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Central nervous system metastatic epithelial ovarian cancer. Clinical parameters and prognostic factors: a multicenter study of Anatolian Society of Medical Oncology

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Summary

Central nervous system (CNS) metastasis is a rare event in the course of late stage epithelial ovarian cancer (EOC); however its incidence is increasing in parallel with prolonged survival of patients. *Objective:* The authors assessed the clinical parameters and potential prognostic features in patients with CNS metastatic disease. *Materials and Methods:* Clinical data of the 33 patients from the participating centers were retrospectively collected and analyzed. Median age at the time of CNS metastasis was 57 years. Median time from the diagnosis of primary EOC until CNS metastatic disease was 22 months. Nearly half (45.5%) of the patients had single CNS metastatic lesions and all patients in the study group except two received radiotherapy as palliative treatment. Median overall survival (OS) from the time of CNS metastasis was 15 months (0-66). At univariate analysis only number of brain metastatic lesions ($p = 0.001$) and presence of extracranial disease ($p = 0.004$) were strongly associated with OS whereas multimodal treatment, size of metastatic lesions, platinum sensitivity, age, grade, and disease stage at presentation were not. Development of CNS metastasis carries a poor prognosis, however patients with single metastatic lesions and only intracranial metastatic disease can have prolonged survival after appropriate palliative management of their disease.

Key words: Central nervous system epithelial ovarian cancer; Metastasis; Palliative management.

Introduction

Epithelial ovarian cancer (EOC) is the major cause of death from gynecological tumors and is also the fifth-common cause of cancer associated death in women. Unfortunately majority of the patients present at a late stage of the disease because its initial symptoms are vague and non-specific such as abdominal pain. Although patients often show a good initial response to platinum based chemotherapy regimens, most of them die as a cause of progressive disease [1]. Historically the incidence of CNS metastases in EOC is low with near 600 cases reported so far in the literature [2]. Although the incidence of CNS metastatic lesions are reported in a wide range (2-12%) majority of the studies report an incidence of 1-2%. Better control of systemic disease with new chemotherapeutical agents and targeted therapies have led to increased survival of patients with advanced disease. Thus it has been suggested that with improved treatment of systemic disease, there will be more patients whose cancer is recurring in the CNS [2].

Many of the agents used in the treatment of advanced disease have poor penetration to CNS, therefore it is hypothesized that CNS acts like a reservoir for cancer cells who have crossed the blood brain barrier. CNS metastasis of epithelial ovarian cancer still carries a poor prognosis in the era of modern chemotherapy, and because of its low incidence, data about prognostic factors and treatment algorithms from large clinical studies are lacking in literature. However multimodal treatment strategies aiming at local control of the disease, such as surgery and radiotherapy, as well as systemic treatment with chemotherapy, can potentially provide a survival advantage to certain subgroups of patients. The present authors aimed to assess the potential prognostic factors and the impact of various treatment approaches on the survival of CNS metastatic EOC patients.

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Table 1. — *Clinical characteristics of patients with brain metastatic lesions in the study group.*

Characteristics (n=33)	
Age, median (range) years	57 (40-74)
Interval from EOC diagnosis to BM, median (range) months	22 (4-115)
Median survival after BM, median (range) months	15 (0-66)
Grade	
II, n. (%)	18 (54.6)
III, n. (%)	15 (45.6)
Stage	
III, n. (%)	24 (72.7)
IV, n. (%)	
N. of brain metastatic lesions	
Single, n. (%)	15 (45.5)
Multiple, n. (%)	18 (54.5)
Presence of extracranial disease	
Absent, n. (%)	18 (58.1)
Present, n. (%)	13 (41.9)
Platinum sensitive disease, n. (%)	9 (27.3)
Platinum resistant disease, n. (%)	24 (72.7)
BM maximum diameter	
≤ 2 cm, n. (%)	12 (36.4)
> 2 cm, n. (%)	21 (63.6)

BM: brain metastasis; EOC: epithelial ovarian cancer.

Table 2. — *Factors affecting overall survival in univariate analysis.*

Variables	Univariate analysis *p*-value	HR (95% CI)
Age (median) < 56 *vs.* > 56	0.930	1.042 (0.41-2.61)
Stage III *vs.* IV	0.137	0.480 (0.175-1.312)
Occurrence of brain metastasis ≤ 2 *vs.* > 2 years	0.979	1.012 (0.410-2.496)
Platin resistance	0.272	0.599 (0.234-1.528)
Size of brain metastatic lesion ≤ 2 *vs.* > 2 cm	0.282	1.655 (0.647-4.229)
Number of brain metastatic lesions single/multiple	< 0.001	9.241 (2.608-32.751)
Presence of extracranial metastasis	0.002	0.228 (0.082-0.629)

HR: hazard ratio; CI: confidence interval.

Materials and Methods

A total of 33 patients treated for EOC and who presented with or later developed CNS metastatic disease in the course of disease, in the medical oncology departments of the participating centers between 2003 and 2010, were included in the study group. In all of the patients, CNS metastatic disease was confirmed by magnetic resonance imaging. Patients with a previous history of known CNS mass lesions or tumor diagnosis other than EOC were not included in the study group. Relevant clinical, demographical, and pathological data, treatment methods, and survival times were retrieved from the medical records of the patients retrospectively.

Results are given as medians with minimum and maximum values. Mann-Whitney U test was used for comparison of continuous variables between groups. Fisher's exact test was used for categorical variables. Kaplan-Meier survival curves were calculated using univariate survival analysis. The log-rank test was used to compare survival curves. Statistical analysis was performed with Statistical Package of Social Science (SPSS) (version 16.0) software. A two-tailed *p*-value of < 0.05 was considered statistically significant

Results

Median age of patients at the time of brain metastasis was 57 (40-74) years. All patients had EOC. Majority of the study group had Stage 3 disease at the time of initial diagnosis of EOC (24 cases; 72.7%), while there were nine patients with Stage IV disease. The median time from the diagnosis of EOC to the detection of CNS metastatic disease was 22 (4-115) months. Fifteen (45.5%) patients had solitary CNS metastatic lesions while the remaining 18 (54.5%) patients had multiple brain lesions. At the time of detection of CNS metastasis, extracranial disease was present in 21 (63%) patients. Twenty-four (72%) patients were operated for brain metastatic lesions while 22 (66.6%) patients also received additional systemic chemotherapy after receiving local treatments (surgery and/or radiotherapy, RT) for brain lesions. Except for the two patients, all patients in the study group received RT as palliative treatment of CNS metastatic lesions. Five patients received all three treatment modalities. Median survival from the detection of CNS metastatic disease was 15 (0-66) months. At the time of analysis 13 patients were alive. Twenty-one (36.4%) patients had a brain lesion wider than two cm in largest diameter while in 12 (63.4%) patients, the largest lesion was measured less than two cm. The clinical and treatment characteristics of the study group are summarized in Table 1.

In univariate analysis, various factors such as time to brain metastasis, presenting stage at the time of diagnosis, number of treatment modalities received for CNS metastatic disease, platinum sensitivity, diameter of brain lesions, and tumor grade were not found to have prognostic value in univariate analysis (Table 2). Patients with single intracranial metastatic lesion had a median overall survival (OS) of 19 (2-66) months, while patients with multiple metastatic intracranial lesions survived a median of 6 months (0- 44) (p = 0.001). Patients with extracranial disease had a significantly shorter survival compared to patient with brain only metastasis (four *vs.* 17 months; p = 0.002) (Figure 1).

Time interval between diagnosis of EOC and occurrence of CNS metastatic disease was not associated with OS (p = 0.979). Patients with an interval shorter than 24 months to CNS metastatic disease had a median survival of 14 (0-66) months while those with a longer time duration had a median survival of 16 (0-46) months.

Patients receiving only RT for their CNS lesions had a

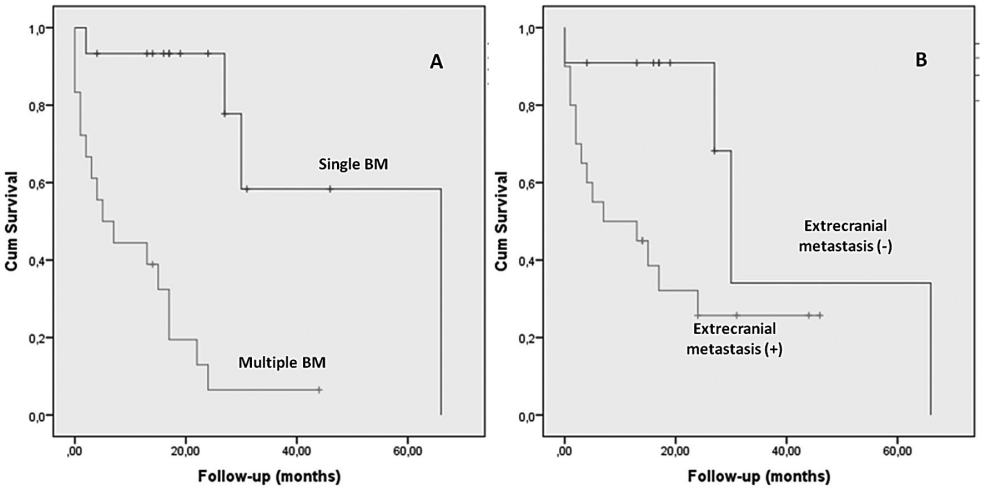

Figure 1. — Kaplan-Meier survival curve of CNS metastatic patients based on factors influencing the survival time: (A) presence of extracranial disease (presence *vs*. absence); (B) number of CNS metastatic lesions (single *vs*. multiple).

Table 3. — *Effect of treatment modalities on survival.*

Treatment modality	Univariate	
	p-value	HR (95% CI)
RT *vs.* RT+surgery	0.120	2.147 (0.725-6.359)
RT *vs.* RT+CT	0.160	0.487 (0.171-1.390)
RT *vs.* RT+surgery+CT	0.341	2.152 (0.405-11.448)
RT *vs.* other	0.079	0.427 (0.158-1.152)

RT: radiotherapy; CT: chemotherapy; HR: hazard ratio;
CI: confidence interval.

median survival of 2.5 (0-66) months after diagnosis of brain metastatic disease, while patients receiving any kind of additional therapy (surgery, RT, and chemotherapy) in addition to RT had a significantly prolonged OS (16.5 months). While the difference in OS did not reach a statistical significance, there was a strong trend ($p = 0.07$) (Table 3).

Discussion

Ovarian cancer is a rare cause of CNS metastasis. Various retrospective studies have reported the incidence of CNS metastases in EOC between 0.29-12%. It is unclear why the incidence of CNS metastasis is low in ovarian cancer. Inability of main chemotherapeutic agents cisplatin and paclitaxel to cross blood brain barrier have allowed cancerous cells to take shelter in a relatively protected environment in CNS. Although the clinical series dating before 1970s where effective chemotherapy was not present, report the incidence of brain metastasis as 0.9% while recent studies evaluating the incidence of CNS metastasis give an incidence of 1-3% [3]. The main route of CNS metastasis is hypothesized to be by hematogenous spread from pulmonary veins to the brain tissue [4]. The incidence of solitary metastatic disease is reported to be around 50% in the literature which is slightly higher than other types of cancer which cause CNS metastasis more often, such as lung cancer and melanoma [5].

Among the commonly cited risk factors for development of CNS metastatic lesions are disease stage at first diagnosis and grade. The fact that majority of the present patients had Stage III disease underlies the observation that a long survival time is needed for development of CNS metastatic disease. Several clinical series in the literature also state Stage III disease as the most common stage at presentation [6-9]. The present authors' observation that nearly half of the patients had Grade III disease is consistent with the rates reported in literature [6, 9, 10]. It is reported that in Grade III/IV tumors, the time to develop CNS metastasis is considerably shorter compared to more differentiated tumor types (1.5 *vs*. 4.7 years) [11, 12].

In the present group, the median time to develop CNS metastatic disease from the initial diagnosis was 22 months, which is in line with the time range reported in the literature (15-33 months) [11, 13-15]. The relatively long period of time to develop CNS metastatic disease (near two years) adds support to the theory that better systemic control of extracranial disease with platinum taxane combination based treatments and optimal debulking surgical approach have provided time for CNS metastatic disease for development and growth [11, 15].

Generally, it is accepted that the prognosis for CNS metastatic EOC patients is poor, however there are some subsets of patients which can have a more favorable outcome. The present authors have observed that patients with single metastatic lesions have a longer survival period compared to patients with multiple brain lesions (19 *vs*. six months). The distribution of patients with single *vs*. multiple metastatic lesions is in accordance with the literature, nearly half of the patients had a single metastatic CNS le-

sion (45.5%) [2, 12, 13].

Whether the number of metastatic lesions is a significant prognostic factor is a controversial issue. In reports by several authors [11, 16, 17], patients with either single or multiple CNS metastatic lesions have shown to have similar survival rates with application of radiotherapy and surgical excision of lesions. However, there are other reports that state that presence of single metastatic lesion is favorably associated with prolonged survival [3, 10, 18]. The contradictory conclusions about the prognostic value of single metastatic brain lesion may be as a result of the various treatment algorithms given in different clinical series. Single metastatic lesion patients appear to derive more benefit from multimodal treatment consisting of surgery, whole-brain radiation therapy (WBRT) and chemotherapy compared to multi-lesion metastatic patients [3, 19].

Time interval between development of CNS metastatic disease and initial diagnosis was found to be 22 months, which is in line with the literature [14, 16]. Time to development of CNS metastatic disease is reported to be a prognostic factor in a clinical series by Cormio *et al.* (median OS nine *vs*. 16 months for time to CNS metastatic disease to occur shorter than 40 months *vs*. longer; $p = 0.03$) [13]. However this was not confirmed by other studies in the literature (median OS 4.7 *vs*. 8.7 months for time to CNS metastatic disease to occur shorter than 22 months *vs*. longer; $p = 0.03$) [11].

Performance status is reported to have a strong influence on survival of patients with CNS metastatic disease [2, 10, 20]. It could be speculated that good performance status patients are more likely to be patients with single metastatic lesions, without extracranial disease and receive multimodal treatment. These factors are commonly associated with improved prognosis. The performance status was not included in the database of the study group, therefore the impact of this factor on survival could not be measured in the present study.

Other prognostic factors reported to have a significant relation with survival are listed as tumor stage at diagnosis, presence of extra cranial disease, diameter of the largest metastatic lesion, and single brain metastasis. In the present analysis of the study group, factors of age and diameter of the largest metastatic lesion were not found to have a significant association with survival. The percentage (63%) of the patients who had extra-cranial disease at the time of CNS metastases is in line with the literature [13, 16]. The presence of systemic disease was significantly associated with survival after diagnosis of CNS metastatic disease (four *vs*. 17 months). The negative effect of extracranial disease on survival is also reported in the literature. Anupol *et al.* reported the median survival of patients with extra-cranial disease at the time of CNS metastasis to be three months where as it is around eight months in patients with CNS only metastatic disease [18]. Cohen *et al.* reported the median survival of patients in terms of extracranial disease as 12.2 *vs*. 3.5 months [11].

Single CNS metastatic lesion was found to be significantly associated with a favorable prognosis in the present study (19 *vs*. six months). In a recent review by Pakneshan *et al.*, patients having a single metastatic lesion had a median survival of 21 months, which is very close to the present series [20]. Although the survival advantage of single metastatic patients was higher compared to patients with multiple CNS lesions (21 *vs*. nine months), the difference did not reach statistical significance ($p = 0.17$). Interestingly, the majority of the older reviews published between 1990–2010 report median survival for single metastatic lesions between six to seven months [11, 13, 18], while in more recent reviews median survival for single metastatic lesion patients is reported to be between 16 and 40 months [2, 19, 20]. Whether improved surgical or radiotherapy techniques account for this difference remains to be elucidated.

All of the patients in the study group received locoregional and/or systemic treatment after the diagnosis of brain metastatic disease. In the literature, the prognosis of patients who do not receive any treatment is very poor with median survival times reported between one to two months [18, 21, 22]. WBRT has been traditionally utilized as an effective treatment approach against CNS metastatic disease. Patients solely receiving WBRT as treatment are reported to have a median OS by three to six months, while in the present study this was around five months in accordance with the literature [11, 14, 18]. Although there was a two-month median survival advantage in patients who received surgery, in the present study group it was not statistically significant. It has been suggested that surgical resection of brain metastatic disease in addition to WBRT can provide a better survival outcome when compared to WBRT alone [3, 11, 23].

Multimodality treatment with chemotherapy in addition to surgery and radiotherapy has been reported to be associated with best outcomes reported in literature [16]. Accordingly in the present study patients who received surgery and/or chemotherapy after WBRT had better outcomes when compared to patients who did not receive additional treatment (15 months *vs*. five months), albeit the numerical difference did not translate into a statistical significance, the present authors believe that larger studies with higher number of patients can define specific patient groups who could benefit most from either surgery or additional systemic chemotherapy. The median OS for patients who receive chemotherapy after surgery/WBRT median survival is reported to be around 16 to 22 months [6, 18, 24].

In clinical series reported by the HeCOG group, the group of patients who received chemotherapy had a median survival of ten months while those who only had WBRT had only 1.5 months for survival [6]. In a recent review by Piura *et al.* including 520 patients from 34 series, median survival

of patients receiving WBRT/surgery plus chemotherapy had a median survival of 20 months, while those receiving WBRT/surgery had a median survival of 17 months [2]. The benefit of chemotherapy was also reported in a series by Anupol *et al.* where patients receiving chemotherapy compared to those who only received surgery and WBRT had a three-month longer median survival (20 *vs.* 17 months) [10, 18]. It is generally presumed that intravenous chemotherapeutic agents does not penetrate into CNS and reach clinically effective doses because of blood brain barrier; however several studies point to the fact that in the presence of CNS metastasis, this barrier may be impaired. In addition previously applied radiotherapy may also help in degrading the integrity of the blood brain barrier, however it should be noted that the benefit of chemotherapy in the setting of CNS metastatic disease has not been validated in a prospective study and the data is derived from retrospective studies with a limited number of patients.

It must be kept in mind that retrospective analysis is subject to bias. It is possible that patients with the best performance score and who can tolerate treatment may have been favored for receiving multimodal therapy compared to patients with resistant systemic disease or those with already poor performance status.

Conclusion

In conclusion CNS metastatic disease is expected to occur late in the disease course. Although brain metastatic disease is generally considered a poor prognostic state, deferring these patients from treatment is detrimental to their outcome. The present study results provide further support to data in literature that patients with single metastatic lesions with no extracranial involvement may benefit from receiving multimodal treatment and can have prolonged survival of over 12 months.

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