Original Article

Central nervous system metastasis in gynecologic cancers: Seeking the prognostic factors

Yagmur Minareci, Naziye Ak[1], Ozgur Aydın Tosun[2], Hamdullah Sozen[3], Pinar Mualla Saip[1], Samet Topuz[3], Mehmet Yavuz Salihoglu[3]

Department of Gynecologic Oncology, Eskisehir City Hospital, Eskisehir, [1]Department of Medical Oncology Istanbul University, Institute of Oncology, Istanbul University, Istanbul, [2]Department of Gynecology and Obstetrics, Division of Gynecologic Oncology Istanbul Medeniyet University, Goztepe Research and Training Hospital, Istanbul, [3]Department of Gynecology and Obstetrics, Division of Gynecologic Oncology, Faculty of Medicine, Istanbul University, Istanbul, Turkey

For correspondence: Dr. Yagmur Minareci, Eskisehir City Hospital, Department of Gynecologic Oncology, B Blok, 1. Kat. Jinekolojik Onkoloji Polikliniği, 71. Evler mah. 26080 Odunpazarı, Eskişehir, Turkey.
E-mail: dryagmurminareci@gmail.com

Submitted: 28-Feb-2022
Revised: 27-Jun-2022
Accepted: 27-Jun-2022
Published: 27-Apr-2023

Access this article online

Website: https://journals.lww.com/cancerjournal
DOI: 10.4103/jcrt.jcrt_499_22
Quick Response Code:

ABSTRACT

Objective: Central nervous system (CNS) metastasis originating from gynecological cancer is a very rare and late manifestation of the disease. Therefore, there is still limited data on prognostic factors for survival. The objective of the present study is to identify prognostic factors for survival in patients with CNS metastasis originating from gynecological cancer.

Study Design: The present retrospective study analyzed the patients with gynecological cancers who were treated due to CNS metastases between January 1999 and December 2019 at Istanbul University Hospital.

Results: Forty-seven patients with CNS metastasis of gynecological origin were included in the study. The median age at the time of CNS metastasis was 59 (range 34–93). The median time from initial cancer diagnosis to CNS metastasis was 24.9 (range: 0–108.2) months. Most patients had epithelial ovarian cancer (EOC) (76.6%), followed by endometrial cancer (EC) (14.8%), cervical cancer (CC) (4.3%), and vulvar cancer (VC) (4.3%). By multivariate analysis, the presence of extracranial metastasis (HR: 5.10; 95% CI: 1.71-15.18), Eastern Cooperative Oncology Group (ECOG) performance status ≥3 (HR: 2.92; 95% CI: 1.36-6.26), palliative care only for the treatment of CNS metastasis (HR: 1.47; 95% CI: 0.58-4.11), and treatment-free interval (TFI) <6 months (HR: 2.74; 95% CI: 1.23-6.08) were independent factors that associated with worse survival.

Conclusion: Patients with CNS metastasis who have favorable prognostic factors are considered to be appropriate candidates for aggressive and long-term treatment strategies. Extracranial metastasis, ECOG performance status, treatment history of CNS metastasis, and TFI were determined as independent prognostic factors that improved survival. TFI might be taken into account as a prognostic factor for patients with CNS metastasis in gynecological cancer.

KEY WORDS: Brain metastasis, central nervous system metastasis, gynecologic cancer, prognostic factors, TFI, treatment-free interval

INTRODUCTION

Central nervous system (CNS) metastasis originating from gynecological cancer is a very rare and late manifestation of the disease. CNS metastasis rates were about 40% for lung cancer, 15% for breast cancer, and 10% for melanoma, whereas only 1–2% of clinically diagnosed CNS metastasis are of gynecologic origin.[1-4] With the administration of modern chemotherapeutics, survival in gynecological cancers has increased in recent years, concordantly, the number of cases with CNS metastases has also increased. The incidences of CNS metastasis of ovarian, endometrial, and cervical cancer were reported to be 0.3–2.2%, 0.4–1.2%, and 0.3–0.9%, respectively.[5,6] Unfortunately, the prognosis for patients with CNS metastasis is extremely poor, median survival without intervention after the diagnosis is 1–2 months.[7] According to recent large studies, median survival with a variety of treatment modalities is 7–8 months.[8,9] On the other hand, selected patients who have been treated with accurate multimodal treatment might survive longer than 2 years.[10] Thus, effective and accurate treatment modalities may have a favorable impact on survival, and individualization of the treatment should be considered for each patient.

Given the rarity of CNS metastasis arising from gynecological cancers, there is still limited data on prognostic factors. During the past

Cite this article as: Minareci Y, Naziye Ak, Tosun OA, Sozen H, Saip PM, Topuz S, *et al*. Central nervous system metastasis in gynecologic cancers: Seeking the prognostic factors. J Can Res Ther 2023;19:S523-9.

two decades, several scoring algorithms have been developed to predict the prognosis after CNS involvement of metastatic cancers.[11-13] However, none of them have been validated in the cohort of gynecologic cancers. Several prognostic factors may affect survival including age, performance status, the number, location, volume of CNS lesions, presence of extracranial disease, definitive treatment approach, primary tumor origin, and state of control of the primary tumor.[14-16] Finally, treatment-free interval (TFI) is a novel and promising prognostic factor for patients with CNS metastasis of gynecologic origin. To date, TFI has only been evaluated in the study of Takeshita *et al*.[17] Defining the prognostic factors that affect survival may enable the physician to opt for a more appropriate and individualized treatment strategy.

In the present study, we aimed to identify prognostic factors for survival in patients with CNS metastasis originating from gynecological cancer.

MATERIAL AND METHOD

We retrospectively evaluated the patients treated for gynecological cancers at Istanbul University Hospital, Istanbul Faculty of Medicine, Division of Gynecologic Oncology and Institute of Oncology from January 1999 to December 2022. Gynecological cancers were divided into four groups according to their origin, including epithelial ovarian cancer (EOC), endometrial cancer (EC), cervical cancer (CC), and vulvar cancer (VC). Inclusion criteria were (a) pathological diagnosis of primary gynecological cancer with the concomitant finding of CNS metastasis as diagnosed by magnetic resonance imaging (MRI) and/or computed tomography (CT), (b) the absence of a previously known primary CNS malignancy. Exclusion criteria were (a) presence of CNS disease which was not associated with CNS metastasis (e.g., neuromuscular diseases), (b) presence of synchronous cancer accompanying gynecological cancer, (c) history of treatment for non-gynecological malignancies and choriocarcinoma. Medical records were reviewed and all data at the time of diagnosis of the primary tumor and CNS metastasis were collected. Performance status was evaluated according to the Eastern Cooperative Oncology Group (ECOG) scoring scale.

TFI was determined as the time from the last treatment of gynecologic cancer to the diagnosis of CNS metastasis. CNS metastasis-free interval was determined as the time from the diagnosis of the disease to the diagnosis of CNS metastasis. CNS metastasis-specific survival was determined as the time from the initial diagnosis of CNS metastasis to death of any cause or last contact. The cut-off date for survival analysis of patients was December 2021. In the EOC subgroup, all patients had received at least six cycles of paclitaxel and carboplatin combination chemotherapy in adjuvant or neoadjuvant settings. The primary endpoint of the study was to determine the prognostic factors affecting survival in patients with CNS metastasis of gynecologic origin. The institutional review board and ethics committee approved our study protocol (ethics number: 279, date: 2020).

The SPSS software (IBM Co, Armonk, NY, USA) v20.0 was used for data interpretation and statistical analysis. For the analysis, seven variables were used and classified in binary format as follows: age at the time of CNS metastasis (<65 vs ≥65), primary tumor origin (EC/CC/VC vs EOC), presence of concomitant extracranial metastasis (no vs yes), ECOG performance status (1–2 vs 3–4), number of CNS metastasis (solitary vs multiple), CNS metastasis-free interval (<1 year vs ≥1 year), TFI (<6 months vs ≥6 months) and treatment strategy for CNS metastasis (palliative care vs surgery ± radiotherapy ± chemotherapy). Survival curves were designed using the Kaplan–Meier method. Univariate and multivariate analyses were performed using Cox regression models. Hazard ratio (HR) and 95% CIs were calculated for each comparison. *P* values less than 0.05 were statistically significant.

RESULTS

Forty-seven patients with CNS metastasis of gynecological origin were included in the study. Clinicopathological features of the patients are shown in Tables 1 and 2. Of the 47 patients, one patient had metastasis of the upper cervical segment of the medulla spinalis caused by CC, and the rest of the patients had brain metastasis. The median time from initial cancer diagnosis to CNS metastasis was 24.9 (range: 0–108.2) months. Most patients had EOC ($n = 36$, 76.6%), followed by EC ($n = 7$, 14.8%), CC ($n = 2$, 4.3%), and VC ($n = 2$, 4.3%). The median age at the time of CNS metastasis was 59 (range 34–93). Twenty-six patients (55.3%) had multiple foci and 21 patients (44.7%) had a single focus of CNS metastasis at presentation. On the other hand, 28 patients (59.6%) had concurrent extracranial metastases at the time of diagnosis of CNS metastasis. In patients with extracranial metastasis, most of them had pulmonary metastasis (35.7%) followed by liver (28.6%), and distant lymph node metastasis (21.4%). In 46 patients (97.9%), CNS metastasis was diagnosed at the recurrence of the disease, and in one patient (2.1%), CNS metastasis was detected at the time of primary cancer diagnosis. Thirty-seven patients (78.7%) had an ECOG performance score ≥3. The median TFI was 8.2 (range 0.9–103.1) months.

The Kaplan–Meier curve for the entire cohort is shown in Figure 1. The median CNS metastasis-specific survival was 6 (range 0.2–75.1) months. Only one patient was alive at the time of analysis. The CNS metastasis-specific survival of the entire cohort was 48.9% at 6 months, 24.6% at 1 year, and 13.4% at 2 years. The Kaplan–Meier curves by primary origin are shown in Figure 2. Univariate and multivariate analyses of prognostic factors are shown in Table 3. By multivariate analysis, the presence of extracranial metastasis (HR: 5.10; 95% CI: 1.71-15.18),

Table 1: Profile of the patients at the time of initial diagnosis (n=47)

	Cervix	Endometrium	Ovary	Vulva
No. of patients (%)	2 (4.3%)	7 (14.8%)	36 (76.6%)	2 (4.3%)
Median age at the time of initial diagnosis (years)	51 (range 32-69)	67 (range 51-81)	59 (range 34-80)	89 (range 83-95)
FIGO stage¶				
I	1 (50%)	3 (42.8%)	1 (2.8%)	1 (50%)
II	0 (0%)	1 (14.3%)	0 (0%)	0 (0%)
III	1 (50%)	1 (14.3%)	30 (83.3%)	1 (50%)
IV	0 (0%)	2 (28.6%)	5 (13.9%)	0 (0%)
Menopausal status				
Premenopausal	1 (50%)	1 (14.3%)	10 (27.8%)	0 (0%)
Postmenopausal	1 (50%)	6 (85.7%)	26 (72.2%)	2 (100%)
Histological characteristics				
Serous adenocarcinoma	0 (0%)	0 (0%)	23 (63.9%)	0 (0%)
Endometrioid	0 (0%)	4 (57.1%)	3 (8.3%)	0 (0%)
Clear cell	0 (0%)	1 (14.3%)	2 (5.6%)	0 (0%)
Transitional cell	0 (0%)	0 (0%)	1 (2.8%)	0 (0%)
Dedifferantiated	0 (0%)	1 (14.3%)	0 (0%)	0 (0%)
Adenocarcinoma, NOS	0 (0%)	0 (0%)	4 (11.1)	0 (0%)
Mixed	0 (0%)	0 (0%)	3 (8.3%)	0 (0%)
Squamous cell carcinoma	2 (100%)	0 (0%)	0 (0%)	2 (100%)
Carcinosarcoma	0 (0%)	1 (14.3%)	0 (0%)	0 (0%)
Chemotherapy before surgery				
Yes	1 (50%)	0 (0%)	10 (27.8%)	0 (0%)
No	1 (50%)	7 (100%)	26 (72.2%)	2 (100%)
Radiotherapy before surgery				
Yes	1 (50%)	0 (0%)	0 (0%)	0 (0%)
No	1 (50%)	7 (100%)	36 (100%)	2 (100%)

¶FIGO: International Federation of Gynecology and Obstetrics; all gynecologic cancers were staged according to FIGO cancer record 2021 (https://www.figo.org/figo-cancer-report-2021); NOS: Not otherwise specified

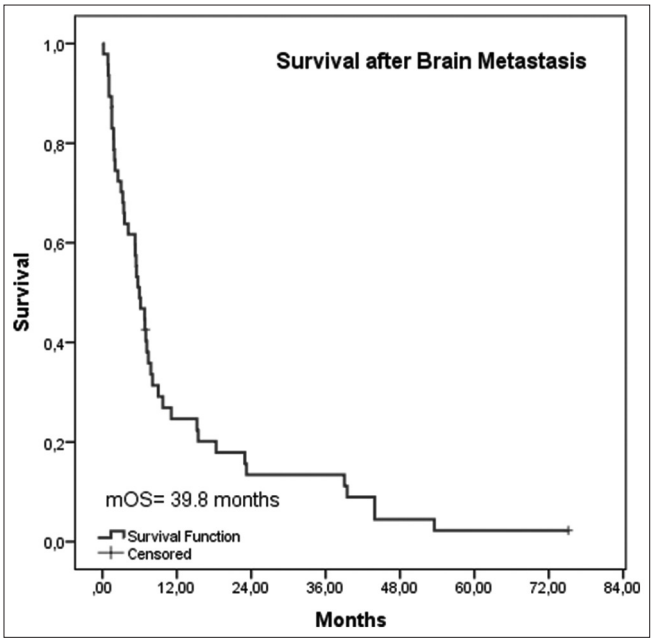

Figure 1: Kaplan–Meier survival curves after the diagnosis of CNS metastasis in all patients. mOS = median overall survival

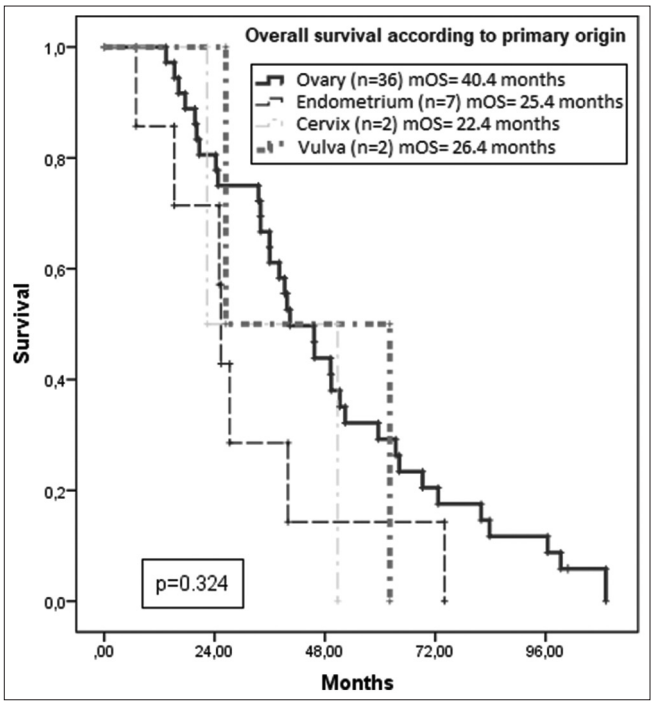

Figure 2: Kaplan–Meier survival curves of the patients by the primary origin of the disease after the diagnosis of CNS metastasis. mOS = median overall survival

ECOG performance status ≥3 (HR: 2.92; 95% CI: 1.36-6.26), palliative care only for the treatment of CNS metastasis (HR: 1.47; 95% CI: 0.58-4.11), and TFI <6 months (HR: 2.74; 95% CI: 1.23-6.08) were independent factors that associated with worse survival.

Patients who survived more than twelve months after the diagnosis of CNS metastases were described as long-term survivors. The clinical features of 11 long-term survivors are described in Table 4. Of the 11, three had extracranial metastasis at the diagnosis of CNS metastasis and six had multifocal CNS metastasis. Finally, TFI was less than 6 months in two of long-term survivors.

Table 2: Clinical characteristics of the patients with CNS metastasis (n=47)

	Cervix	Endometrium	Ovary	Vulva	Total
No. of patients (%)	2 (4.3%)	7 (14.9%)	36 (76.5%)	2 (4.3%)	47 (100%)
Age at the time of CNS metastasis, median (years)	53 (range 34-72)	65 (range 48-75)	61 (range 35-82)	87 (range 81-93)	59 (range 34-93)
ECOG performance status 3 or 4[†]	2 (100%)	4[†] (57.1%)	29[†] (80.6%)	2 (100%)	37 (78.7%)
Multiple CNS metastasis	1 (50%)	2 (28.6%)	22 (61.1%)	1 (50%)	26 (55.3%)
Previous CT or RT history	1 (50%)	5 (71.4%)	36 (100%)	2 (100%)	44 (93.6%)
Onset of CNS metastasis					
Initial presentation	0 (0%)	1 (14.3%)	0 (0%)	0 (0%)	1 (2.1%)
Initial progression	1 (50%)	1 (14.3%)	18 (50%)	0 (0%)	20 (42.6%)
subsequent progression	1 (50%)	5 (71.4%)	18 (50%)	2 (100%)	26 (55.3%)
Overall survival, median (months)	36.6 (range 22.4-50.8)	25.4 (range 6.9-74)	40.4 (range 13.4-109.1)	44.3 (range 26.4-62.1)	39.3 (range 6.9-109.1)
CNS metastasis-free interval, median (months)	33.5 (range 17.1-49.9)	23.9 (range 0-65.9	28.1 (range 7.9-108)	23.8 (range 22.6-24.9)	25.7 (range 0-108.2)
Treatment-free interval, median (months)	3.1 (range 1.0-5.2)	3.1 (range 1.0-10.1)	12.8 (range 0.9-103.1)	9.7 (range 3.0-16.3)	8.2 (range 0.9-103.1)
Treatment to CNS metastasis					
Surgery alone	0 (0%)	0 (0%)	1 (2.8%)	0 (0%)	1 (2.1%)
Surgery + RT	0 (0%)	1 (14.3%)	1 (2.8%)	0 (0%)	2 (4.3%)
Surgery + CT	0 (0%)	0 (0%)	1 (2.8%)	0 (0%)	1 (2.1%)
Surgery + RT + CT	1 (50%)	1 (14.3%)	3 (8.4%)	0 (0%)	5 (10.6%)
RT alone	0 (0%)	0 (0%)	10 (27.7%)	0 (0%)	10 (21.3)
RT + CT	0 (0%)	3 (42.8%)	16 (44.3%)	2 (100%)	21 (44.7%)
CT alone	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SRS + RT + CT	0 (0%)	0 (0%)	2 (5.6%)	0 (0%)	2 (4.3%)
Palliative care alone	1 (50%)	2 (28.6%)	2 (5.6%)	0 (0%)	5 (10.6%)
Residual tumor volume after surgery					
<1 cm	N/A	N/A	23 (63.9%)	N/A	N/A
≥1 cm	N/A	N/A	13 (36.1%)	N/A	N/A
Extracranial metastasis	2 (100%)	5 (71.2%)	19 (52.8%)	2 (100%)	28 (59.6%)
CNS metastasis-specific interval, median (months)	3.1 (range 0.9-5.3)	2.0 (range 1.5-18.3)	6.1 (range 0.2-75.1)	20.5 (range 1.5-39.5)	5.9 (range 0.2-75.1)

[†]Data were missing for five patients (one patient in the endometrial cancer group, four patients in the epithelial ovarian cancer group), HR: Hazards Ratio, RT: Radiotherapy, CT: Chemotherapy, CNS: Central nervous system, ECOG: Eastern Cooperative Oncology Group SRS: Stereotactic radiosurgery, N/A: Not applicable

DISCUSSION

The present study aims to determine the prognostic factors for survival in patients with CNS metastasis of gynecological origin. As mentioned earlier, the tumors of the female genital system are a rare source of CNS metastasis, and therefore we still have limited data on prognostic factors. Treatment choices for CNS metastasis are composed of neurosurgery, chemotherapy, and radiotherapy including whole-brain radiation and stereotactic radiosurgery (SRS). The principles of treatment are typically based on prognosis. In patients with poor survival expectations due to unfavorable prognostic factors, less aggressive and short-term treatment strategies may be appropriate. On the other hand, in the presence of favorable prognostic factors, more aggressive and long-term treatment strategies including neurosurgery should be encouraged. Therefore, the treatment strategy should be built on an individual basis by carefully assessing the prognostic factors.

To date, many researchers evaluated the prognostic factors for CNS metastasis in gynecologic cancer patients. Marchetti *et al*.[18] published a multicentric retrospective analysis of brain metastasis in 174 patients with EOC and highlighted that age, extracranial metastasis, number of brain metastasis, and multimodal treatment strategy were significantly associated with overall survival (OS) in multivariate analysis. A review of 36 studies including 513 EOC patients with brain metastasis concluded that age, performance status, state of control of the primary disease, extracranial metastases, the number of brain metastases, and mode of therapy for brain metastases were the prognostic factors affecting survival.[2] Recently, Borella *et al*.[15] also stated the same prognostic factors in 1135 EOC patients with brain metastases. Indeed, performance

Table 3: Prognostics factors of survival period from the diagnosis of CNS metastasis

	Univariate analysis			Multivariate analysis		
	HR	CI 95%	*P*	HR	CI 95%	*P*
Age						
<65						
≥65	1,15	0,61-2,14	0,661	0,72	0,33-1,56	0,409
Primary Origin						
EC/CC/VC						
EOC	0.69	0,35-1,38	0,290	0,65	0,23-1,15	0,423
Extracranial metastasis						
No						
Yes	3,53	1,60-7,76	0,002	5,10	1,71-15,18	0,003
Performance status (ECOG)						
0-2						
3-4	3,07	1,63-5,78	0,001	2,92	1,36-6,26	0,006
Number of CNS metastasis						
Solitary						
Multiple	1,11	0,61-2,01	0,732	0,99	0,46-2,15	0,980
CNS metastasis-free interval						
≥1 year						
<1 year	1,00	0,39-2,57	0,996	1,73	0,55-5,50	0,354
Treatment-free interval						
≥6 months						
<6 months	2,18	1,14-4,18	0,019	2,74	1,23-6,08	0,014
Treatment for CNS metastasis						
Surgery±RT±CT						
Palliative care only	3,90	1,69-8,98	0,001	1,47	0,58-4,11	0,039

HR: Hazards Ratio, CI: Confidence interval, RT: Radiotherapy, CT: Chemotherapy, CNS: Central nervous system, ECOG: Eastern Cooperative Oncology Group, EC: Endometrial cancer, EOC: Epithelial ovarian cancer, VC: Vulvar cancer, CC: Cervical cancer

Table 4: Clinical features of the long-term survivors (>12 months) with CNS metastasis (*n*=11)

Age	Primary disease	Extracranial metastasis	ECOG PS	No of CNS metastasis	TFI (months)	Treatment for CNS metastasis	Clinical Outcome	Survival after CNS metastasis (months)
65	EC	No	2	Solitary	1.0	S + RT	DOD	15.2
48	EOC	No	2	Multiple	14.8	RT + CT	DOD	43.9
57	EOC	Yes	2	Multiple	17.3	RT + CT	DOD	39.0
81	VC	No	3	Solitary	16.3	RT + CT	DOD	39.5
53	EC	No	2	Solitary	3.1	S + RT + CT	DOD	18.3
64	EOC	Yes	2	Solitary	16.6	S + RT	AWD	75.1
47	EOC	No	3	Multiple	8.2	SRS + RT + CT	DOD	53.5
70	EOC	No	2	Multiple	7.2	RT	DOD	23.0
54	EOC	No	2	Solitary	22.6	RT	DOD	23.2
65	EOC	Yes	2	Multiple	18.4	RT + CT	DOD	15.4
50	EOC	No	2	Multiple	10.1	RT + CT	DOD	45.6

DOD: Died of disease, AWD: Alive with disease, TFI: Treatment-free Interval, CNS: Central nervous system, ECOG PS: Eastern cooperative oncology group performance score, S: Surgery, RT: Radiotherapy, CT: Chemotherapy, SRS: Stereotactic radiosurgery, EC: Endometrial cancer, EOC: Epithelial ovarian cancer, VC: Vulvar cancer

status,[19-21] extracranial metastasis,[17,21-23] and treatment history of CNS metastasis[16,20,23,24] have been confirmed by many other researchers as independent prognostic factors.

As stated above, the number of CNS metastasis was an independent prognostic factor affecting survival according to the results of two large reviews.[2,15] However, in the present study, the number of CNS metastasis was not validated as an independent prognostic factor. Accordingly, we found that unifocal or multifocal lesions had similar survival rates on multivariate analysis. In light of the literature, we consider that the implementation of aggressive multimodal treatment strategies including surgery, radiotherapy, and chemotherapy have similar survival rates for both solitary and multiple intracranial lesions, particularly for oligometastatic ones. Besides, this hypothesis is supported by the data from the study of many authors.[23,25,26] Additionally, the current literature has successfully described the multimodal treatment of either solitary or multiple intracranial metastatic lesions with SRS that are not suitable for conventional neurosurgery.[25,27-29] In our study, one patient with EOC who had the diagnosis of CNS metastasis with oligometastatic foci underwent SRS followed by radiotherapy plus chemotherapy in May 2011 and she succumbed to the disease in October 2015 due to the recurrence of CNS metastasis. Indeed, isolated case reports have described complete remission of multifocal disease as long as two years of follow-up period after multimodal therapy following diagnosis of CNS metastasis.[28,30] We should underline that these patients with good performance status were more likely to receive

multimodal and aggressive treatment strategies including neurosurgery and SRS. Furthermore, patients with solitary CNS metastasis are more prone to neurosurgery than those with multiple ones.[21,31] In a nutshell, there might be patient selection bias here.

On the other hand, in the study of Growdon *et al.* and Nasu *et al.*, the presence of serous papillary histology was found as an independent prognostic factor for improved survival.[16,23] Recently, Kim *et al.*[24] reported that patients with brain metastasis due to gynecologic cancer of uterine origin had a better prognosis in terms of survival. Whereas, other authors were not able to show any survival difference between primary tumor origin.[17,32] In the same vein, primary tumor origin was not validated as an independent prognostic factor in the present study, either.

Finally, the present study revealed that TFI was an independent prognostic factor affecting survival. TFI has been previously investigated in the study of Takeshita *et al.*[17] and has been confirmed as an independent prognostic factor in gynecologic tumors with brain metastasis. It is possible that patients with shorter TFI may have a higher burden of tumor cells that were resistant to treatment and this may lead to the proliferation of resistant tumor clones more rapidly which is related to poor survival. With the present study, we hypothesize that the recurrence of the disease as metastasis to CNS might be assumed as a prognostic reset. Accordingly, prolongation of TFI is a sign of more effective treatment probability and TFI might be evaluated as an independent prognostic factor for patients with CNS metastasis of gynecologic origin.

The present study has some limitations. Firstly, due to its retrospective nature, there might be undetected bias. Secondly, our cohort did not include a sufficient number of patients to conclude statistically definitive results as it was conducted at a single center. Finally, there was no standard treatment scheme for patients with CNS metastases of gynecological origin. However, a single-center study in which patients were treated by the same experienced team might be considered as a strength of the present study. Treatment standardization by a center basis might contribute to better survival results.

In conclusion, patients with CNS metastasis who have favorable prognostic factors are considered to be appropriate candidates for aggressive and long-term treatment strategies. In the present study, neither the number of CNS metastasis nor the primary origin of the disease was confirmed as independent prognostic factors. On the other hand, extracranial metastasis, performance status, treatment history of CNS metastasis, and TFI were determined as independent prognostic factors that improved survival. TFI might be taken into account as a prognostic factor for patients with CNS metastasis in gynecological cancer. Future studies are needed to evaluate TFI and confirm its prognostic value.

Acknowledgements

There is not a non-author contributor for this article. We declare that the manuscript has been read and approved by all the authors. *This article was not published in any journal or presented at any congress/meeting.*

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer 2002;94:2698-705.
2. Piura E, Piura B. Brain metastases from ovarian carcinoma. ISRN Oncol 2011;2011:527453.
3. Piura E, Piura B. Brain metastases from endometrial carcinoma. ISRN Oncol 2012;2012:581749.
4. Piura E, Piura B. Brain metastases from cervical carcinoma: Overview of pertinent literature. Eur J Gynaecol Oncol 2012;33:567-73.
5. Ogawa K, Yoshii Y, Aoki Y, Nagai Y, Tsuchida Y, Toita T, *et al*. Treatment and prognosis of brain metastases from gynecological cancers. Neurol Med Chir (Tokyo) 2008;48:57-62; discussion 62-3.
6. Hasegawa H, Yamamoto M, Shin M, Barfod BE. Gamma knife radiosurgery for brain vascular malformations: Current evidence and future tasks. Ther Clin Risk Manag 2019;15:1351-67.
7. Markesbery WR, Brooks WH, Gupta GD, Young AB. Treatment for patients with cerebral metastases. Arch Neurol 1978;35:754-6.
8. Sperduto PW, Mesko S, Li J, Cagney D, Aizer A, Lin NU, *et al*. Beyond an updated graded prognostic assessment (Breast GPA): A prognostic index and trends in treatment and survival in breast cancer brain metastases from 1985 to today. Int J Radiat Oncol Biol Phys 2020;107:334-43.
9. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, *et al*. Summary report on the graded prognostic assessment: An accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 2012;30:419-25.
10. Hall WA, Djalilian HR, Nussbaum ES, Cho KH. Long-term survival with metastatic cancer to the brain. Med Oncol 2000;17:279-86.
11. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, *et al*. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997;37:745-51.
12. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, *et al*. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: A multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 2010;77:655-61.
13. Zindler JD, Rodrigues G, Haasbeek CJ, De Haan PF, Meijer OW, Slotman BJ, *et al*. The clinical utility of prognostic scoring systems in patients with brain metastases treated with radiosurgery. Radiother Oncol 2013;106:370-4.
14. Siu G, Springer EA, Hedrick SM. The biology of the T-cell antigen receptor and its role in the skin immune system. J Invest Dermatol 1990;94 (6 Suppl):91S-100S.
15. Borella F, Bertero L, Morrone A, Gambella A, Bovetti M, Cosma S, *et al*. Brain metastases from ovarian cancer: Current evidence in diagnosis, treatment, and prognosis. Cancers (Basel) 2020;12:2156.
16. Nasu K, Satoh T, Nishio S, Nagai Y, Ito K, Otsuki T, *et al*. Clinicopathologic features of brain metastases from gynecologic malignancies:

A retrospective study of 139 cases (KCOG-G1001s trial). Gynecol Oncol 2013;128:198-203.
17. Takeshita S, Todo Y, Furuta Y, Okamoto K, Minobe S, Yamashiro K, *et al*. Prognostic factors for patients with brain metastasis from gynecological cancer: A significance of treatment-free interval of more than 6 months. Jpn J Clin Oncol 2017;47:604-10.
18. Marchetti C, Ferrandina G, Cormio G, Gambino A, Cecere S, Lorusso D, *et al*. Brain metastases in patients with EOC: Clinico-pathological and prognostic factors. A multicentric retrospective analysis from the MITO group (MITO 19). Gynecol Oncol 2016;143:532-8.
19. Walter AC, Gunderson CC, Vesely SK, Algan O, Sughrue M, Slaughter KN, *et al*. Central nervous system metastasis in gynecologic cancer: Symptom management, prognosis and palliative management strategies. Gynecol Oncol 2015;136:472-7.
20. Rades D, Fischer D, Veninga T, Stalpers LJ, Schild SE. Prognostic factors for survival and intracerebral control after irradiation for brain metastases from gynecological cancer. Gynecol Oncol 2009;114:506-8.
21. Gressel GM, Lundsberg LS, Altwerger G, Katchi T, Azodi M, Schwartz PE, *et al*. Factors predictive of improved survival in patients with brain metastases from gynecologic cancer: A single institution retrospective study of 47 cases and review of the literature. Int J Gynecol Cancer 2015;25:1711-6.
22. Keskin S, Kucucuk S, Ak N, Atalar B, Sari M, Sozen H, *et al*. Survival impact of optimal surgical cytoreduction in recurrent epithelial ovarian cancer with brain metastasis. Oncol Res Treat 2019;42:101-6.
23. Growdon WB, Lopez-Varela E, Littell R, Oliva E, Seiden M, Krasner C, *et al*. Extent of extracranial disease is a powerful predictor of survival in patients with brain metastases from gynecological cancer. Int J Gynecol Cancer 2008;18:262-8.
24. Kim YZ, Kwon JH, Lim S. A clinical analysis of brain metastasis in gynecologic cancer: A retrospective multi-institute analysis. J Korean Med Sci 2015;30:66-73.
25. Anupol N, Ghamande S, Odunsi K, Driscoll D, Lele S. Evaluation of prognostic factors and treatment modalities in ovarian cancer patients with brain metastases. Gynecol Oncol 2002;85:487-92.
26. Geisler JP, Geisler HE. Brain metastases in epithelial ovarian carcinoma. Gynecol Oncol 1995;57:246-9.
27. Cormio G, Maneo A, Colamaria A, Loverro G, Lissoni A, Selvaggi L. Surgical resection of solitary brain metastasis from ovarian carcinoma: An analysis of 22 cases. Gynecol Oncol 2003;89:116-9.
28. Kawana K, Yoshikawa H, Yokota H, Onda T, Nakagawa K, Tsutsumi O, *et al*. Successful treatment of brain metastases from ovarian cancer using gamma-knife radiosurgery. Gynecol Oncol 1997;65:357-9.
29. Alexander E 3rd, Moriarty TM, Davis RB, Wen PY, Fine HA, Black PM, *et al*. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. J Natl Cancer Inst 1995;87:34-40.
30. Park SH, Ro DY, Park BJ, Kim YW, Kim TE, Jung JK, *et al*. Brain metastasis from uterine cervical cancer. J Obstet Gynaecol Res 2010;36:701-4.
31. Niu X, Rajanbabu A, Delisle M, Peng F, Vijaykumar DK, Pavithran K, *et al*. Brain metastases in women with epithelial ovarian cancer: Multimodal treatment including surgery or gamma-knife radiation is associated with prolonged survival. J Obstet Gynaecol Can 2013;35:816-22.
32. Pakneshan S, Safarpour D, Tavassoli F, Jabbari B. Brain metastasis from ovarian cancer: A systematic review. J Neurooncol 2014;119:1-6.