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Original Article

Controversies in the efficacy of adjuvant chemotherapy in different epithelial ovarian carcinoma histologies

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ABSTRACT

Aim: In this retrospective study, the efficacy of adjuvant chemotherapy and its contribution to prognosis were investigated in patients diagnosed with different subgroups of ovarian carcinoma at stages 1–3.
Material and Method: Epithelial ovarian carcinoma cases treated at Ankara Oncology Training and Research Hospital of Health Sciences University between January 2014 and May 2018 were retrospectively analyzed.
Results: A total of 145 patients were diagnosed and treated for EOC during the study period. According to histopathological subgroups, serous EOC was the most common (84.8%), followed by endometrioid (6.6%), mucinous (4.8%) and clear cell types (3.8%). Local recurrence and distant recurrences were observed in 39 (43.8%) and 7 (7.9%) cases in the serous EOC group, respectively. The median follow-up was 39 months (10–217 months). Median survival was 91.4 months (58.9–123.9 months) in the whole group and 100.9 months in serous EOC. Median survival in mucinous EOC was 26.2 months, whereas median survival in endometrioid EOC and clear cell EOC were not reached. A statistically significant difference of survival was found between serous and mucinous types of tumors (p: 0.04.
Conclusions: According to the results of this study examining the survival outcomes of epithelial ovarian cancer subtypes after chemotherapy, there was a statistically significant difference between the prognosis of different epithelial ovarian cancer cases after taxane and platinum-containing adjuvant chemotherapy. Mucinous type of tumors exhibited less overall survival compared to endometrioid and clear cell types which needs to be confirmed with prospective clinical trials.

1. Introduction

The term epithelial ovarian cancer (EOC) refers to a group of malignancies that suggested to be originated from the ovarian epithelium, including various histological subtypes. According to the results of recent research, the majority of serous histologic cancers develop from the fallopian tube epithelium and endometrioid and clear cell subtypes arise from the ovarian or pelvic endometriosis foci.[1]

As the carcinogenesis mechanisms of ovarian cancer subtypes are more clearly understood, changes in the prognosis of epithelial ovarian cancer has become more evident. Endometrioid type epithelial ovarian cancer (EEOC) often represents low-grade tumors, usually detected at an early stage and has a better prognosis. Sub-classification further complicated by new genetic profiling methods have shown that low-grade EEOCs may differ from high-grade EEOCs. In the light of this information, American guideline recommendations differ with respect to both grade and stage[2].

Clear cell epithelial ovarian carcinoma subtype which is similar to serous cell carcinoma, is rare (5–10%), more aggressive and high-grade.[1] Mucinous EOC, on the other hand, comprises approximately 10% patients, has good prognosis when detected at an early stage, but worse in the advanced stage than other subtypes.[3,4]

Treatment of ovarian carcinoma is usually planned based on clinical research in serous carcinomas. Beyond serous carcinoma subtype, there are limited data on the prognosis of chemotherapy sensitivity and disease prognosis of other histological ovarian carcinomas.

In this retrospective study, the efficacy of adjuvant chemotherapy and its contribution to prognosis were investigated in patients diagnosed with different subgroups of ovarian carcinoma at stages 1–3.

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2. Materials and methods

In this study, we aimed to investigate the relationship between EOC subgroups and chemotherapy efficacy; PFS, OS and recurrence rates. EOC cases treated at Ankara Oncology Training and Research Hospital of Health Sciences University between January 2014 and May 2018 were retrospectively analyzed. The study protocol was approved by the local board. The study end date was chosen in order to enable for at least 12 months follow-up. Patients diagnosed with stage I-III disease who were treated with complete or optimal cytoreduction according to FIGO (International Federation of Gynecology and Obstetrics) guidelines were included, but patients who were operated after neoadjuvant therapy were excluded. All patients received platinum-based adjuvant chemotherapy after surgery. Data were obtained from the electronic information system or printed-written patient files, taking into account the exclusion criteria. The following parameters were examined: Histology, age, date of diagnosis, stage of disease at the time of diagnosis, disease grade, presence of acid and/or lymph node involvement, type of chemotherapy, number of chemotherapy cycles, treatment response, time to progression, date of last visit and last disease status. All epithelial ovarian cancer subtypes were included. Progression-free survival (PFS) was defined as the time from diagnosis to progression (months); overall survival (OS) was calculated from the date of diagnosis to the date of death-last visit (months).

Kaplan-Meier method was used for survival analysis. The log-rank test was used to investigate the factors on PFS and OS. Confidence interval was accepted as 95% during the study ($\leq$0.05). IBM SPSS version 20 (BM Inc; Armonk, NY, USA) was used for statistical analysis.

3. Results

A total of 145 patients were diagnosed and treated for EOC during the study period. 105 cases of EOC were included in the study considering the inclusion and exclusion criteria. The median age of the whole group was 56 ± 11 years; and for serous, endometrioid, mucinous and clear cell EOC it was 58 ± 11, 48 ± 10, 47 ± 13 and 45 ± 13, respectively. Clinical, pathological and surgical characteristics of the patients are summarized in Table 1.

All EOC patients received Carboplatin (Area under curve-AUC: 5) - Paclitaxel (175 mg/m2) as adjuvant regimen. All adjuvant treatment schemes were administered in 6 cycles of 21 days.

According to histopathological subgroups, serous EOC was the most common (84.8%), followed by endometrioid (6.6%), mucinous (4.8%) and clear cell types (3.8%). When the stage distribution at the time of diagnosis was examined, serous and mucinous EPC patients were mostly diagnosed as Stage III, whereas endometroid type EOC was equally distributed in Stage I and II and clear cell EOC patients were mostly in Stage I.

Local recurrence and distant recurrences were observed in 39 (43.8%) and 7 (7.9%) cases in the serous EOC group, respectively. In contrast, only one case of mucinous tumors had distant metastasis (20%). There was statistically significant difference between EOC subtypes in PFS rates (Fig. 1.) Endometrioid EOC patients had local recurrence in 3 cases (42.9%) and distant metastasis in one case (14.3%). While 12.7% of recurrences in serous EOC were platinum resistant, recurrence in mucinous EOC was platinum resistant. 50% of endometrioid type EOC showed platinum resistance.

The median follow-up was 39 months (10–217 months). In total, 36 cases (34.3%) reported to have cancer related mortality, while 34.8% died of serous EOC. Mortality rate in mucinous EOC was 80% (4 cases). Death in endometrioid EOC occurred in one case (14.3%).

Median survival was 91.4 months (58.9–123.9 months) in the whole group and 100.9 months in serous EOC. Median survival in mucinous EOC was 26.2 months, whereas median survival in endometrioid EOC and clear cell EOC were not reached. A statistically significant difference of survival was found between serous and mucinous types of tumors (p: 0.04-Fig. 2). In multivariate analysis, histopathological subtype was found as an independent prognosticator for OS (p: 0.03, HR = 3.1%95 CI 0.3–13.7). In the whole patient group, progression-free survival (23.9 vs. 21.2 months, p: 0.08) and overall survival (91.5 vs. not reached, p: 013) were not different between maximal and optimal resected subgroups. When survival was compared according to FIGO staging, a statistically significant difference was found between Stage I-II and III (p: 0.0001). The difference in survival according to FIGO staging was statistically significant for each histopathological subgroup ($p < 001$ for serous, mucinous and endometrioid types of tumors). FIGO staging was found as independently prognostic factor for OS in multivariate analysis ((p: 0.02, HR = 0.34%95 CI 0.13–0.86).

Table 1
Patient characteristics.

Total N: 105	Serous EOC n (%)	Mucinous EOC n (%)	Clear Cell EOC n (%)	Endometrioid EOC n (%)
	89 (84.8)	5 (4.8)	4 (3.8)	7 (6.6)
Grade				
Grad 1	5 (5.6)	–	–	2 (28.6)
Grad 2	–	2 (40)	–	3 (42.8)
Grad 3	84 (94.4)	3 (60)	4 (100)	2 (28.6)
Stage[a]				
Stage IA	3 (3.7)	1 (20)	1 (25)	–
Stage IB	2 (2.2)	–	–	1 (14.3)
Stage IC	13 (14.6)	–	3 (75)	2 (28.5)
Stage IIA	4 (4.5)	1 (20)	–	2 (28.5)
Stage IIB	12 (13.5)	–	–	2 (28.5)
Stage IIIA	4 (4.5)	–	–	–
Stage IIIB	5 (5.6)	–	–	–
Stage IIIC	46	3 (60)	–	–
HIPEC	6 (6.7)	1 (20)	yok	yok
Surgical Type				
Optimal debulking	74	4	3	5
Maximal debulking	14	1	1	2

HIPEC: Hypertermic Intraperitoneal Chemotherapy.
[a] FIGO (International Federation of Gynecology and Obstetrics) Staging.

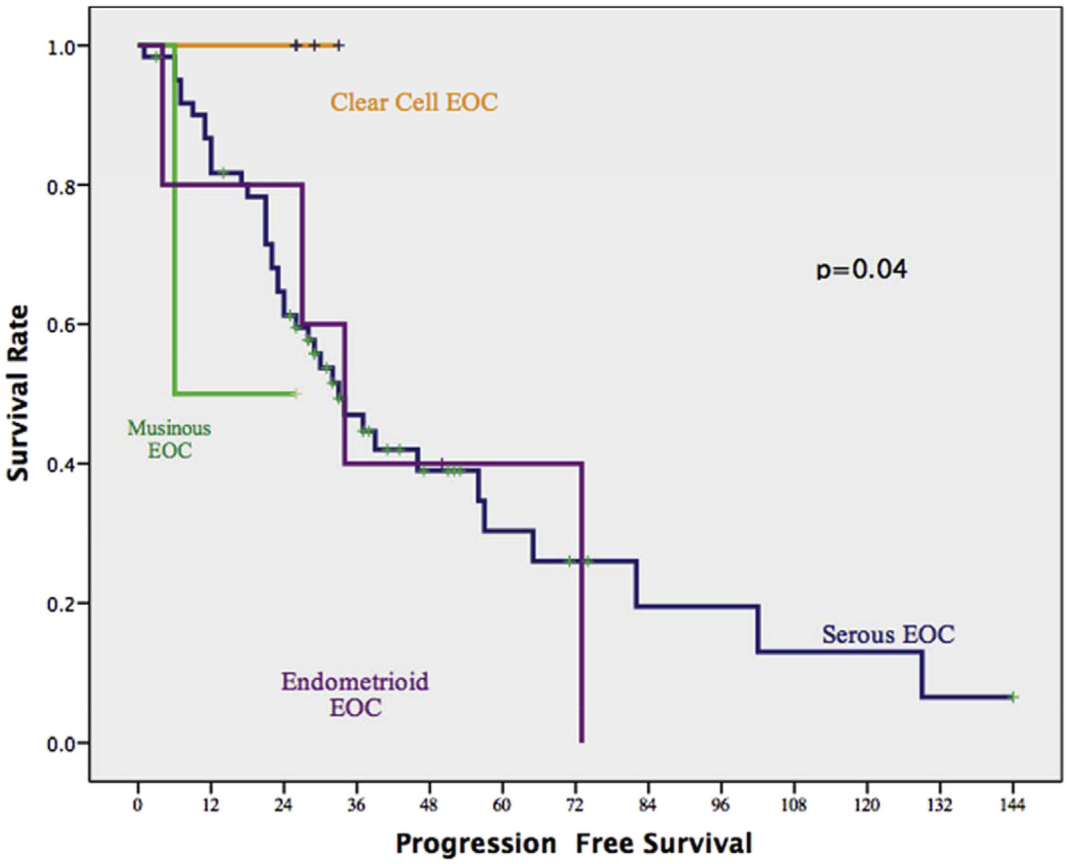

Fig. 1. Progression free survival according to different epithelial ovarian carcinoma histologies.

4. Discussion

According to the results of this study examining the survival outcomes of epithelial ovarian cancer subtypes after chemotherapy, there was a statistically significant difference between the prognosis of different epithelial ovarian cancer cases after taxane and platinum-containing adjuvant chemotherapy.

Epithelial ovarian cancer has the worst prognosis among all gynecologic malignancies. Adjuvant taxane and platinum chemotherapy after maximal cytoreduction is the recommended treatment for all epithelial ovarian carcinoma subtypes. In the literature, most of the studies have been performed for the high-grade serous EOC which is the most common type of EOC. However, there are limited studies investigating the survival outcomes of other rare endometrioid, clear cell and mucinous subtypes after adjuvant chemotherapy. Hess et al. compared the mucinous and serous EOC groups and found that chemotherapy response and long-term survival were significantly worse in the mucinous which included 27 cases.[5]Bamias et al. compared serous EOC and mucinous and clear cell EOC patients and found that mucinous EOC cases had a worse prognosis.[6] The results of the SOCRATES study also showed that the mucinous EOC type had worse prognosis than the other subgroups.[7] In this study, 20 mucinous EOC cases were compared with the control group of 388 cases with other histologies. The mucinous group was characterized by a lower grade and early stage tumor, while survival results were significantly worse (17.9m vs. 28.8m, p: 0028). While most clinical trials included advanced stage epithelial ovarian cancer, Shimada et al. investigated all cases of EOC from early stage retrospectively.[8] In general, standard platinum-containing chemotherapy response was found to be low in the advanced stage metastatic EOC. Besides this, it was discussed that adjuvant regimens containing fluorouracil and oxaliplatin may be more effective in mucinous tumors.[9] In the literature with the largest case population, survival for early-stage mucinous and serous tumors was similar, on the other hand, survival for advanced-stage mucinous neoplasms was inferior to that of serous carcinomas.[10] In a recent retrospective study, stage III and IV serous EOCs were compared with mucinous EOC.[11] Overall survival in mucinous EOC was 35 months, with a significantly higher risk of death (HR: 2.14, 95% CI 1.34–3.42).

When long-term follow-up EOC cases in the cohort of this study were examined, a statistically significant difference was found between serous EOC and mucinous EOC in terms of survival (100.8m vs. 26.2m, p: 0.05). Mortality due to mucinous EOC was observed in 80% of cases.

In general, prognosis in epithelial ovarian cancer is inversely related to disease grade, stage, and age.[7,12] In our study, the rate of recurrence increased; PFS decreased with increasing age, but survival did not differ significantly with age (100.9m vs. 69.9m, p: 0.24).

In summary, according to the results of our research, survival was associated with epithelial ovarian cancer types, disease grade, age and disease stage. Similarly, the incidence of subgroups and the relationship between survival and progression free survival were in parallel to the literature results.

There were some negative aspects of this study. Although the number of patients was sufficient, the non-serous subgroups were less represented in the study cohort because they were rare tumors.

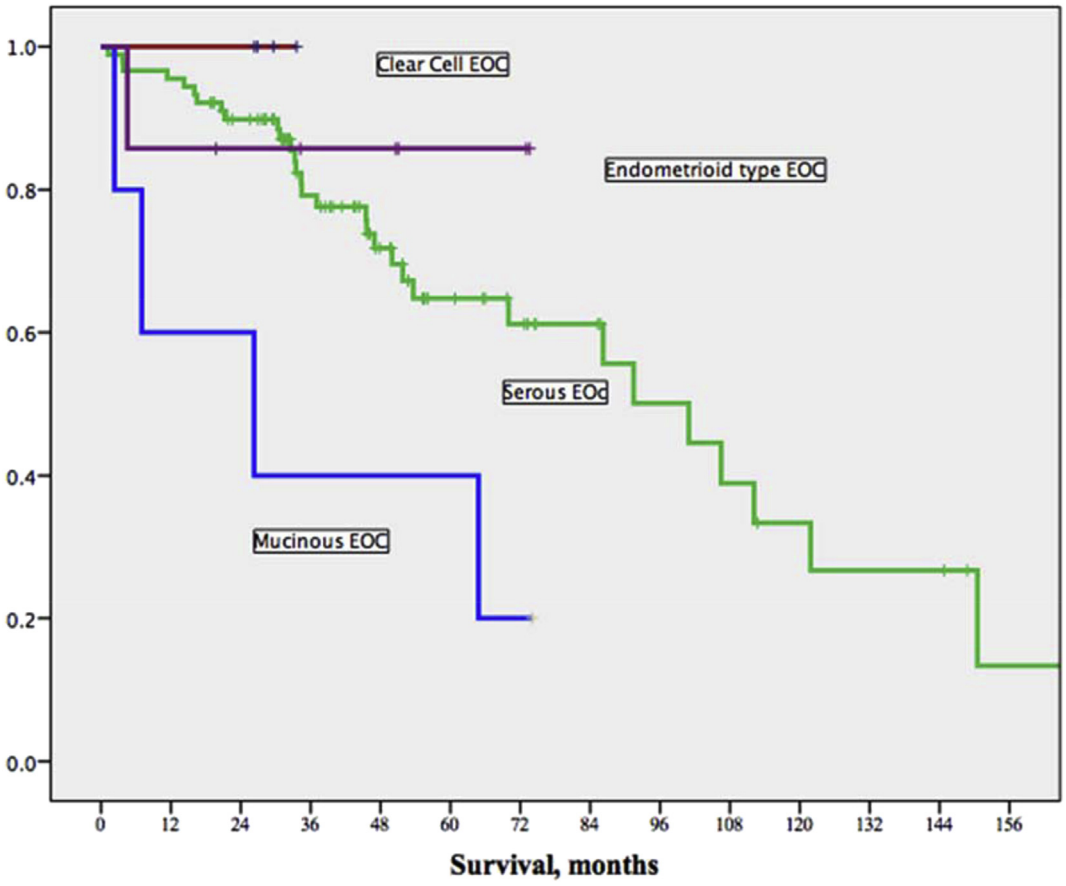

Fig. 2. Overall survival differences in epithelial ovarian carcinoma subtypes.

Therefore, although numerical differences could be considered clinically significant, no statistical significance was found. However, in our study, presence of long-term follow-up results of the cases was also important to reflect real-life outcomes.

In conclusion, although epithelial ovarian cancer is referred to as a single group of diseases, it is actually a heterogeneous entity in which different histological subgroups exhibit different biological background. Especially mucinous type EOC was found to have a worse outcome than other subgroups. According to the guidelines, although the standard treatment for all EOC subgroups of the same stage is adjuvant platinum-based chemotherapy after maximal surgery, it should be considered that not all subgroups may benefit from the same adjuvant therapy and may have differences in terms of long-term survival. In the light of new clinical trials for adjuvant therapy of mucinous subgroup, new treatment options are needed for better survival results.

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