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Comparison of advanced stage mucinous epithelial ovarian cancer and serous epithelial ovarian cancer with regard to chemosensitivity and survival outcome: a matched case-control study

Emine Karabuk[1], M. Faruk Kose[2], Deniz Hizli[3], Salih Taşkin[4], Burak Karadağ[1], Taner Turan[1], Nurettin Boran[1], Ahmet Ozfuttu[5], U. Fırat Ortaç[4]

[1]Department of Gynecologic Oncology, Etlik Zübeyde Hanım Women's Health Teaching and Research Hospital, Ankara; [2]Department of Obstetrics and Gynecology, Bahcesehir University Faculty of Medicine, Istanbul; [3]Department of Obstetrics and Gynecology, Fatih University Faculty of Medicine, Ankara; [4]Department of Gynecologic Oncology, Ankara University Faculty of Medicine, Ankara; [5]Department of Pathology, Etlik Zübeyde Hanım Women's Health Teaching and Research Hospital, Ankara,Turkey

Objective: The aim of this study was to compare clinicopathologic characteristics, surgery outcomes and survival outcomes of patients with stage III and IV mucinous epithelial ovarian cancer (mEOC) and serous epithelial ovarian carcinoma (sEOC).

Methods: Patients who had surgery for advanced stage (III or IV) mEOC were evaluated retrospectively and defined as the study group. Women with sEOC who were matched for age and stage of disease were randomly chosen from the database and defined as the control group. The baseline disease characteristics of patients and platinum-based chemotherapy efficacy (response rate, progression-free survival and overall survival [OS]) were compared.

Results: A total of 138 women were included in the study: 50 women in the mEOC group and 88 in the sEOC group. Patients in the mEOC group had significantly less grade 3 tumors and CA-125 levels and higher rate of para-aortic and pelvic lymph node metastasis. Patients in the mEOC group had significantly less platinum sensitive disease (57.9% vs. 70.8%; p=0.03) and had significantly poorer OS outcome when compared to the sEOC group (p=0.001). The risk of death for mEOC patients was significantly higher than for sEOC patients (hazard ratio, 2.14; 95% confidence interval, 1.34 to 3.42).

Conclusion: Advanced stage mEOC patients have more platinum resistance disease and poorer survival outcome when compared to advanced stage sEOC. Therefore, novel chemotherapy strategies are warranted to improve survival outcome in patients with mEOC.

Keywords: Chemosensitivity, Mucinous epithelial ovarian cancer, Serous epithelial ovarian cancer, Survival

INTRODUCTION

Of all the gynecologic cancers, epithelial ovarian cancer (EOC) accounts for 25%–30% of all cases and has the highest fatality-to-case ratio [1]. Primary cytoreductive surgery and taxane/platinum-based adjuvant chemotherapy are the cornerstones of the initial treatment for all histological subtypes of EOC [2,3]. The mucinous cell type accounts for 10% of all primary

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Correspondence to Deniz Hızlı
Department of Obstetrics and Gynecology, Fatih University Faculty of Medicine, Vatan Street No: 81, 06530 Demetevler, Ankara, Turkey. Tel: +90-5332484399, Fax: +90-3123462388, E-mail: denizhizli@yahoo.com

EOC [4]. The early stages have a better overall prognosis for survival, while the advanced disease is associated with a poorer survival compared to the other histological subgroups [5-8]. The exact mechanism of this finding has not yet been clarified. Either the aggressive characteristic of the tumor or chemoresistance or both mechanisms were claimed to be the reason for poor prognosis of advanced mucinous EOC (mEOC) [9-11]. However, to date, patients with advanced mEOC receive the same treatment as patients with other histologic subtypes of EOC.

In the present study, we aimed to compare the clinicopathologic characteristics and surgery outcomes between patients with advanced stage mEOC and serous EOC (sEOC). We also investigated whether the survival of women with advanced stage mEOC treated with the same protocols is significantly different from that of sEOC.

MATERIALS AND METHODS

1. Patient population

Patients who had surgery for advanced stage (International Federation of Gynecology and Obstetrics [FIGO] stage III or IV) mEOC at the Gynecologic Oncology Department of Etlik Zübeyde Hanım Women's Health Teaching and Research Hospital and Ankara University Faculty of Medicine between January 1999 and January 2011 were evaluated retrospectively and defined as the study group (Table 1). Women with sEOC who were matched for age, date of diagnosis and stage of disease were randomly chosen from the database and defined as the control group. At surgery, all patients underwent comprehensive surgical staging procedures, including total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymph node dissection, peritoneal cytology, and peritoneal biopsies according to FIGO guidelines, and also underwent maximal debulking surgery to achieve complete or optimal cytoreduction. Additional performed surgical procedures are presented in Table 2. After the surgery, all patients

Table 2. Other surgical procedures performed in addition to total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymph node dissection, appendectomy

Surgical procedures	Number
Splenectomy	10
Splenectomy, colon resection	1
Splenectomy, distal pancreatomy	1
Peritoneal tumor resection	3
Colon resection	8
Colon+small intestine resection	1
Colon resection, partial liver resection	1
Partial liver resection	1

Table 1. Comparison of both groups according to demographic and clinical features

Characteristic	Variable	Mucinous	Serous	p-value
Age (yr)		53.2±12.3	52.6±11.5	0.79
Grade	1	28 (56)	14 (15.9)	0.001
	2	15 (30)	50 (56.8)	
	3	7 (14)	24 (27.3)	
Stage	IIIA	3 (6)	2 (2.3)	0.48
	IIIB	7 (14)	10 (11.4)	
	IIIC	37 (74)	73 (8.3)	
	IV	3 (6)	3 (3.4)	
Preoperative CA-125 level (IU/mL)		343±717	1,121±2,381.9	0.002
Surgery outcome	Suboptimal	9 (18)	15 (17)	0.714
	Optimal	41 (82)	73 (83)	
Presence of preoperative ascites		37 (74)	72 (81.8)	0.125
Para-aortic lymph node metastasis		26 (52)	64 (72.7)	0.01
Pelvic lymph node metastasis		24 (48)	59 (67)	0.02
Para-aortic and pelvic lymph node metastasis		17 (34)	50 (56.8)	0.01
Type of chemotherapy	Platinum-taxane	36 (72)	76 (86.4)	0.038
	Platinum-cyclophosphamide	14 (28)	12 (13.6)	

Values are presented as mean±SD or number (%).

received platinum based adjuvant chemotherapy. Imaging (usually computed tomography scan or ultrasonography) was performed after every two to three cycles or at the first sign of progressive disease.

Data were retrospectively extracted from patient charts and computerized medical records. The following parameters were recorded: histology, age, date of diagnosis, stage of disease, grade, presence of ascites and lymph node metastasis, residual disease after primary surgery, serum CA-125 level before and after chemotherapy, chemotherapy regimen (type of platinum-based therapy), number of cycles, response to treatment, time to progression, CA-125 level at recurrence and date of death or last follow-up. In all patients, the diagnosis was confirmed histologically. Patients with borderline EOC, non-seromucinous EOC, non-epithelial ovarian tumors and primary peritoneal tumors were not included in the study. All patients underwent detailed preoperative and surgical exploration to exclude primary colorectal and appendix tumor. In all cases, frozen/section examination was performed and appendectomy was added to the routine procedure if the frozen/section showed "mucinous tumor". Immunohistochemical study was performed in situations where metastatic tumor can not be excluded. With careful exclusion of noninvasive,and metastatic mucinous tumors, patients who had final pathologic diagnosis as "primary mEOC" were included in the study. The study protocol was approved by the Institutional Ethics Committee.

2. Definitions

Tumorectomy was defined as resection of the tumor without resection of part or all of the involved organ, which includes optimal and suboptimal cytoreduction. Patients were staged according to FIGO criteria and surgery was defined as optimal if the largest dimension of the largest residual tumor was ≤0.5 cm and suboptimal if the dimension was >0.5 cm [12]. Progression-free survival (PFS) was defined as the time, in months, from the first day of chemotherapy treatment to the date of disease recurrence (confirmed on physical, radiologic or serologic exam). Overall survival (OS) was defined as the time, in months, from the first day of chemotherapy treatment to the date of death, last follow-up, or censoring.

3. Statistical analysis

The primary endpoints of the study were to assess the baseline disease characteristics of patients and to compare platinum-taxane based chemotherapy efficacy (response rate, PFS and OS) in patients with advanced mEOC or sEOC.

Continuous variables were expressed as mean, median, minimum and maximum, whereas percentages and frequencies were used for categorical variables. Groups were controlled in terms of conformity to normal distrubution by graphical check and Shapiro Wilk test. Mann-Whitney test was performed for not normally distributing variables and independent t-test was used for normally distributed variables.

PFS and OS were estimated using the Kaplan-Meier method and univariate analysis evaluating the risk factors associated with PFS and OS was performed by comparing the PFS and OS rates using the log-rank test. All prognostic variables found to be significant in univariate analysis were included in multivariate analysis using Cox's proportional hazards model. For this procedure, the forward selection of the parameter was processed using the chi-square test score and backward elimination using the Wald test. p-values ≤0.05 in two-sided tests were regarded as significant. Data analysis was carried out using SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, a total of 138 women were included in the study: 50 women in the mEOC group and 88 in the sEOC group. The mean ages of the study and control groups at diagnosis were 53.2±12.3 years and 52.6±11.5 years, respectively. Clinicopathologic characteristics of patients are summarized in Table 1. The groups were not different with regard to age, stage, surgery outcome (optimal vs. suboptimal) and presence of ascites. However, patients in the mEOC group had significantly less grade 3 tumors and lower CA-125 levels compared to the sEOC group (p=0.001). Moreover, patients with sEOC had a significantly higher rate of para-aortic and pelvic lymph node metastasis (p=0.01 and p=0.02, respectively) (Table 1).

Thirty-six (72.0%) patients in the mEOC and 76 (86.4%) in the sEOC group received a taxane+platinum chemotherapy regimen. The median number of cycles in both groups was 6 (range, 2 to 12). Thirty-eight patients (76.0%) in the mEOC group and 65 (78.4%) in the sEOC group had recurrence. Of these patients with recurrence, 57.9% of the patients in the mEOC group had platinum sensitive disease while 70.8% of patients in the sEOC group had platinum sensitive disease. The difference was statistically significant (p=0.03).

The median follow-up period was 40 months (range, 3 to 193 months). Seventy-one (51.4%) patients died of disease, 33 (66.0%) in the mEOC group and 38 (43.2%) in the sEOC group. The difference was statistically significant (p=0.01).

Median PFS was 7 months (range, 6 to 50 months) for patients with mEOC and 11 months (range, 3 to 144 months) for patients with sEOC. The groups were not different (p=0.693) (Fig. 1A). PFS according to chemotherapy regimen

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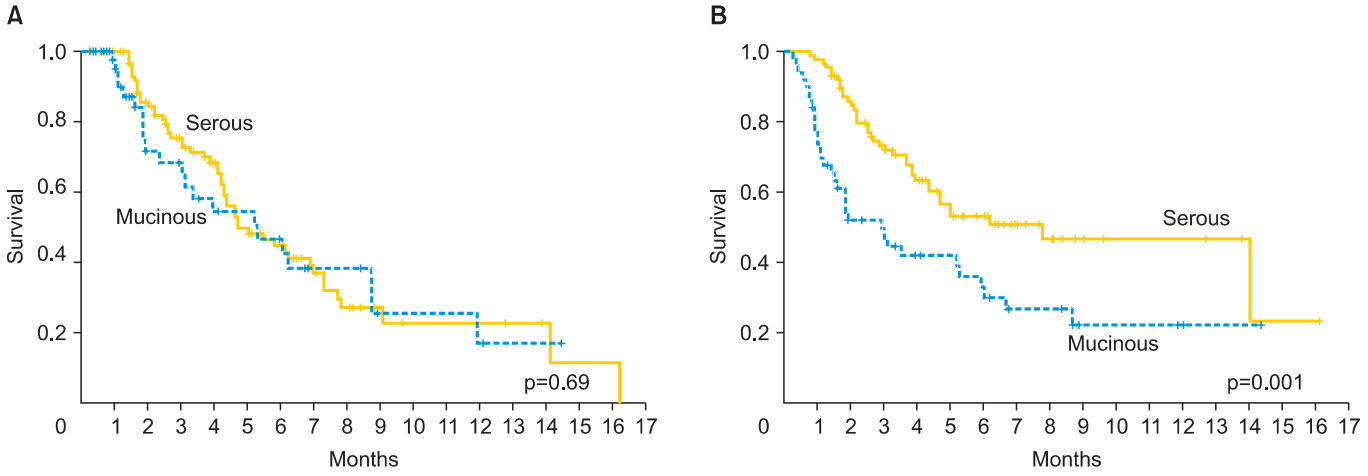

Fig. 1. Progression-free survival (A) overall survival (B) for patients with 50 mucinous and 88 serous epithelial ovarian cancer.

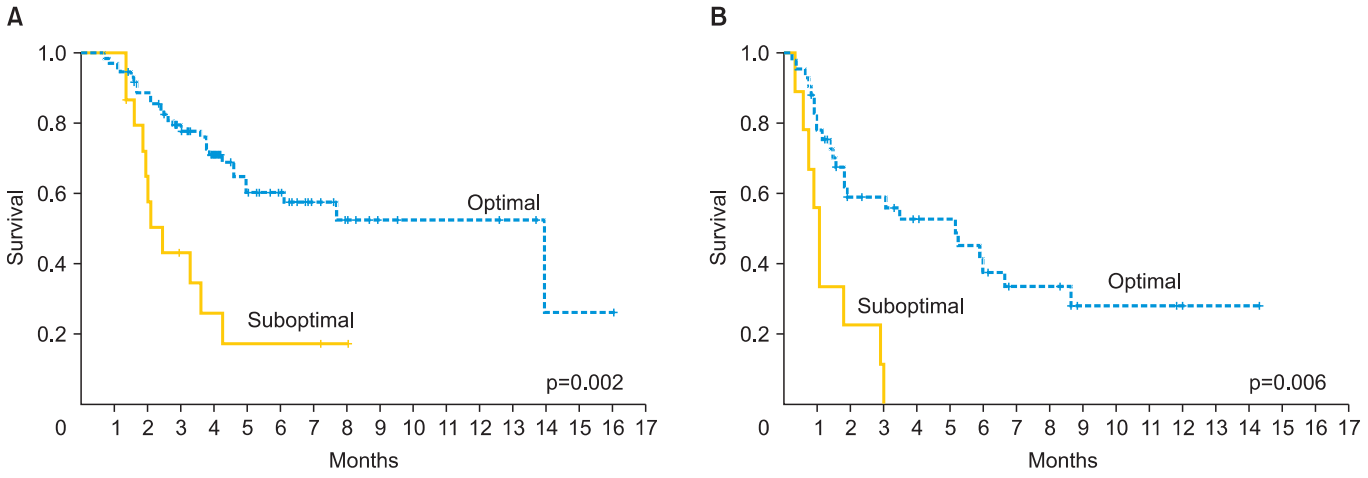

Fig. 2. Overall survival according to surgery outcome for patients with serous (A) and mucinous (B) epithelial ovarian cancer.

(platinum+cyclophospamide vs. platinum+taxane) did not show statistical significance (p=0.322 and p=0.099, respectively).

Median OS was 35 and 94 months for patients with mEOC and sEOC, respectively. Women in the mEOC group had a significantly poorer OS outcome when compared to the sEOC group (p=0.001) (Fig. 1B). The risk of death for mEOC patients was significantly higher than for sEOC patients (hazard ratio, 2.14; 95% confidence interval, 1.34 to 3.42). Moreover, patients who had optimal surgery had significantly longer OS in the study and control groups (p=0.002 and p=0.006, respectively) (Figs. 2). In the mEOC group, OS was 3.8 fold increased in patients who had optimal surgery (95% confidence interval, 2.07 to 6.1). OS was higher in both groups for patients who had chemosensitive disease (p=0.001).

DISCUSSION

The poor survival outcome of advanced stage mEOC is the main problem in the treatment of EOC. Previous reports have suggested that mEOC behaves differently from the other histological subtypes of EOC [5-9]. The current treatment modality for advanced stage mEOC is maximal cytoreductive surgery followed by taxane/platinum based adjuvant chemotherapy as utilized in sEOC [2,3]. However, the efficacy of taxane/platinum based adjuvant chemotherapy is controversial, because approximately 70–80% of patients with advanced stage mEOC will have chemoresistant disease [9-11,13].

Hess et al. [13] evaluated 27 advanced stage mEOC patients, and reported a lower response rate to first-line chemotherapy (26.3% vs. 64.9%) and survival outcome (12.0 months vs. 36.7 months) in patients with mEOC when compared to sEOC.

Bamias et al. [14] compared the data of 24 mEOC patients to 367 sEOC patients and similarly found a worse prognosis in the mEOC group. Moreover, a meta-analysis including 7 randomized trials with 264 advanced stage mEOC stated that mEOC was an independent predictor of poor prognosis when compared to sEOC [15]. On the other hand, in a study including 47 mEOC cases, a significant lower response rate to chemotherapy was found in the mEOC group (38.5% vs. 70%) than the sEOC group. However, survival and time to tumor progression were not significantly different between the two groups [16]. Similarly, Shimada et al. [11] reported a lower response rate to chemotherapy in mEOC group when compared to those in sEOC group.

Good prognostic factors, such as younger patient age, lower tumor grade and less peritoneal carcinomatosis were reported for mEOC [9,17]. In the present study, patients with mEOC had significantly less grade 3 tumors, lower CA-125 level and less para-aortic and pelvic lymph node metastasis. Despite these good prognostic factors, this case-controlled study confirmed that patients with advanced mEOC had more platinum resistance disease and poorer survival outcome when compared to advanced sEOC.

Optimal debulking is associated with a survival advantage in all EOC types. In 2009, Cheng et al. [18] reported that optimal primary cytoreductive surgery for advanced mEOC was an important prognostic factor for survival. Alexandre et al. [9] compared 54 mEOC cases to 786 sEOC cases and noted that macroscopic complete resection was more frequently achieved in patients with mEOC [19]. However, we did not find a statistical difference with regard to complete resection between patients with mEOC and sEOC. This finding may be due to the low number of patients who had suboptimal surgery. Approximately 80% of patients had optimal surgery in our patient population.

It is hard to draw conclusions in studies evaluating mEOC due to the limited number of studies and the small patient population. Also, our study has several limitations inherent to its retrospective design and small sample size. Although the number of mEOC patients included in the present study is still limited, it is one of the largest studies on advanced stage mEOC thus far. Previous studies which have evaluated the clinicopathologic characteristics of mEOC are summarized in Table 3.

The main problem with mEOC seems to be the manage-

Table 3. Studies evaluated the clinicopathologic characteristics of mucinous ovarian cancer

Study (author, year)	Type	Patient population	No. of patients included in the study	No. of patients with mEOC	Stage	Summary
Omura et al. 1991 [5]	Retrospective	All EOC types	726	33	III/IV	mEOC is a poor prognostic factor.
Pectasides et al. 2005 [16]	Retrospective	mEOC, sEOC	141	47	III/IV	mEOC has low response to platinum-based chemotherapy.
Pignata et al. 2008 [17]	Retrospective	All EOC types	408	20	I–IV	mEOC has low response rate to chemotherapy.
Shimada et al. 2009 [11]	Retrospective	mEOC, sEOC	719	64	I–IV	mEOC has low response rate to chemotherapy.
Alexandre et al. 2010 [9]	Retrospective	All EOC types	840	54	IIB/IV	mEOC has low response rate to chemotherapy and has poor prognosis.
Bamias et al. 2010 [14]	Retrospective	mEOC, sEOC, clear cell	420	24	III/IV	mEOC but not clear cell histology is associated with poor prognosis.
Mackay et al. 2010 [15]	Retrospective	All EOC types	8,704	264	III/IV	mEOC and clear cell carcinomas are independent predictors of poor prognosis in advanced stage EOC.
Schiavone et al. 2011 [8]	Retrospective	All EOC types	40,571	4,811	I–IV	Advanced stage mEOC is associated with poor survival.
Zaino et al. 2011 [7]	Prospective	All EOC types	3,435	44	III/IV	Advanced stage mEOC is associated with poor survival.
Present study	Retrospective	mEOC, sEOC	138	50	III/IV	mEOC has low response rate to chemotherapy and has poor prognosis.

mEOC, mucinous epithelial ovarian cancer; sEOC, serous epithelial ovarian cancer.

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ment of patients at an advanced stage due to the reasons described above. The mechanisms leading to this more aggressive course for patients with advanced disease have been studied in limited trials [9,10,13,16]. Failure to respond to platinum-based treatment, as demonstrated here, would explain a poorer survival in mEOC patients, because platinum-sensitivity is one of the main prognostic factors for patients with advanced EOC [10]. The Hellenic Cooperative Oncology Group reported an overall response rate to platinum based chemotherapy of 70% for advanced-stage sEOC compared with only 39% for Meoc [16]. Shimada et al. [11] reported response rates of 13% for invasive mucinous tumors compared with 68% with serous adenocarcinomas. In the present study, response rate to platinum based chemotherapy was 57.9% and 70.8% for patients in mEOC and sEOC groups (p=0.038).

In contrast to these data, patients with advanced stage mEOC receive the same first-line chemotherapy regimen as patients with other histologic subtypes in current practice. However, recent ongoing studies have focused on new chemotherapy strategies for mEOC. The Gynecologic Oncology Group and the Gynecologic Cancer Intergroup have initiated a trial of carboplatin/paclitaxel with or without bevacizumab compared with oxaliplatin/capecitabine with or without be bevacizumab as initial chemotherapy specifically for women with mucinous tumors [20]. Moreover, Japanese researchers are examining a newe agent functions like 5-fluorouracil which has efficacy in vitro [21,22].

In conclusion, our data showed that advanced stage mEOC patients have more platinum resistance disease and poorer survival outcome when compared to advanced stage sEOC. Therefore, novel chemotherapy strategies are warranted to improve survival outcome in patients with mEOC. The results of ongoing prospective studies will shed light on the management of patients with advanced stage mEOC.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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