e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(12); 1388-1393
Original Research Article

Assessment of Prognostic Variables and Treatment for Brain Metastases from Ovarian Cancer

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Received: 19-09-2022 / Revised: 13-10-2022 / Accepted: 28-11-2022
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Conflict of interest: Nil.

Abstract

Aims and Objectives: To examine a group of individuals at a single facility who have ovarian cancer brain metastases. to explain treatment options, their results, and to identify prognostic variables.

Methods: 25 patients with ovarian cancer brain metastases received treatment at Patna Medical College and Hospital between January 2015 and December 2021. The information on the therapy modalities utilised and their results, as well as the demographic, clinical, and imaging data, were all gathered retrospectively from the medical records.

Results: The average patient was 62.7 years old when a brain metastasis was diagnosed. The median time between the primary cancer diagnosis and the brain metastasis was 42.3 months. Seizures, headaches, and neurologic impairments were the most prevalent signs and symptoms. In 20% of the patients, the brain was the only location of metastases. In half of the patients with systemic disease, active ovarian cancer was found at the time of brain metastasis diagnosis. In 25% of the patients, there were many brain metastases. 11 patients were treated with surgical and radiation treatment procedures in a variety of sequences, including surgery, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgery, WBRT, and adjuvant SRS. Five patients underwent surgery alone and nine patients were treated with radiation alone (WBRT, SRS, or both). Univariate analysis for predictors of survival demonstrated that age above 62.7 years at the time of central nervous system involvement was a significant risk factor and leptomeningeal disease was a poor prognostic factor in reference to supra-tentorial lesions. Multivariate analysis for predictors of survival, however, showed that multiple brain lesions (>4) were a poor prognostic factor, and multivariate analysis of the time to progression revealed that combined treatments of surgery and radiation resulted in longer median periods of progression-free survival than each modality alone.

Conclusion: We come to the conclusion that the number of brain metastases and the kind of treatment were the only important indicators of survival or progression-free survival in our group.

Keywords: Brain Metastases, Outcome, Ovarian Cancer.

Introduction:

According to the American Cancer Society's 2017 report, 3% of malignancies in women are ovarian cancer, with a 1.3% lifetime risk. Serous adenocarcinoma, the most common subtype, accounting for 90% of malignant ovarian tumours and is the main diagnosis in 85% of cases. [1] A recent series of studies showed a rate as low as 0.3%[14] of brain metastases from ovarian cancer, however a rate of 6% has also been observed. [2,3] Despite the scarcity of the disease, it has long been postulated that the incidence of central nervous system (CNS) metastatic involvement in ovarian cancer is increasing, probably due to improvements in the primary therapeutic options and the consequent prolongation of survival.[4,5] In several recent studies, the median duration of survival following the diagnosis of CNS involvement ranged from 1–18 months.[5-9]

There are currently known statistically significant risk factors for patients with ovarian brain metastases, including distant spread at the time of the diagnosis of CNS involvement,[4] the presence of multiple brain lesions,[7–10] and the shortened time between the diagnosis of the primary disease and the development of CNS metastasis. [9,11] A well-controlled initial illness at the time of cerebral involvement,[8] a low tumour grade,[5] platinum-sensitive tumour cells,[9] and the patient's excellent performance level are other positive prognostic variables that have been identified. [7]

Currently, in addition to systemic chemotherapy and supportive care, two main therapeutic arms are being used to treat brain metastasis: radiation therapy [e.g. whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and gamma-knife radiosurgery] and surgical resection; either in combined regimens or separately. Although the treatment choice is influenced by multiple factors and should be tailored individually, the superiority of combined therapy (surgery and radiation) has been established in several series of patients.[4,5] In the absence of Class A guidelines and a sound treatment algorithm, the choice between the different treatments remains subject to the clinician’s preference.

In this study, we describe a single institute's experience treating a group of patients who had brain metastases from ovarian cancer. Based on various treatment modalities, we assessed predictive markers for survival and progression-free survival (PFS).

Methods

The institutional database of the Patna Medical College and Hospital was searched for all patients diagnosed with "ovarian cancer" and "metastases" after receiving consent from the ethics committee (approval number. 328-13 SMC). Several hundred records were used to find patients who had CNS metastases. The study comprised 25 women of all ages who were first diagnosed with ovarian cancer between 2015 and 2021, were later found to have CNS metastatic involvement, and were being treated at Patna Medical College and Hospital. The medical records of these patients were reviewed. We collected data regarding patient demographics and clinical characteristics, including patient age, surgical stage, and histologic grade of the ovarian tumor; treatment, modalities used for primary cancer, and the status of the systemic disease at the time brain metastasis was diagnosed.

The International Federation of Gynecology and Obstetrics (FIGO) staging score at the time of initial diagnosis was condensed in our analysis to the presence or absence of distal organ metastases, and the main tumour cell type was classified as "serous" or "non-serious." Both a PFS analysis and a survival analysis were carried out. The time between the discovery of an ovarian cancer brain metastasis and the onset of progressive disease is referred to as the PFS analysis.

Statistical Analysis

Through histogram analysis, continuous variables were checked for a normal distribution and given as the median and interquartile range (IQR) or range. A frequency and percentage are used to represent categorical variables. To compare various treatment modalities, the Chi-square test, Fisher's exact test, Kruskal Wallis test, and Mann Whitney test were employed. The Kaplan Meier estimator was used to characterise the survival analysis in respect to the various treatment methods, and a log-rank test was used to assess it. To assess the relationship between each predictor and mortality, univariate Cox regression was performed. Multivariate Cox regression was applied to evaluate the association between mortality and variables with $P < 0.2$ on univariate analysis. When evaluating the modality of treatment, age at the time of primary CNS involvement was adjusted. A P value less than 0.05 was considered statistically significant. All statistical analyses were two-sided. SPSS software (version 22) was used for all statistical analyses.

Results

The study's inclusion criteria were met by 25 patients. The median age at ovarian cancer diagnosis was 58 years old (IQR 53.1–64.8). At the time of the initial CNS involvement diagnosis, the median age was 62.7 years (IQR 54.7–68.8). The median amount of time between the diagnosis of primary ovarian cancer and the presence of brain metastases was 42.3 months (IQR 25–49.7) Almost all of the patients (24/25) had chemotherapy for the main illness. Seven patients (28%) had four or more lesions in their brains, compared to 18 patients (72%) who only had one. By the time of the analysis, 22 (88%) of the 25 patients had passed away and 24 (98%) had displayed advancement. Ten patients received consequent therapeutic regimens, 14 did not, and one patient was progression-free. The median PFS was 22.4 months (IQR 3.7–28.53). Additional characteristics of the study population are shown in Table 1, which provides the data in relation to the treatment modalities.

According to the distribution of treatment methods, 44% of patients had radiation treatment alone, 20% underwent surgery alone, and 36% received both surgery and radiation. 54.5% of the patients who received only radiation therapy received WBRT, 36.4% had only SRS, and 9.1% received treatment with both modalities. Of the patient group that received both surgical and radiation treatment, 44.4% received surgical treatment together with complimentary WBRT, 22.2% received surgical treatment along with WBRT and SRS (both within 6 months), and 33.3% received surgical treatment along with SRS.

Table 1: Patient characteristics according to treatment modalities

Variable	Study Population	Treatment Modality			*P*
		Surgery	Surgery + Radiation	Radiation therapy	
Serous primary cell type	11 (73.3)	3 (100)	3 (60)	5 (71.4)	0.765
Distal metastasis at diagnosis of Ovarian Ca	12 (52.2)	2 (40)	2 (28.5)	7 (63.3)	0.425
Chemotherapy to primary disease	24 (100)	6 (100)	7 (100)	11 (100)	-
Age at Dx of first CNS involvement (years), median (IQR)	62.7 (54.7-68.8)	69.4 (60.8-77.3)	58.5 (55-64.4)	61.7 (52.8-70.7)	0.097
Time interval from primary ovarian cancer dx to brain metastases dx (months)	42.3 (25-49.7)	40.6 (28.54-51.7)	38.2 (20.8-60.7)	46 (23-49.3	0.923

KPS >70	24 (96)	6 (100)	7 (100)	11 (91.7)	>0.99
Evidence of extra cranial metastases	16 (80)	4 (80)	4 (80)	8 (80)	>0.99
Active Ovarian Cancer at Dx of brain metastasis	9 (53)	2 (66)	5 (83.3)	2 (25)	0.111
Motor deficit at Dx of brain metastasis	8 (32)	2 (33.3)	2 (28.6)	4 (33.3)	>0.99
Dysphasia at Dx of brain metastasis	8 (32)	2 (33.3)	4 (57.1)	2 (16.7)	0.21
Seizure at Dx of brain metastasis	3 (12)	1 (16.7)	0	2 (16.7)	0.574
Headache/vomiting/nausea at Dx of brain metastasis	13 (52)	4 (66.7)	4 (57.1)	5 (41.7)	0.672
Gait disturbance/Ataxia at Dx of brain metastasis	8 (53.3)	2 (50)	4 (80)	2 (33.3)	0.365
Number of brain lesions					
3 lesions (or less)	18 (72)	6 (100)	7 (100)	5 (41.7)	0.008
4 lesions (or more)	7 (28)	0	0	7 (58.3)	
Site of brain metastasis					
Infra-tentorial	9 (36)	2 (33.3)	3 (43)	4 (33.3)	0.415
Supra-tentorial	11 (44)	4 (66.7)	4 (57)	3 (25)	
Both (supra- and infra-tentorial)	3 (12)	0	0	3 (25)	
Leptomeningeal disease	2 (8)	0	0	2 (16.7)	
Size of lesion's maximal diameter (mm)	29.8 (19-40)	37.5 (27-51)	33 (23-40)	23 (15.2-29.2)	0.031

Headache, nausea, and/or vomiting are the symptoms that present clinically [P = 0.027, HR 2.67 (1.12-6.36)]. Age above 62.7 years at the time a CNS involvement diagnosis was made (P = 0.02, HR 1.064 [CI 1.01-1.12]). In the univariate analysis of survival (P = 0.015, HR 9.08 [CI 1.53-53.76]) and PFS (P = 0.023, HR 7.456 [CI 1.31-42.22]), leptomeningeal disease was associated with supra-tentorial lesions.

Combined treatment with surgery and radiation resulted in longer median periods of progression-free survival than each modality alone, whereas surgery as mono-therapy was a poor prognostic factor (*P* = 0.029, HR 6.154 [CI 1.2–31.5]). The following variables did not have a statistically significant influence on survival and PFS in our analyses: extracranial metastases, ovarian carcinoma that was active at the time of diagnosis of brain metastatic involvement, primary cell type, distal metastases at the time of diagnosis of ovarian carcinoma, time interval between primary ovarian cancer diagnosis and brain metastatic involvement diagnosis, motor deficit at presentation, dysphasia at presentation, seizure at presentation, gait disturbance/ataxia at presentation, and diameter of the largest metastasis.

Discussion

We describe a retrospective analysis with the goal of determining the predictive markers for survival and PFS following the identification and management of CNS metastases from ovarian cancer. The study was based on a group of 25 patients who were treated and tracked at a single institute between the years 2015 and 2021 after receiving a diagnosis. The median age of diagnosis for CNS metastases in our cohort of patients was 62.7 years, which is older

than the age suggested by the literature (54–56.8 years). [8,10,11] Our findings show that a predictive factor for poor survival is age older than 62.7 years [P = 0.02, HR 1.064 (1.01-1.12)]. The increased median age at diagnosis of CNS metastases is probably due to improvements in the primary therapeutic options. It is possible, however, that a delayed diagnosis of brain involvement in some of the cohort accounts for its appearance as a prognostic factor because the disease would be more advanced by the time of detection in that group of patients.

Patients with metastatic ovarian cancer who have distant metastases to the liver, lung, brain, or bone have lower overall survival rates. [12] The presence of extracranial metastases and active systemic disease at the time of the diagnosis of brain metastatic involvement, however, were not predictive in our study. The modest number of patients in this subgroup in our sample who had active disease may help to explain this.

High ICP was not an independent bad prognostic factor in our series, but clinical signs and symptoms suggesting increased ICP, such as headache, nausea, or vomiting, did signal poor prognosis in our study's univariate analysis. It is relatively unusual for patients to arrive with an increased ICP; in some series, this prevalence might reach 50%. [6]

Increased ICP is not as an independent poor prognostic factor in the literature, but in a published review of 13 studies, clinical indicators for increased ICP were correlated with metastatic involvement of the posterior fossa and with multiple brain lesions.[13] These factors are associated with poor prognosis in numerous studies,[7-10] and in our series as well—both with decreased PFS and increased mortality, in the multivariate analysis. An infra-tentorial site of the lesion, which may cause increased ICP, was not independently associated with poor prognosis in our results, which may be related to the small number of patients. Unsurprisingly, the leptomeningeal spread was significantly associated with poor prognosis ($P = 0.015$, HR 9.08 [CI 1.53–53.76]).

The multimodal therapeutic approach has repeatedly demonstrated superiority over mono- therapeutic approaches.[4,11,14] Patients who are treated non-operatively seem to benefit from multimodal regimens as well. Celejewska *et al*.[9] showed that WBRT followed by SRS significantly improves prognosis in comparison with single-type radiation therapy. According to Lee *et al*.,[11] who compared a group of patients treated with WBRT to a group that was treated with gamma-knife radiosurgery, the gamma-knife group enjoyed a longer median survival. In that group, a trend was found toward the superiority of any combined regimen over any mono-therapeutic approach in terms of survival.

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