Prognostic Factors Affecting Survival in Patients with Brain Metastases from Gynecologic Cancer

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ABSTRACT

Brain metastasis (BM) from gynecologic carcinomas (GCs) is a rare but increasing phenomenon, with the rising life expectancy of patients with GCs. This study aimed to review a series of patients with BM from GCs and describe their clinical features, treatment outcomes, and prognostic factors. In this retrospective cohort study, 49 GC patients with BM were examined, and factors associated with survival were analyzed. The primary carcinomas were ovarian cancer in 27 (55.1%) patients, uterine cancer in 14 (28.6%), and cervical cancer in 8 (16.3%). For the total cohort, the median time from the initial diagnosis to BM was 24.0 (1.0-148.0) months; for ovarian, uterine, and cervical cancer, it was 32.0 (1.0-148.0), 13.0 (1.0-74.0), and 6.0 (2.0-44.0) months, p= 0.001; for stage 1-2, stage 3 and stage 4 tumors, it was 36.0 (13.0-94.0), 24.0 (1.0-148.0), and 13 (1.0-26.0) months, respectively, p= 0.006. The median survival from BM was 7.0 (95% CI: 3.68-10.32) months in the entire cohort. Three or more BMs (HR= 5.79, 95% CI:1.27-26.36; p=0.023), extracranial disease progression (HR= 4.38, 95% CI: 1.22-15.72; p= 0.024), and whole-brain radiotherapy (WBRT) (HR= 5.80, 95% CI: 1.88-17.92; p= 0.002) were associated with worse survival. Three or more BMs, extracranial disease progression, and WBRT compared to stereotactic radiotherapy (SRT) adversely affect the prognosis of GC patients with BMs. Additionally, GC type and disease stage at diagnosis affect the time to BMs.

Keywords: Gynecological cancer, Brain metastasis, Uterine, Ovarian, Cervical cancer

INTRODUCTION

Brain metastasis (BM) from GCs is very rare[1-3], with a prevalence ranging from 0.3-11%.[4-9] Because of its rarity, very limited information about its clinical characteristics, optimal management, and prognosis is known. However, although rare, the incidence of BM is increasing[10], likely associated with improved survival with early diagnosis enabled by better imaging techniques and modern therapeutic modalities.[11,12]

Peritoneal and lymphatic spread are the most common ways for gynecologic tumors to disseminate, whereas hematogenous spread is rarely observed.[13] BM is presumed to occur through hematogenous seeding or a direct invasion from some previous bone metastasis.[8] The development of metastatic foci is thought to be related to tumor cell behavior, host immune responses, and the number of tumor cells that embolize.[14] Additionally, chemotherapeutic agents cross the blood-brain barrier poorly. Therefore, the brain may be a pharmacological sanctuary from systemic treatment.[13,15]

The presence of metastatic brain lesions from GCs indicates a poor survival rate lasting only a few months.[9,16] However, there is hope in the form of modern surgical techniques, radiation therapy, and new treatment modalities, which have the potential to significantly improve outcomes and even lead to long-term survival in some patients.[9,17]

Additionally, if the brain is the first and only site of recurrent disease or a solitary lesion in the brain and controlled extracranial disease, longer survival can be achieved.[4,6,9,18-21]

Clinicopathological features that may predict patient prognosis or data regarding the optimal treatment strategy for BM in GCs are uncertain. Therefore, there is an unmet need for understanding prognostic indicators and performing extensive treatment risk/benefit analyses.[9] Any data regarding this rare phenomenon will improve our knowledge. This study retrospectively collected data on gynecologic cancer patients with BM from a single institute over 14 years and aimed to analyse the clinicopathological features, prognostic factors, and treatment strategies that will improve the overall survival of patients with BMs from GCs.

MATERIALS AND METHODS

Study Design and Patients

The present study was a retrospective cohort analysis of 49 patients with BM from GCs from a single institution between July 2009 and May 2023. Among the 1227 ovarian cancer (OC) patients, 608 uterine cancer (UC) patients, and 500 cervical cancer (CC) patients, patients diagnosed with brain metastases were screened during the 14-year study period. The medical records were systematically reviewed regarding demographic and clinical characteristics, including age, Eastern Cooperative Oncology Group performance score (ECOG PS) at initial diagnosis of BM, cancer type (ovarian, uterine, or cervical), histology (adenocarcinoma vs. other carcinomas), tumor stage at first diagnosis, treatment regimens for primary tumor (surgery, chemotherapy, radiotherapy), CT lines before the diagnosis of BM, time from initial GC diagnosis to BM, number of brain lesions, the largest diameter of brain tumor, extracerebral disease progression at the time of BM diagnosis, RT type for BM (whole-brain radiotherapy (WBRT) vs. stereotactic radiotherapy (SRT)), second RT for BM, surgery for BM, and CT after BM. The date of diagnosis of the primary tumor, the date of BM diagnosis, and the date of death or last follow-up visit were also recorded.

Statistical Analysis

The medians and ranges were reported for continuous variables. Categorical variables were summarized as percentages. Adjusted chi-square tests and one-way ANOVA were used for statistical analysis of the comparisons of patient characteristics among the three different types of cancer. Overall survival (OS) was calculated from the date of diagnosis of BM to the date of death for any reason or the last day of follow-up according to Kaplan-Meier estimates. Prognostic factors were analysed using the log-rank test for univariate analysis, and factors reaching a level of significance in univariate analysis were additionally evaluated for independence with a Cox proportional hazards model. The results were considered statistically significant when the p-value was less than 0.05. Analyses were performed using SPSS Version 26.

Ethical Approval: Our study was approved by the Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Ethics Committee (ethics committee number: 2023-10/73). According to national legislation and institutional standards, participation in this study does not require written informed consent.

RESULTS

Patient Characteristics

Forty-nine patients were enrolled, and their characteristics are listed in Table 1. The median age at diagnosis of BM was 59 (36-80) years. The primary origin was OC in 27 (55.1%) patients, UC in 14 (28.6%), and CC in 8 (16.3%). The majority of the patients had serous adenocarcinoma (53.0%) or endometrioid carcinoma (22.4%). At the time of first diagnosis, 25 (51.0%) patients presented with stage III and 9 (18.3%) patients presented with stage IV disease.

Forty-five (91.8%) patients had their primary tumor surgically removed. Before the diagnosis of BM, 46 (93.8%) patients received CT, with a median number of CT lines being 1 (0-6). A total of 28 (57.1%) patients were treated with 1-line CT, and 8 (16.3%) patients with 2-line CT. Eighteen (36.7%) patients received RT for the primary tumor before BM.

Table 1. Patient demographic and clinical characteristics

Characteristic	Freq.(%)		
Age at BM diagnosis		*Primary operated*	
< 65 years	33 (67.3)	Yes	45 (91.8)
≥ 65 years	16 (32.6)	No	4 (8.1)
Primary Cancer Type		*CT before BM*	
Cervical	8 (16.3)	Yes	46 (93.8)
Ovarian	27 (55.1)	No	3 (6.1)
Uterine	14 (28.6)		
Tumor Histology		*CT lines before BM*	
Serous carcinoma	26 (53.1)	0-2	40 (81.6)
Endometrioid carcinoma	11 (22.4)	≥ 3	8 (16.3)
Others	12 (24.5)	Unknown	1 (2.0)
Tumor stage at diagnosis		*RT for primary tumor*	
I-II	11 (22.4)	Yes	18 (36.7)
III	25 (51.0)	No	31 (63.2)
IV	9 (18.3)		
Unknown	4 (%8.1)		
ECOG at the time of BM		*The interval from the initial diagnosis to BM*	
0-1	25 (51.0)	< 1 year	13 (26.6)
2-3	13 (26.6)	1-3	20 (40.8)
Unknown	11 (22.4)	3-10	14 (28.5)
		10 years ≤	2 (4.1)

BM= brain metastasis; RT= radiotherapy; CT= chemotherapy; ECOG= Eastern Cooperative Oncology Group

The median time from the initial diagnosis to BM was 24.0 (1.0-148.0) months. BM was diagnosed in 13 (26.5%) patients within one year of the initial diagnosis, 12 (24.4%) patients between 1 and 2 years from the initial diagnosis, and 2 (4.0%) patients ten years after the initial diagnosis. The ECOG PS scores were 1 for 25 (51.0%) patients and 2 for 10 (20.4%) patients at the time of BM diagnosis.

Clinical Characteristics and Treatment Modalities for Brain Metastasis

The brain metastasis characteristics of the 49 patients are listed in Table 2. The median number of BMs was 4 (1-7). Nine (18.3%) patients had a single BM, 5 (10.2%) patients had two BMs, and 32 (65.3%) patients had ≥3 BMs. The median size of the largest BMs was 21 (7-58) mm. Twenty-four (48.9%) patients had cerebral area metastases, 5 (10.2%) had cerebellar area metastases, 15 (30.6%) had cerebral and cerebellar area metastases, and 6 (12.2%) had brain stem metastases. Thirty-three (67.3%) patients experienced extracranial disease progression, and 11 (22.4%) did not at the time of BM diagnosis.

Thirty-one (63.2%) patients received WBRT, and 17 (34.6%) patients received SRT for BM. WBRT was administered in fractions of 9 for total doses ranging from 20 to 50 Gy, with a median of 28 Gy. SRS was administered in fractions of 3 for total doses ranging from 18 to 66 Gy, with a median of 30 Gy. In addition, 12 (24.4%) patients received second-line RT. Twelve (24.4%) patients underwent surgical excision of their BM, but 36 (73.4%) patients did not. Fifteen (30.5%) patients received CT after BM, 22 (44.8%) patients did not receive CT due to poor performance status, and CT information after BM was unavailable for 12 patients. Twenty (40.8%) patients received single-agent therapy (RT) for brain metastasis, and 17 patients received combination therapy (RT+surgery vs RT+CT vs RT+CT+surgery). Twelve (24.4%) patients had missing data for any treatment regimens.

The median time from initial diagnosis to BM was 24.0± 2.99 (95% CI: 18.12-29.98) months in

Table 2. Characteristics and treatment modalities for brain metastases

Characteristic	Freq. (%)		
Number of BMs		*Second-line RT for BM*	
1	9 (18.3)	Yes	12 (24.4)
2	5 (10.2)	No	37 (75.5)
≥ 3	32 (65.3)		
Unknown	3 (6.1)		
Site of BMs		*Surgery for BM*	
Cerebral	24 (48.9)	Yes	12 (24.4)
Cerebral and cerebellar	15 (30.6)	No	36 (73.4)
Cerebellar	5 (10.2)	Unknown	1 (2.0)
Brain stem	6 (12.2)		
Extra-BM disease progression			
No	11 (22.4)	*CT after BM*	
Yes	33 (67.3)	Yes	15 (30.5)
Unknown	5 (10.2)	No	22 (44.8)
		Unknown	12 (24.4)
First-line RT type for BM		*Treatment modality for BM*	
WBRT	31 (63.2)		
SRT	17 (34.6)		
No	1 (2.0)		
First-line RT doses for BM (median Gy [range])			
WBRT	28 (20-50)	RT	20 (40.8)
SRS	30 (18-66)	RT+CT	9 (18.3)
		RT+CT+surgery	6 (12.2)
		RT+surgery	2 (4.0)
		Missing data	12 (24.4)

WBRT= whole-brain radiotherapy, SRT= stereotaxic radiotherapy, BM= brain metastasis, CT= chemotherapy, RT=radiotherapy

the entire cohort and was shortest in the CC cohort [6.0± 2.12 (95% Cl: 1.84-10.15) months], followed by the UC cohort [13.0± 3.74 (95% CI: 5.66-20.33) months] and, most prolonged in the OC cohort [32.0± 4.51 (95% CI: 23.14-40.85) months] (p= 0.001). For patients with stage 4, stage 3, or stage 1-2 disease at initial diagnosis, the median times from the initial diagnosis to BM were 13.0± 8.94 (95% CI: 0.00-30.53), 24.0± 4.99 (95% CI: 14.20-33.79) and 36.0± 8.25 (95% CI: 19.81-52.18) months, respectively (p= 0.006). According to multivariate analysis, disease stage at diagnosis and tumor type continued to significantly affect the time to BMs.

A Clinical Comparison of Brain Metastasis by Primary Cancer

A clinical comparison of 49 patients with OC, UC, and CC is listed in Table 3. The median age at BM diagnosis was 61.5 (47-80) years in the OC cohort, 57.3 (36-74) in the UC cohort, and 54.6 (45-67) in the CC cohort (p=0.126). Stage 3 disease was the most common tumor stage at initial diagnosis across all tumor types (p=0.183). The most common tumor histology in OC patients was serous carcinoma (88.8%), and in UC patients was endometrioid carcinoma (71.4%), whereas the most common histology in CC patients was squamous carcinoma (37.5%) (p< 0.001).

The three groups did not differ regarding patient performance status at the time of BMs (p= 0.952). The ECOG PS 1 was the most common for all the types at the time of BM. Most of the patients underwent surgery on the first tumor side in all groups. Notably, the percentage of patients who underwent surgery was highest for UC and OC patients and lowest for CC patients (100.0%, 100%, and 50.0% of the patients, respectively) (p< 0.001). RT for the primary tumor was given to 11 (78.5%) patients with UC, 6 (75.0%) with CC, and 1 (3.7%) with OC (p< 0.001). CT before BM was given to 27

Table 3. Clinical comparison of brain metastatic gynecological cancer patients

	OC	UC	CC	p value
Total no. patients, n (%)	27 (55.1)	14 (28.6)	8 (16.3)	
Age(yr)at BM diagnosis median ± SDc(range)	61.5± 8.2 (47-80)	57.3±1 1.1 (36-74)	54.6± 8.5 (45-67)	0.126
Stage				0.183
I-II	4 (14.8)	5 (35.6)	2 (25.0)	
III	16 (59.2)	6 (42.8)	3 (37.5)	
IV	4 (14.8)	3 (21.4)	2 (25.0)	
Unknown	3 (11.1)	0 (0.0)	1 (12.5)	
Tumor histology				<0.001
Serous carcinoma	24 (88.9)	2 (14.3)	0 (0.0)	
Endometrioid carcinoma	3 (11.1)	10 (71.4)	0 (0.0)	
Others		2 (14.3)	8 (100.0)	
ECOG at the time of BM				0.952
0-1	14 (51.8)	7 (50.0)	4 (50.0)	
2-3	8 (29.6)	3 (21.4)	2 (25.0)	
Unknown	5 (18.5)	4 (28.5)	2 (25.0)	
Primary tumor operated				<0.001
Yes	27 (100)	14 (100.0)	4 (50.0)	
No	0 (0.0)	0 (0.0)	4 (50.0)	
RT for primary tumor				<0.001
Yes	1 (3.7)	11 (78.5)	6 (75.0)	
No	26 (96.2)	3 (21.4)	2 (25.0)	
CT before BM				0.034
Yes	27 (100.0)	13 (92.8)	6 (75.0)	
No	0 (0.0)	1 (7.1)	2 (25.0)	
CT lines before BM	1.5 (1-6)	1.0 (0.0-4.0)	1.0 (0.0-3.0)	0.019
Interval from initial diagnosis to BM, median(range), mo	32.0 (1.0-148.0)	13.0 (1.0-74.0)	6.0 (2.0-44.0)	0.001
< 24months	9 (33.3)	9 (64.2)	6 (75.0)	
≥ 24months	18 (66.6)	5 (35.7)	2 (25.0)	
Extracranial disease progression			0.970	
Yes	19 (70.3)	9 (64.2)	5 (62.5)	
No	6 (22.2)	3 (21.4)	2 (25.0)	
Unknown	2 (7.4)	2 (14.2)	1 (12.5)	
Number of BM				0.046
1	6 (22.2)	3 (21.4)	0 (0.0)	
2	1 (3.7)	1 (7.1)	3 (37.5)	
≥ 3	18 (66.6)	10 (71.4)	4 (50.0)	
Unknown	2 (7.4)	0 (0.0)	1 (12.5)	
Site of brain lesions				0.343
Cerebral	14 (51.8)	6 (42.8)	4 (50.0)	
Cerebral+Cerebellar	6 (22.2)	7 (50.0)	2 (25.0)	
Cerebellar	4 (14.8)	0 (0.0)	1 (12.5)	
Brain stem	6 (22.2)	0 (0.0)	0 (0.0)	
RT for BM				
Yes	26 (96.2)	14 (100.0)	8 (100.0)	
No	1 (3.7)	0 (0.0)	0 (0.0)	
Second RT for BM				0.181
Yes	9 (18.4)	1 (7.1)	2 (25.0)	
No	18 (36.7)	13 (92.8)	6 (75.0)	
Surgery for BM				0.181
Yes	4 (14.8)	5 (35.7)	3 (37.5)	
No	23 (85.1)	8 (57.1)	5 (62.5)	
Unknown	0 (0.0)	1 (7.1)	0 (0.0)	
CT after BM				0.538
Yes	10 (37.0)	3 (21.4)	2 (25.0)	
No	11 (40.7)	8 (57.1)	3 (37.5)	
Unknown	6 (22.2)	3 (21.4)	3 (37.5)	
Tumor largest diameter (mean), ± SD			0.053	
< 21 mm	12 (44.4)	8 (57.1)	0 (0.0)	
≥ 21 mm	10 (37.0)	5 (35.7)	5 (62.5)	
Unknown	5 (18.5)	1 (7.1)	3 (37.5)	

Abbreviations: Eastern Cooperative Oncology Group (ECOG), BM (brain metastasis), CT (chemotherapy), RT (radiotherapy), OC (ovarian cancer), EC (endometrial cancer), CC (cervical cancer), WBRT (whole-brain radiotherapy), SRT (stereotactic radiotherapy), PFS (progression-free survival), and OS (overall survival). Bold p values indicate statistically significant results.

(100.0%) patients with OC, 13 (92.8%) with UC, and 6 (75.0%) with CC (p= 0.034). The median number of CT lines before BM was 1.5 (1-6) in the OC cohort, 1.0 (0.0-4.0) in the UC cohort, and 1.0 (0.0-3.0) in the CC cohort (p= 0.019).

The median time from initial diagnosis to BM differed among the three primary tumor types since BMs from the OC were diagnosed at a median of 32.0 (1.0-148.0) months, BMs from the UC were diagnosed at a median of 13.0 (1.0-74.0) months, and those from the CC were diagnosed at 6.0 (2.0-44.0) months (p= 0.001). Most patients in all subtypes had extracranial disease progression at the time of BM (70.3%, 64.2%, and 62.5% in the OC, UC, and CC groups, respectively) (p= 0.970). Most patients in all three subtypes had three or more BMs (66.6%, 71.4%, and 50.0% in the OC, UC, and CC groups, respectively). A total of 22.2% of the OCs, 21.4% of the UCs, and 0.0% of the CCs had solitary BMs (p= 0.046).

All patients except one received first-line RT for BMs. A total of 55.5% with OC, 78.5% of patients with UC, and 62.5% with CC were given WBRT (p= 0.461). A total of 14.8% of the patients with OC, 35.7% of the patients with UC, and 37.5% of the patients with CC underwent neurosurgery for BM (p= 0.181). CT after BM was given to 37.0% of patients with OC, 21.4% with UC, and 25.0% with CC (p= 0.538).

There was no significant difference between the groups regarding the largest diameter of the BMs (p= 0.053). Overall survival from the first diagnosis was 60.0± 6.03 (48.18-71.81) months in the OC cohort, 36.0± 14.18 (8.19-63.80) months in the UC cohort, and 18± 10.60 (0.00-38.78) months in the CC cohort (p< 0.001).

Prognostic Factor Analysis for Survival after Brain Metastasis

The median follow-up time after BM was 7.5 months (1-105) in the entire cohort. At the end of the follow-up, 43 (87.8%) patients had died, while 6 (12.2%) patients were still alive. The median survival after BM diagnosis was 7.0± 1.69 (95% CI: 3.68-10.32) months. The median OS after BM was 8.0± 3.11 (1.90-14.09) months in the OC cohort, 3.0± 1.34 (0.35-5.64) months in the UC cohort, and 6.0± 2.12 (1.84-10.15) months in the CC cohort (p= 0.304).

Prognostic factors affecting survival were evaluated via univariate analyses; the median OS after BM was 2 months in patients with an ECOG PS score of 2-3 and 13 months in patients with an ECOG PS score of 1 (p= 0.002). The median survival after BM was 2 months in patients with ≥ 3 CT lines and 8 months in patients with 1-2 CT lines before BMs (p= 0.019). Survival was also greater in patients without extracranial disease progression than in those with extracranial disease progression (23 vs. 3 months, respectively) (p= 0.037). Sixty-six percent of single-BM patients and 60% of two-BM patients underwent surgical resection, whereas only 9% of those with multiple lesions did. The median OS was 18 and 3 months in patients with 1-2 and ≥ 3 BMs, respectively (p= 0.002). SRT was associated with a significantly better life expectancy than WBRT (23 vs. 3 months, respectively) (p< 0.001). The absence of CT after BM was also found to be quite significant in terms of poor prognosis (median OS; 26 vs. 2 months in the presence or absence of CT) (p< 0.001). The median OS was 23 and 2 months in patients who underwent combined therapy (RT+CT vs. RT+CT+surgery vs. RT+surgery) and single-agent treatment (RT) for BMs, respectively (p< 0.001). The median survival times after BMs were 3 months and 9 months in patients with intervals from initial diagnosis of ≥ 24 months and < 24 months, respectively (p= 0.001).

A multivariate analysis was performed, incorporating the significant factors in the univariate analysis. The results revealed survival differences according to the number of BMs (p= 0.023), extracranial disease progression (p= 0.024), and RT type (WBRT vs SRT) (p= 0.002). The prognostic factors for OS are listed in Table 4.

DISCUSSION

BM is rare in GC patients, and the current understanding of its risk factors, prognosis, and optimal treatment methods is limited. In this study, we aimed to evaluate a number of patients with BM from GC. Our collaborative efforts, united by a shared purpose, are directed towards making a significant contribution to the literature, enhancing

Table 4. Multivariate Cox proportional hazards analysis for clinical variables of interest for the outcome of OS after BMs

	HR	Lower (95% CI)	Upper (95% CI)	p
ECOG at diagnosis of BM 2-3 / 0-1	1.17	0.35	3.92	0.790
CT lines before BM ≥ 3 / 1,2	1.28	0.40	4.09	0.673
Extracranial disease progression Yes / No	4.38	1.22	15.72	**0.024**
Number of BM ≥ 3 / 1-2	5.79	1.27	26.36	**0.023**
RT type for BM WBRT/ SRT	5.80	1.88	17.92	**0.002**
Surgery for BM No / Yes	2.60	0.57	11.80	0.213
The time from initial diagnosis to BM ≥ 24months/ < 24 months	1.302	0.520	3.26	0.573

OS= overall survival; CI= confidence interval; HR= hazard ratio; BM= brain metastasis; ECOG= Eastern Cooperative Oncology Group; RT= radiotherapy; CT= chemotherapy

our collective understanding of this complex topic. Our findings, revealed that BMs from GCs are indeed rare, with incidences of 2.3%, 2.2%, and 1.6% for UC, OC, and CC, respectively, are consistent with other studies' results.[1,9,16,22-25] As anticipated, our study's results indicated poor prognoses in patients with BM from GCs, with a median OS after BM diagnosis of 7 months in the entire cohort[16,24,26-28], 8 months in the OC cohort[18,24,29], 3 months in the UC cohort 24, 30, and 6 months in the CC cohort[15,21,31], consistent with other studies' results.

In the current study, we found that the median interval from the initial diagnosis to BM was shorter in CCs than in UCs or OCs; moreover, this interval was shorter in stage 4 tumors than in stage 1-3 tumors. These findings underscore the need for closer follow-up for patients at higher risk of developing BMs. Larger-scale studies are needed to validate this idea. In the literature, only a few studies have provided detailed information about the interval between primary tumor diagnosis and BM from GCs. Karpathiou et al. showed that BMs from UCs and OCs differed in the interval between primary cancer and BM diagnosis (27.8 and 53.5 months, respectively) 28. Takeshita et al. reported 22- and 28-month intervals for UC and OC, respectively.[32] Gill, D'Andrea, et al. reported 1.5-year and 2.3-year intervals for UC and OC, respectively[1] However, Zhang et al. did not observe differences in the intervals between UCs and OCs[33], and Kim et al. reported longer intervals for UCs than for OCs (27.8 and 21.6 months, respectively).[8]

Our study found that a longer interval from the primary diagnosis to the diagnosis of BM and a greater number of previous treatment lines before BM were associated with significantly shorter survival in univariate analysis, possibly related to the development of chemotherapy resistance or tumor aggressiveness. The median survival after BM decreased in patients who received at least three CT lines before BM. Moreover, median survival was significantly decreased in patients whose interval from initial diagnosis to BM was ≥24 months. In agreement with our findings, da Costa et al. showed that three or more previous treatment lines had a negative impact on OS.[29] The negative effect of longer time intervals from primary diagnosis on survival has also been addressed in a few previous studies.[13,29,34]

Our study, in line with several others, has shown that extracranial disease status at the diagnosis of BM in patients with GC may affect patient survival.[26,27,35,36] Our multivariate analysis has revealed that extracranial disease progression at the time of BM diagnosis is a powerful prognostic indicator for decreased survival.

Surgical resection is usually more amenable for solitary BMs than multiple BMs.[20,35,37] In the present study, 66% of the single-BM patients and 60% of the two-BM patients underwent surgical resection, whereas only 9% of those with multiple lesions did. Patients with multiple BMs appeared to have lower survival rates when the treatment modality and extent of extracranial disease were considered in multivariate analysis, consistent with previous studies' findings.[8-10,23,38-40] In contrast to our study, several studies have shown that patients with multiple and solitary BMs tended to have similar survival rates.[16,21,24,29,41]

Recent studies have described the successful treatment of solitary and multiple BMs from GCs via RT.[16,35,42] SRT was associated with significantly better life expectancy than WBRT, according to the multivariate analyses in our study, which was consistent with the findings of previous studies.[20,43,44] However, it is important to note that the use of SRT may introduce a selection bias due to its application in treating a lower volume of intracranial disease. This underscores the need for high-volume prospective studies to further explore this area. Our study found that the median survival of patients treated with radiation in conjunction with surgery was longer than that of patients receiving only radiation, a result that aligns with existing literature.[8,13,38] The combination of surgical resection and RT emerges as the optimal strategy for controlling BM from GCs, particularly for patients with solitary BM and controlled extracranial disease.[8,9,24, 27]

A better performance status at the initial diagnosis of BM, likely reflecting suitability for surgery and tolerance of CT, was a significant prognostic factor for OS, according to univariate analysis. This issue has also been mentioned in previous studies. Da Costa et al. showed that while all patients with an ECOG PS score of 2-3 died before the fifth month, 28% of those with an ECOG PS score of 0-1 were still alive in the 2nd year after receiving a BM diagnosis from OC 29. Rades et al. showed that while the OS rates at 3, 6, and 12 months with ECOG PS scores of 1-2 were 100%, 88%, and 48%, respectively, they were 62%, 15%, and 12%, respectively, in brain metastatic GC patients with ECOG PS scores of 3-4.[26] Sehouli et al. showed that in OC patients with a Karnofsky Performance Status (KPS) of 50% or less, 60%–80%, or 90%–100%, the 1-year OS rates were 0%, 10%, or 19%, respectively.[23] The 1-year OS was 0% in patients with a KPS below 70 and 25% in patients with a KPS of 70 or above with BM from GCs.[22] Kim et al. showed that a KPS of 70 or above was independently associated with a longer OS. The OS rate was 55% at the 20th month in patients with KPS of 70 or above and 10% in those with KPS below 70 among brain metastatic gynecologic cancer patients.[8] Karpathiou G. et al.[28] and Takeshita et al.[32] reported that among patients with brain metastatic gynecological cancer, those with an ECOG PS score of 0-1 had a statistically significant improvement in OS.

The absence of CT after BM was also found to be quite significant in terms of poor prognosis in univariate analyses. However, when the patients were examined in detail, it was observed that all patients who did not receive CT after BM were evaluated for the initiation of chemotherapy but were considered intolerant for chemotherapy due to poor performance. Therefore, whether or not to receive CT was not included in the multivariate analyses. Our study revealed that multimodal treatment is superior to single-agent treatment in terms of survival in BMs. The literature also reports that multimodal treatment is associated with longer survival.[8,9,38,44] Due to selection bias caused by the retrospective nature of the data, patients with outstanding performance status are more likely to undergo aggressive therapy and have better overall survival. This underscores the need for more extensive prospective randomized trials with specific treatment modalities for patients with BM of GC. Otherwise, the treatment choices for BM from GCs should be made individually, carefully considering the final purpose of treatment. It is important to note that patients with poor performance and widespread metastases may not benefit from definitive treatment, but there is hope in the form of symptomatic care that can be helpful and improve their quality of life.

Several factors need to be considered in determining the best individual treatment program for patients, including patient preference, social status, characteristics of BM, and life expectancy. Knowl-

edge of the prognostic factors of BMs from patients with GC can improve patient outcomes and the management of individual patients. Our study can contribute to patient management by expanding the literature on this subject.

To mention a few limitations of this study, our study was conducted at a single, academic, tertiary care center, and patients with BM from GCs, which are essentially very rare, may have been overrepresented at our institution. Although we assembled one of the largest cohorts thus far, we included only 49 patients, and our statistical analyses were limited in power. As in any retrospective study, selection bias was a concern. In conclusion, despite these limitations, this study provided essential data on BMs from GCs.

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