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Original Research

The clinical outcomes of ovarian cancer in patients with brain metastasis

Seda Yuksel Simsek[1,*], Ozan Cem Guler[2], Gülşen Doğan Durdag[1], Sezin Yüce Sari[3], Melis Gultekin[3], Ferah Yildiz[3], Husnu Celik[1], Gurcan Erbay[4], Huseyin Cem Onal[2]

[1] *Department of Obstetrics and Gynecology, Baskent University Medical School Adana Training Hospital, 01000 Adana, Turkey*

[2] *Department of Radiation Oncology, Baskent University Medical School Adana Training Hospital, 01000 Adana, Turkey*

[3] *Department of Radiation Oncology, Hacettepe University Medical School, 06000 Ankara, Turkey*

[4] *Department of Radiology, Baskent University Medical School Adana Training Hospita, 01000 Adana, Turkey*

*Correspondence: dryukselseda@hotmail.com (Seda Yuksel Simsek)

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Objective: To present the clinical characteristics and treatment outcomes of patients with ovarian cancer with brain metastasis. *Methods*: This study was designed as a retrospective observational study. Patients' data were obtained from hospital records. Patients who were diagnosed with brain metastatic ovarian cancer in two tertiary referral centers between 2012 and 2020 were included in the study. *Results*: In total, there were 56 patients diagnosed as having brain metastatic ovarian cancer. The median age was 56 years, 91% of patients were at an advanced stage at initial diagnosis. The median time from the initial diagnosis to brain metastasis was 34.0 months. Sixty-seven percent of patients were determined as having multiple brain metastatic lesions. Whole brain radiotherapy (WBRT) , stereotactic radiosurgery (SRS) and combined approach were utilized as primary treatment. The 1 and 2-year survival rates were 38% and 17%, respectively. Patient age and tumor histology were found to be significant prognostic factors that impact the survival in univariate analyses. The 1-year survival of patients aged younger than 55 years was 49.2%, and 28.2% for patients aged over 55 years ($p = 0.04$). Patients with nonserous histology had significantly longer one year overall survival compared to serous histology (61.4% vs 29.8%) ($p = 0.01$). *Conclusion*: The brain is one of the rarest locations for ovarian cancer metastasis. Radiotherapeutic approaches are the mainstay of treatment but survival rates are low. Age and tumor histology were determined as significant parameters that affected survival rates.

Keywords

Ovarian cancer; Brain metastasis; Whole-brain radiotherapy; Stereotactic radiosurgery

1. Introduction

The majority of intracranial neoplasms are grounded on extracranial malignancies [1]. Brain metastasis can be detected in 20% of all malignancies. Lung cancer, malignant melanoma, breast, and colorectal carcinoma are the leading malignancies that metastasize to the brain [2]. Ovarian cancer is the leading cause of death from gynecologic malignancies. The vast majority of patients have recurrence despite surgical and medical treatment [3]. Brain metastasis occurs in approximately 1–2% of cases of ovarian cancer, and 5-year survival is approximately 40% [4–7]. However, over the last decade, the incidence of brain metastasis has increased, which may be due to the global increase in malignancies, the success of new treatment options and improved survival, the development of new imaging techniques that enable the detection of metastatic lesions, and the inability of chemotherapeutic agents to penetrate the blood-brain barrier [7–10].

Most data on brain metastasis in ovarian cancer arose from case series because the incidence is low. The clinicopathologic characteristics of patients with ovarian cancer with brain metastasis have been previously investigated [5–7, 11, 12]. High-grade serous ovarian tumors and advanced-stage disease are the common features of patients with brain metastatic ovarian cancer [13]. The number of metastatic lesions and treatment modalities are the leading independent prognostic factors [7, 14]. The BRCA mutation and androgen receptor status of the primary tumor are new emerging prognostic factors [10, 13, 15, 16].

Surgical resection, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and chemotherapy are the treatment modalities described in the literature [5, 17, 18]. Numerous studies have found combined treatment modalities to be more successful regarding longer survival [5, 7, 17, 19]. A multimodal treatment approach, surgery followed by WBRT is a positive prognostic factor for survival [7, 14]. The scarcity of brain metastasis in patients with ovarian cancer makes all data valuable. In this retrospective study, we aimed to analyze the characteristics of patients with brain metastasis and clinical outcomes of these patient group.

2. Materials and methods

2.1 Patient and data collection

This study was designed as a retrospective observational study. Patients diagnosed as having epithelial ovarian cancer

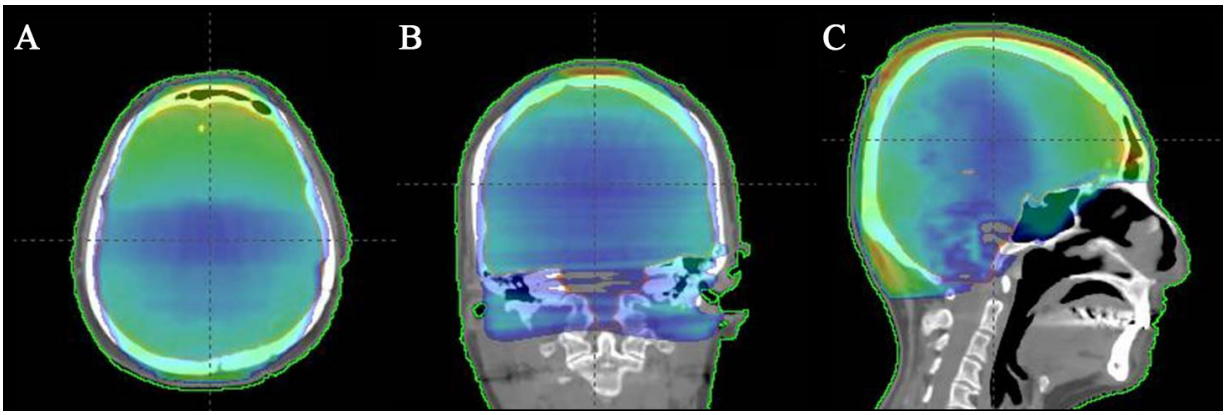

Fig. 1. Whole brain radiotherapy images. Axial (A), coronal (B) and sagittal (C) dose distribution of whole brain radiotherapy.

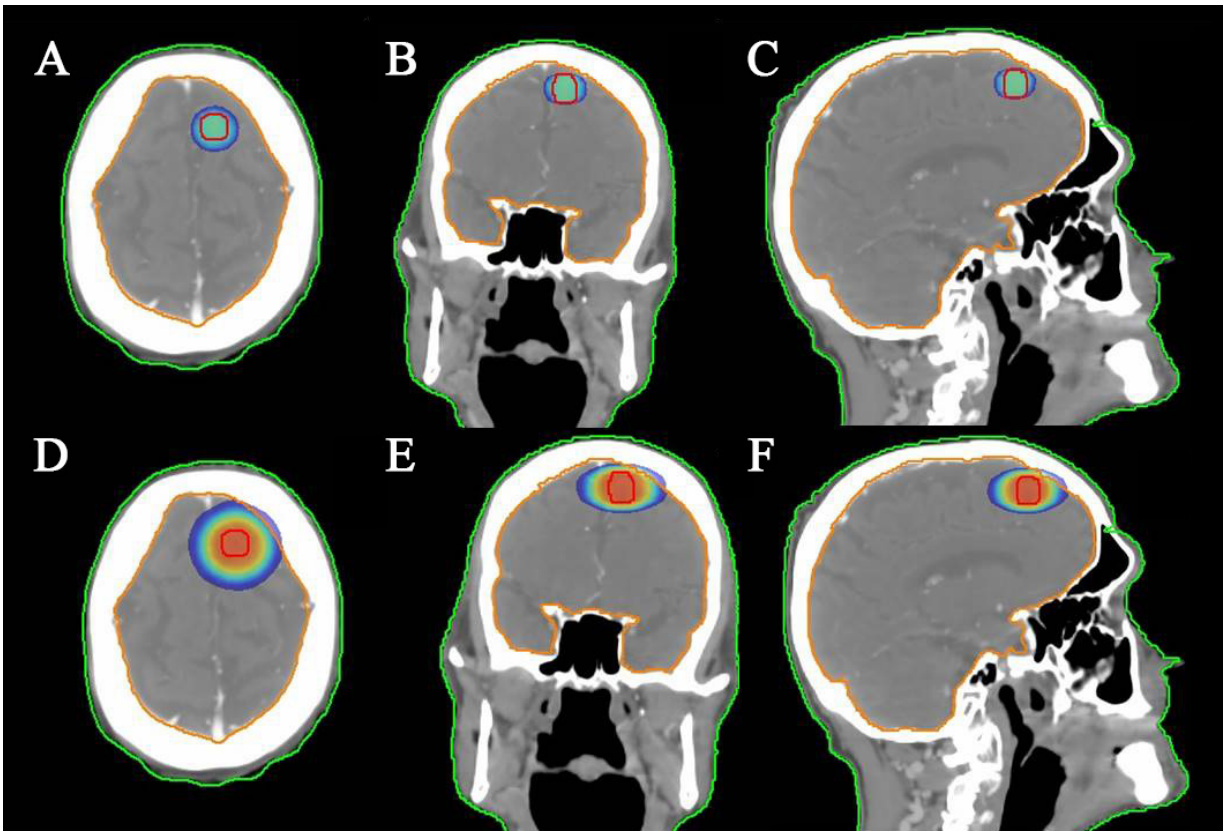

Fig. 2. Sterotactic radiotherapy images. Axial (A,D), coronal (B,E) and sagittal (C,F) dose distribution of stereotactic radiotherapy for 95% and 50% sodoses, respectively.

and brain metastasis between 2012 and 2020 were included from two reference centers. The diagnosis of brain metastasis was based on magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography (PET) findings. Brain metastasis is managed in a patient-tailored fashion. Whole-brain radiotherapy, SRS, chemotherapy and of metastatic lesions are used alone or in combination.

2.2 Radiotherapy techniques

WBRT has been used as a standard radiation oncologic approach for all histologic types of brain metastases, especially for multiple metastases for a long period in both study centers. The standard regime was 300 cGy delivered in 10 fractions. WBRT has been preferred, particularly those with multiple metastatic lesions that are not amenable to surgery or SRS (Fig. 1).

SRS involves the administration of a single or limited number of high doses of ionizing radiation to a small, well-demarcated tumoral lesion within the brain parenchyma. Limited metastatic lesions in the brain are treated with SRS. An experienced radiation oncologist evaluated patients before the initiation of SRS (Fig. 2).

2.3 Follow-up

The National Comprehensive Cancer Network (NCCN) clinical guideline recommendations were tracked during the follow-up of patients [20]. During the first 2 years after initial diagnosis, patients were evaluated every 2–4 months. After the first 2 years, visits were at 3–6 months for 3 years, and then annually for 5 years. Routine physical and pelvic examinations including laboratory tests comprising CA-125 levels, chest and abdominopelvic imaging tests including CT, MRI or PET were performed as clinically indicated. Routine intracranial imaging was not performed, except for suspected cases. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by Baskent University Medical School Ethical Committee with the project number KA21/345.

2.4 Statistical analysis

Statistical analyses were performed using the SPSS 22.0 software (SPSS for Windows, IBM Corp., Armonk, NY, USA). The local control (LC), overall survival (OS), and progression-free survival (PFS) rates were estimated using Kaplan-Meier analyses. The time to event was calculated from the date of LM to the first clinical or radiologic finding suggesting the recurrence or disease, last follow-up visit or death. Log-rank testing was used to evaluate the association between patient-related factors and treatment outcome. Correlations between parameters were calculated using Pearson's correlation test. Receiver operating characteristics (ROC) analysis was used to divide patients according to the gross tumor volume (GTV). All tests were double-sided and p-values of <0.05 were considered statistically significant.

3. Results

In this study, 56 patients with ovarian cancer with brain metastasis were included from two different tertiary treatment centers. The median age of the patients was 56 years (range, 27–80 years). Considering the initial cancer staging, only one patient (1.8%) was stage 1 and four patients (7.1%) had stage II disease. The vast majority of the patients (91.1%) were at an advanced stage (Table 1). All these patients with ovarian cancer were initially treated with a combination of cytoreductive surgery and adjuvant chemotherapy. Neoadjuvant chemotherapy was preferred in five (8.9%) patients. Chemotherapy regimen details are remarked in Table 1 and all of these regimens utilized as first line adjuvant or neoadjuvant therapies after initial diagnosis and surgical treatment of ovarian cancer. The median time from diagnosis to brain metastasis was 34.0 months (range, 2.9–100.0 months). The brain metastasis was diagnosed with MRI, CT, PET CT imaging in 79.3%, 16.1%, and 3.6% of patients, respectively. Brain metastasis was solitary in 16 (28.5%) patients and multiple in 38 (67.9) patients, and two patients (3.6%) presented with leptomeningeal metastasis. WBRT was the leading treatment modality, used in 43 patients (76.8%). SRS were used alone or in combination with WBRT in 10.7% and 12.5% of patients, respectively. Neither intracranial chemotherapy nor surgical excision of metastatic lesion has been utilized in this study group. Extracranial metastases have been identified in 76.8% of patients at the time of diagnosis of brain metastasis.

Table 1. Clinicopathologic characteristics of patients.

Age	56 (27–80 years)
Stage	Number of patients %
1	1 (1.8%)
2	4 (7.1%)
3	28 (50%)
4	23 (41.1%)
Pathology	
Serous	40 (71.4%)
Mucinous	6 (10.7%)
MMMT	3 (5.4%)
Undifferentiated	2 (3.6%)
Others	5 (8.9%)
Chemotherapy after ovarian cancer diagnosis	
Neoadjuvant Chemotherapy	5
Adjuvant Chemotherapy	51
Chemotherapy regimen	
Paclitaxel + Carboplatin	53
Paclitaxel + Cisplatin	2
Endoxan + Cisplatin	1
Time of BM after initial diagnosis	
$\leq$2 years	22 (39.3%)
$>$2 years	34 (60.7%)
Extracranial metastasis	
None	13 (23.2%)
Lung	7 (12.5%)
Abdomen	23 (41.1%)
Lung and abdomen	11 (19.6%)
Bone	2 (3.6%)
Radiotherapy	
WBRT	43 (76.8%)
SRS	6 (10.7%)
WBRT + SRS	7 (12.5%)
Lesions	
Solitary	16 (28.5%)
Multiple	38 (67.9%)
Leptomeningeal	2 (3.6%)

Abbreviations: MMMT, Malign mixt Mullerian tumor; BM, brain metastasis; WBRT, whole brain metastasis; SRS, stereotactic radiosurgery.

The median follow-up after a diagnosis of brain metastasis was 7.3 months (range, 1–30 months). The overall 1-year and 2-year survival rates were 38.7% and 17.4%, respectively. One-year survival was 49.2% in patients with solitary metastasis and 34.7% in those with multiple brain metastasis ($p > 0.05$). Patients' age and tumor histology were the statistically significant parameters that affects survival. One-year survival was longer in patients aged under 55 years (49.2%) compared with patients aged over 55 years (28.2%) ($p = 0.04$) and

one year OS of serous histology patients was 29.8% whereas 61.4% in patients with nonserous histology (p = 0.01) (Table 2).

Table 2. Brain metastasis diagnosis, treatment, and survival outcomes.

Overall survival	34 months (median)	p
Age (years)	1-year OS	
<55	28.2%	0.04
>55	49.2%	
Histology		
Serous	29.8%	0.01
Non-serous	61.4%	
Time of BM after initial diagnosis		
≤2 years	27.3%	0.8
>2 years	38.9%	
Extracranial metastasis		
Present	32.1%	0.2
Absent	41.0%	
Radiotherapy		
WBRT	34.3%	0.9
SRS	50.0%	
WBRT + SRS	42.9%	
Number of metastases		
Solitary	49.2%	0.5
Multiple	34.7%	

4. Discussion

We aimed to delineate the clinicopathologic features and prognostic factors of patients with ovarian cancer metastatic to the brain, which is a quite rare condition. Age and tumor histology have been found to be significant prognostic factors for OS. Although the patients' 1-year survival time seemed to be shorter than for patients with solitary metastasis, the difference was not significant.

The brain is an uncommon metastatic site for gynecologic malignancies [21]. According to the 'Surveillance, Epidemiology, and End Results' database, the brain is the least possible metastatic site for uterine, cervical, and ovarian cancers. Despite this rarity, the survival of patients with brain metastasis was found to be shorter than in other metastatic sites [12]. We also noted that the great majority of patients had advanced-stage disease at the time of diagnosis. The 1- and 2-year survival rates were dismal despite treatment. These findings were compatible with the literature. Optimal cytoreductive surgery, platinum sensitivity, prolonged time from diagnosis to metastasis, number of metastatic lesions, and treatment modalities were reported as independent prognostic factors for OS (Table 3, Ref. [5–7, 14, 19, 22–25]). The 1-year survival of patients with solitary metastasis was longer compared with those with multiple metastases but the difference was not significant in this study. Significant prognostic factors for longer survival was patient age and nonserous histology in this cohort. The limited patient number may prevent drawing definite conclusions regarding other prognostic factors.

In the literature, studies are investigating the relationship between BRCA mutation status and brain metastasis in patients with ovarian cancer [10, 15, 26]. The BRCA mutation was found to be more frequent in patients with ovarian cancer with brain metastasis [15, 16]. In a recent study, Stasenko *et al.* [10] remarked that patients with BRCA mutations had longer survival times compared with patients with wild-type BRCA. They associated this finding with the lesser incidence of extracranial disease and lesions being more frequently solitary rather than multiple in patients with BRCA mutations at the time of brain metastasis diagnosis [10]. BRCA status was not known for the large majority of patients in this study. Unfortunately, this shortage of information makes it difficult to comment on this aspect.

Surgical resection, chemotherapy, and different radiotherapy modalities are the mainstay of treatment of metastases. Lesions may be nonresectable due to critical locations and the proximity of lesions to vital parts of the brain. WBRT for metastasis is a well-known modality and it used to be the standard of care for brain metastases despite its detrimental neurocognitive adverse effects. The contemporary approach is to individualize treatment schedules. SRS was used complementary to WBRT in a limited number of brain metastases. Because the application field of SRS is more limited, it has the advantage of less radiation exposure of brain tissue compared with WBRT and this is an important advantage [27]. Many authors also studied the efficacy of the combination of WBRT and SRS. Local disease control has been more successful in the combined approach but OS outcomes were not better [28–30]. As a result, there is no consensus on the most effective treatment and patient-tailored therapy seems to be the most logical approach [31]. In this cohort, SRS was used alone or in combination in approximately 25% of patients. The majority of patients were treated with WBRT. This low rate of SRS use may be related to the limited facilities of radiotherapy units and standard approaches in former times.

The main limitation of this study results from its' retrospective nature. However, the scarcity of this clinical entity and the poor prognosis of this group of patients make prospectively designed studies inconvenient. The heterogeneity of both patient characteristics and treatment modalities is another disadvantage. The distribution of patients within the radiotherapy modalities is unbalanced, which prevents the comparison of these approaches. This is also a result of the rarity and dire prognosis of the pathology. Despite all limitations, the declaration of data of this rare group is important and can contribute to preexisting data. Although the patient number is limited, it seems comparable when we consider the studies in the literature.

Table 3. Previously published studies evaluating the prognostic factors of patients with brain metastatic ovarian cancer.

Author/year	n	Median time to brain metastasis	Treatment modalities	Significant prognostic factors
Kwon *et al.*, 2018 [5]	56	NA	Surgery Radiation	Multimodality of treatment
Wohl *et al.*, 2019 [14]	25	42.3 months	WBRT, SRS, Surgery	Number of metastatic lesions Treatment modality
Keskin *et al.*, 2019 [22]	21	32 months	Surgery, WBRT, SRS	Prolonged elapse time, WBRT, optimal cytoreductive surger
Anupol *et al.*, 2002 [23]	15	22 months	Radiation, Surgery	Presence of extracranial disease
Cohen *et al.*, 2004 [7]	72	1.8 years	WBRT, Surgery	Combined therapy (Surgery + WBRT)
Takeshita *et al.*, 2017 [24]	17	21 months	Radiation, Surgery	Extracranial metastasis, ECOG performance status, TFI
Da Costa *et al.*, 2019 [25]	26	31 months	WBRT, SRS, Chemotherapy	ECOG performance status, platinım sensitivity, number of previous therapy lines
Pakneshan *et al.*, 2014 [6]	591	24 months	WBRT, SRS, Surgery	Age, KPS score, multimodal treatment
Nasioudis *et al.*, 2020 [19]	144	NA	WBRT, SRS, Chemotherapy	SRS
Current study	56	34 months	WBRT, SRS, Combined	Age, Tumor histology

Abbreviations: WBRT, Whole brain radiotherapy; SRS, sterotactic radiosurgery; ECOG, Eastern Cooperative Oncology Group; TFI, Treatment free interval; KPS, Karnofsky performance score; N/A, not available.

5. Conclusions

Brain metastasis in ovarian cancer is a rare clinical entity and standard treatment regimens are generally palliative. SRS and WBRT are the most used modalities and the combined approach seems effective. Before deciding on the treatment, patient characteristics, comorbidities, the number of locations of metastatic lesions, the adverse neurocognitive effects of radiation therapy, and life expectancy should be considered cautiously, and a patient-tailored approach should be embraced. Given that patient age is a significant prognostic factor, younger patients may gain the most benefit from treatment. Prospectively designed studies with an extended number of patients are needed and may contribute to our knowledge.

Author contributions

HCO, OCG and SY Sim designed and performed the research study and wrote the manuscript. HC, GDD, SY Sim, GE, SY Sar, MG, FY contribute to data collection and data analysis. All authors contribute equally to research and editorial changes. All authors read and approve the final version of the manuscript.

Ethics approval and consent to participate

All participants signed the informed consent. The study was conducted in accordance with Declaration of Helsinki. This study was approved by Baskent University Institutional Review Board (Project no: KA 21/345).

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Conflict of interest

The authors declare no conflict of interest. HCO is the Guest Editor of this journal, given his role as Guest Editor, HCO had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

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