence of ascites and lymph node metastasis were not included for DSS, since FIGO stage with tumor type, presence of ascites with ascites volume and lymph node metastasis with lymphadenectomy was highly correlated. Thus, a model was created for DSS using age, preoperative CA125 level, lymphadenectomy, tumor type, cytoreduction type, and ascites volume. Only type of cytoreduction was an independent prognostic factor for survival (Tab. 5). Death rate was 2.624 times higher in patients with optimal cytoreduction than patients with maximal cytoreduction (95% CI: 1.328–5.185; p = 0.005) (Fig. 2).

DISCUSSION

In our study, tumor type was found to have no impact on PFS and DSS on univariate analysis. Receiving maximal cytoreduction was an independent predictor for both PFS and DSS on multivariate analysis. Also, ascites volume was an independent predictor for recurrence in the study group. Maximal cytoreduction rate was higher in patients with non-serous tumor type. Despite the high maximal cytoreduction rate, refractory disease was higher after platinum-based adjuvant chemotherapy in non-serous tumors. However, in patients with complete clinical response after adjuvant chemotherapy recurrence rate was high in serous tumor type.

Primary cytoreductive surgery followed by platinum-based adjuvant chemotherapy is considered as the standard treatment modality in advanced stage EOC. Aebi et al. [11] reported that more than half of the patients will develop recurrence after this treatment combination despite high first response rates. In our study, 183 (56%) patients of entire cohort recurred.

Some authors showed that different tumor types had lower response rates to standard adjuvant chemotherapy. Hess et al. [12] reported that serous tumor type had high response rates to platinum-based chemotherapy when compared to mucinous and clear cell types. In another study by Chan et al. [13] advanced stage clear cell ovarian

Table 5. Prognostic factors affecting death of disease (multivariate analysis)

Factors	OR	95% CI	p value
Age (> 51 vs ≤ 51) [a]	1.231	0.687–2.209	0.485
Preoperative Ca125 (> 35 IU/mL vs ≤ 35 IU/mL)	1.721	0.530–5.591	0.366
Lymphadenectomy (not performed vs performed)	1.386	0.609–3.155	0.437
Tumor type (non-serous vs serous)	1.335	0.706–5.990	0.706
Type of cytoreduction (optimal vs maximal)	2.624	1.328–5.185	0.005
Ascites volume (> 1500 vs ≤ 1500) [a]	1.335	0.605–2.093	0.706

[a] — median value; CI — confidence interval; OR — odds ratio

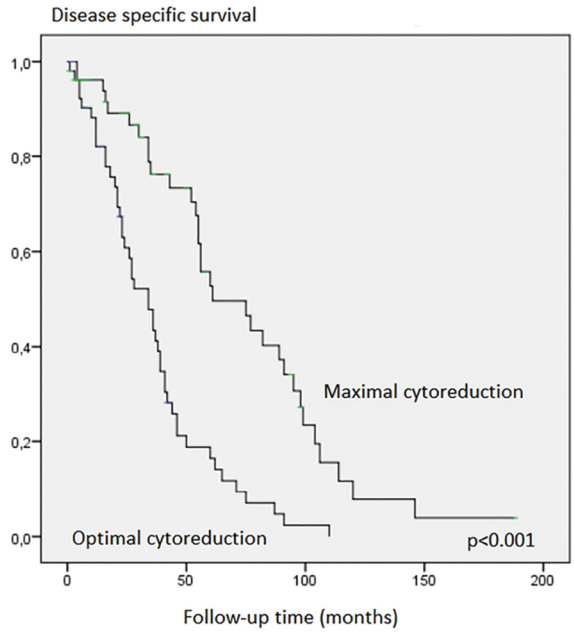

Figure 2. The relationship between type of cytoreduction and disease-specific survival

carcinoma patients were found to have restricted response to platinum-based chemotherapy. Also, this patient group had low 5-year survival compared to high grade serous ovarian carcinomas. Similarly, it was established that different tumor types had different response rates to platinum-based chemotherapy and serous type had better response to first-line treatment [14]. On the other hand, Bamias et al. [15] detected no association between tumor type and platinum-refractory disease. According to this study, endometrioid and clear cell tumors had medium sensitivity and low-grade serous tumors had high sensitivity to platinum-based chemotherapy with no statistical significance. In their study, Fortier et al. [16] compared recurrence rates and survival between endometrioid and serous tumor types. They demonstrated that recurrence was higher in serous tumor group most of whom received platinum-based chemotherapy. We found that serous tumor group had higher complete clinical response rate after adjuvant chemotherapy. However, the risk of recurrence was higher in serous tumor group than non-serous tumor group. This could be related to disseminated disease and lower maximal cytoreduction rate in serous tumor type.

The effect of tumor type on prognosis in EOC was investigated in different reports. Zaino et al. [17] suggested that only mucinous tumor type was an independent prognostic factor in EOCs. Another study supported that mucinous tumor type was less chemosensitive than serous type [18]. According to study results, mucinous tumor type had worse PFS rates and high risk of death. In a recent study by Peres et al. [19] advanced stage clear cell, carcinosarcoma and mucinous tumor types were found to have high mortality rates for first 2 years of follow-up than high grade serous tumor types. Unlikely, PFS and DSS rates were similar between serous and non-serous tumor types in our study.

Amount of residual disease after debulking surgery was proved as one of the most important predictors of survival in EOC [20]. Aggressive cytoreductive surgery with the purpose of leaving no visible residual tumor and adjuvant chemotherapy are main treatment modalities. Tseng et al. [21] demonstrated that complete cytoreduction rate increased from 33% to 62% in a 13 years of follow-up period in stage IIIB and IV disease [21]. According to the results of this study, increase in complete cytoreduction led to improved survival. Risk of death decreased 26% and risk of recurrence decreased 28% in patients with maximal cytoreduction compared to optimal cytoreduction. There are different authors supporting maximal cytoreduction was an independent prognostic factor for survival in advanced stage EOC [22]. Similarly, we found that type of cytoreduction was an independent predictor for risk of recurrence and death in EOC patients. Optimal cytoreduction increased risk of recurrence approximately two times (OR: 1.959, 95% CI: 1.244–3.085; p = 0.004) and risk of death three times (OR: 2.624, 95% CI: 1.328–5.185; p = 0.005) when compared to maximal cytoreduction. Also, maximal cytoreduction rate

was higher in non-serous tumor type. This could be due to early-stage disease at the time of diagnosis.

This study includes EOC patients diagnosed, treated and followed-up in a tertiary gynecologic oncology center. Thus, a homogeneous cohort was obtained. High number of patients is another advantage of our study. On the other hand, retrospective design and relatively low number of non-serous tumor types are the main limitations. For this reason, a homogenization between tumor subtypes could not be provided.

CONCLUSIONS

Serous tumor type responds better to platinum-based adjuvant chemotherapy in epithelial ovarian cancer patients with optimal or maximal cytoreduction. Therefore, different chemotherapeutic agents should be investigated for adjuvant chemotherapy protocols in patients with non-serous tumor type. Also, maximal cytoreduction was an independent prognostic factor for survival on multivariate analysis. Thus, maximal surgical effort is of paramount importance and during debulking surgery, maximal cytoreduction should be the main target in EOC. More prospective studies are needed to confirm our findings.

Article information and declarations

Acknowledgments

Not applicable.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

This study was approved by the local ethical committee (NO:90057706-900).

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Supplementary material

None.

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