Gynecologic Oncology 128 (2013) 198–203

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Clinicopathologic features of brain metastases from gynecologic malignancies: A retrospective study of 139 cases (KCOG-G1001s trial)

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HIGHLIGHTS

- Brain metastases from ovarian/tubal/peritoneal cancer revealed better prognosis compared to those from corpus cancer or cervical cancer.
- Ovarian/tubal/peritoneal origin, KPS >70, single metastasis, absence of extracranial disease, cranial surgery, radiotherapy, and chemotherapy are independent favorable prognostic factors.
- Aggressive multimodal therapy is warranted in the treatment of brain metastases from gynecologic malignancies in carefully selected patients.

ARTICLE INFO

Article history:
Received 1 October 2012
Accepted 1 November 2012
Available online 8 November 2012

Keywords:
Ovarian cancer
Corpus cancer
Cervical cancer
Brain metastases
Radiation
Prognosis

ABSTRACT

Objective. Although brain metastases from gynecologic malignancies are rare, such cases have been gradually increasing in number. The aim of the present study was to evaluate the clinicopathologic features and prognostic factors of brain metastases from gynecologic malignancies.

Methods. Retrospective analysis of 139 patients with brain metastases from gynecologic malignancies was carried out as a multi-institutional study. The clinicophathological data of the patients were collected from medical records.

Results. Median survival time of the patients with brain metastases was 12.5 months for the ovarian cancer group, 6.2 months for the corpus cancer group, and 5.0 months for the cervical cancer group; two-year overall survival rates were 19.7%, 6.1%, and 4.8%, respectively. Multivariate analysis revealed ovarian/tubal/peritoneal origin, KPS >70, single brain metastasis, absence of extracranial disease, cranial surgery, cranial radiotherapy, and chemotherapy to be independent favorable prognostic factors associated with overall survival.

Conclusion. It is considered that aggressive multimodal therapy is warranted in the treatment of brain metastases from gynecologic malignancies in carefully selected patients. The present study may provide a platform for the discussion of management strategies in these rare clinical scenarios.

Introduction

Brain metastases are the most common intracranial neoplasm in adults and represent an important cause of morbidity and mortality

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http://dx.doi.org/10.1016/j.ygyno.2012.11.001

[1]. Fifty to sixty percent of brain metastases are originated from lung cancer, 15–20% from breast cancer, and 5–10% from melanoma [1–6]. Eighty to eighty-five percent of brain metastases are found in the cerebral hemispheres, 10–15% in the cerebellum, and 1–5% in the brainstem [7]. There is a 33% chance of brain metastases presenting as either solitary, oligometastatic (2–3 lesions), or polymetastatic (>4 lesions), and an 80% chance that they will present after the systemic cancer diagnosis [8].

The number of newly diagnosed cases of brain metastases may be increasing due to improvements in modern imaging techniques that can detect previously occult, small metastases in asymptomatic patients, as well as improved therapies that may extend the survival of patients with invasive cancer who have historically died from extracranial disease prior to developing brain metastases [3,9,10]. Presenting symptoms include headaches, seizures, encephalopathy, ataxia, and sensory or motor deficits. Detailed neuropsychological testing demonstrates cognitive impairment in 65% of patients with brain metastases, usually across multiple domains [11,12]. However, many brain tumors are now identified in asymptomatic patients as part of screening neuroimaging studies with high resolution computed tomography (CT), and magnetic resonance imaging (MRI) [1,3,5,6,13,14].

Nevertheless, brain metastases from gynecologic malignancies, apart from choriocarcinoma, are rare and are usually found in association with widely disseminated systemic disease [15–19]. The primary mechanism of spread from the genital tract to the brain is by hematogenous dissemination of tumor cells to the lungs and then to the brain via the carotid arteries [20]. Incidences of brain metastases from ovarian, endometrial, and cervical cancers have been reported to be 0.3–2.2%, 0.4–1.2%, and 0.3–0.9%, respectively [20]. Clinical reports of brain metastases from gynecological cancers have also increased gradually, especially from ovarian cancer [14,16].

Management approaches have included best supportive care, surgical resection, and radiotherapy [21]. In the majority of patients, treatment of brain metastasis is palliative because the primary disease is often advanced and the general condition of these patients often is poor. Treatment algorithms for the heterogeneous population of patients with brain metastases are based on patients' prognosis and whether the aim is symptom palliation, prolongation of survival, or both [22]. As survival depends on disease control both intra- and extracranially, patients with active extracranial disease might also be candidates for systemic treatment. Overall, treatment complexity and resource utilization have increased during the last decades. However, the outcomes of patients with brain metastases remain extremely poor [22].

With increasing numbers of local and systemic treatment options, the issue of patient selection gains importance. In the present study, we collected a number of patient records from multiple institutions and evaluated the general features, current treatment modalities, prognosis, and prognostic factors of brain metastases from gynecologic malignancies. The present study may provide a platform for the discussion of management strategies in these rare clinical scenarios.

Patients and methods

The present study was designated as a multi-institutional retrospective study (KCOG-G1001s trial). Patients enrolled in this study were diagnosed as having brain metastases from gynecologic malignancies between January, 1995 and December, 2009. Further inclusion criteria were pathological diagnosis of primary gynecologic malignancies, diagnosis of metastases by CT, MRI, and/or PET-CT, and no prior therapy to the brain. Exclusion criteria were: history of treatment for malignancies other than gynecologic cancer, presence of active double cancer, choriocarcinoma, or presence of central nerve system disease and/or neuromuscular disease unrelated to brain metastases. This study was approved by the institutional review board (IRB) of each institute.

The following patients' data were collected from medical records; age at initial diagnosis of primary disease, recurrence, and brain metastases, origin and pathology of primary tumor, clinical and pathological stage (FIGO and TNM), initial treatment modalities, treatment modalities for brain metastases, presence of pulmonary metastases during the disease course, presence of extracranial metastases at the diagnosis of brain metastases, symptoms of brain metastases, Karnofsky Performance Status (KPS) score, Recursive Partitioning Analysis (RPA) score, Glasgow Coma Scale (GCS) score, and Japan Coma Scale (JCS) score at the diagnosis of brain metastases, site size, and number of brain metastases, prognosis, cause of death, and complications.

Data are presented as means ± standard deviations (SDs) and appropriately analyzed by the Bonferroni test and χ^2 test (SPSS Ver. 18 for Windows Statistical Package, International Business Machines Corp., New York, New York, USA). The overall survival times were calculated by the Kaplan–Meier method and analyzed by the log-rank test (SPSS). We used the Cox proportional hazards model to assess the impact of multiple covariates for the prognosis of brain metastases from gynecologic malignancies. The origin of primary disease, histology, age at brain metastases, presence of symptoms of brain metastases, KPS score, RPA score, GCS score, and JCS score at the diagnosis of brain metastases, number of brain metastases, largest diameter of brain metastases, presence of extracranial disease, cranial surgery, radiotherapy, and chemotherapy were regarded as candidate prognostic factors. The results of the multivariate analysis are expressed as hazards ratios with 95% confidence intervals (CIs) (SPSS). p values of <0.05 were considered to indicate statistical significance.

Results

One-hundred thirty-nine patients met the above criteria and were studied in this retrospective analysis. Table 1 shows the number of patients with brain metastases classified by the primary site of the tumor. Brain metastases from ovarian, tubal, and peritoneal cancer together constituted 40.3% of the patients and are classified together as the ovarian cancer group because of the similarity of their clinicopathologic characteristics.

Clinical characteristics are summarized in Table 2. Age at the diagnosis of brain metastases was significantly younger in patients with brain metastases from cervical cancer. Time from initial diagnosis to brain metastases was 25.2 ± 31.6 months in the ovarian cancer group, 25.1 ± 32.2 months in the corpus cancer group, and 36.3 ± 59.8 months in the cervical cancer group. Brain metastases were detected at initial diagnosis in 8.9% of the ovarian cancer group, 15.4% of the corpus cancer group, and 2.4% of the cervical cancer group. Symptoms were present at the time of diagnosis of brain metastases in most cases.

Radiographic diagnostic modalities revealed a solitary brain metastasis in 53.6% of the ovarian cancer group, 43.6% of the corpus cancer group, and 33.3% of the cervical cancer group. Small size brain metastases (<2 cm) were detected in 21.4% of the ovarian cancer group, 25.6% of the corpus cancer group, and 16.7% of the cervical cancer group. Pulmonary metastases were present at the time of the

Table 1
Primary site of gynecologic cancer in patients enrolled in the present study.

Site	No. of patients (%)
Ovary/fallopian tube/peritoneum	56 (40.3)
Uterine corpus	39 (28.1)
Uterine cervix	42 (30.2)
Vagina	1 (0.7)
Vulva	1 (0.7)

Table 2
Clinical characteristics of ovarian, corpus, and cervical cancer groups.

Clinical measures	Ovarian	Corpus	Cervical
Age at initial diagnosis [mean ± SD (range)]	55.8 ± 11.3 (22.7–79.4)	60.9 ± 9.4 (39.8–77.9)	50.3 ± 11.6 (28.9–83.3)*
Age at diagnosis of brain metastases [mean ± SD (range)]	58.8 ± 11.1 (29.9–81.0)	63.1 ± 9.2 (39.8–79.2)	53.3 ± 11.9 (32.1–87.3)*
Time from initial diagnosis to brain metastases [mo, mean ± SD (range)]	25.2 ± 31.6 (0–138)	25.1 ± 32.2 (0–156)	36.3 ± 59.8 (0–386)
Brain metastases at initial diagnosis			
Present	5 (8.9%)	6 (15.4%)	1 (2.4%)
Absent	51 (91.1%)	33 (84.6%)	41 (97.6%)
Brain metastases at initial recurrence			
Present	13 (25.5%)	10 (30.3%)	9 (22.0%)
Absent	38 (74.5%)	23 (69.7%)	32 (78.0%)
Time from initial recurrence to brain metastases (mo)	13.7 ± 19.7 (0–85)	7.9 ± 12.4 (0–64)	12.0 ± 14.9 (0–66)
Symptoms at diagnosis of brain metastases			
Present	50 (89.3%)	35 (89.7%)	41 (97.6%)
Absent	6 (10.7%)	4 (10.3%)	1 (2.4%)
Number of brain metastases			
1	30 (53.6%)	17 (43.6%)	14 (33.3%)
2	4 (7.1%)	5 (12.8%)	2 (4.8%)
3	7 (12.5%)	4 (10.3%)	6 (14.3%)
4	3 (5.4%)	3 (7.7%)	1 (2.4%)
5<	12 (21.4%)	10 (25.6%)	19 (45.2%)
Diameter of largest brain metastasis			
<1 cm	6 (10.7%)	1 (2.6%)	3 (7.1%)
1–2 cm	6 (10.7%)	9 (23.0%)	4 (9.5%)
2–4 cm	30 (53.6%)	21 (53.8%)	23 (54.8%)
4 cm<	12 (21.4%)	6 (15.4%)	10 (23.8%)
ND	2(3.6%)	2 (5.1%)	2 (4.8%)
Pulmonary metastases at diagnosis of brain metastasis			
Present	9 (16.1%)**	26 (66.7%)	24 (57.1%)
Absent	46 (82.1%)	13 (33.3%)	18 (42.9%)
ND	1 (1.8%)	0 (0%)	0 (0%)
Extracranial metastases at diagnosis of brain metastasis (including pulmonary metastasis)			
Present	38 (67.9%)	30 (76.9%)	35 (83.3%)
Absent	17 (30.4%)	9 (23.1%)	7 (16.7%)
ND	1 (1.8%)	0 (0%)	0 (0%)
Pulmonary metastases throughout the disease course			
Present	12 (21.4%)**	29 (74.4%)	28 (66.7%)
Absent	43 (76.8%)	10 (25.6%)	14 (33.3%)
ND	1 (1.8%)	0 (0%)	0 (0%)
Recursive Partitioning Analysis score at diagnosis of brain metastasis			
Class 1	19 (33.9%)	6 (15.4%)	12 (28.6%)
Class 2	25 (44.6%)	19 (48.7%)	16 (38.1%)
Class 3	12 (21.4%)	14 (35.9%)	14 (33.3%)
Karnofsky Performance Status at diagnosis of brain metastasis			
0–20%	4 (7.1%)	5 (12.8%)	4 (9.5%)
30–60%	17 (30.4%)	16 (41.0%)	17 (40.5%)
70–90%	27 (48.2%)	17 (43.6%)	21 (50.0%)
100%	8 (14.2%)	1 (2.6%)	0 (0%)
Glasgow Coma Scale at diagnosis of brain metastasis			
0–2	0 (0%)	3 (7.7%)	0 (0%)
3–8	1 (1.8%)	3 (7.7%)	1 (2.4%)
9–13	5 (8.9%)	6 (15.4%)	9 (21.4%)
14–15	50 (89.3%)	27 (69.2%)	32 (76.2%)
Japan Coma Scale at diagnosis of brain metastasis			
0	26 (46.4%)	12 (21.4%)	19 (45.2%)
1–3	26 (46.4%)	23 (59.0%)	20 (47.6%)
10–30	3 (5.4%)	2 (5.1%)	2 (4.8%)
100–300	1 (1.8%)	2 (5.1%)	1 (2.4%)

ND: not described.
* $p<0.025$ vs. ovarian cancer and $p<0.0001$ vs. corpus cancer (Bonferroni test).
** $p<0.0001$ vs. corpus cancer and cervical cancer (χ^2 test).

diagnosis of brain metastasis in 16.1% of the ovarian cancer group, 66.7% of the corpus cancer group, and 57.1% of the cervical cancer group. Interestingly, pulmonary metastases were absent throughout the disease course in 76.8% of the ovarian cancer group, 25.6% of the corpus cancer group, and 33.3% of the cervical cancer group. The incidence of pulmonary metastases in ovarian cancer group at the time of the diagnosis of brain metastasis as well as throughout the disease course was significantly lower than those in corpus cancer and cervical cancer groups ($p<0.0001$, χ^2 test).

Clinical stage and histopathological diagnosis are shown in Table 3. Most of the patients in the ovarian (85.7%) and corpus cancer groups (69.3%) had advanced-stage disease (stage III/IV), whereas only 35.7% in the cervical cancer group had advanced-stage disease.

Treatment modalities of brain metastases of ovarian, corpus, and cervical cancer groups are shown in Table 4. Stereotactic radiosurgery (SRS) was performed for 59.9% and 48.1% of the ovarian and corpus cancer groups, but for only 20.0% of the cervical cancer group (Supplementary Table 1).

The prognoses are shown in Fig. 1. The median survival time was 12.5 months for the ovarian cancer group, 6.2 months for the corpus cancer group, and 5.0 months for the cervical cancer group. Two-year overall survival rates were 19.7%, 6.1%, and 4.8%, respectively. Cases of

Table 3
Clinicopathological characteristics of ovarian, corpus, and cervical cancer groups.

Clinical measures	Ovarian	Corpus	Cervical
Stage (FIGO)			
I	7 (12.5%)	10 (25.6%)	14 (33.3%)
II	1 (1.8%)	2 (5.1%)	12 (28.6%)
III	32 (57.1%)	12 (30.8%)	5 (11.9%)
IV	16 (28.6%)	15 (38.5%)	10 (23.8%)
ND			1 (2.4%)
Histology			
Serous adenocarcinoma	33 (58.9%)	2 (5.1%)	1 (2.4%)
Clear cell adenocarcinoma	7 (12.5%)		
Endometrioid adenocarcinoma	6 (10.7%)	27 (69.2%)	2 (4.8%)
Endocervical adenocarcinoma			3 (7.1%)
Mucinous adenocarcinoma	2 (3.6%)		
Squamous cell carcinoma	1 (1.8%)		27 (64.3%)
Adenosquamous carcinoma		1 (2.6%)	2 (4.8%)
Mucoepidermoid carcinoma			1 (2.4%)
Small cell carcinoma	3 (5.4%)		4 (9.5%)
Carcinoid			1 (2.4%)
Carcinosarcoma		4 (10.3%)	
Leiomyosarcoma		4 (10.3%)	
Undifferentiated endometrial sarcoma		1 (2.6%)	
ND	4 (7.1%)		1 (2.4%)

ND: not described.

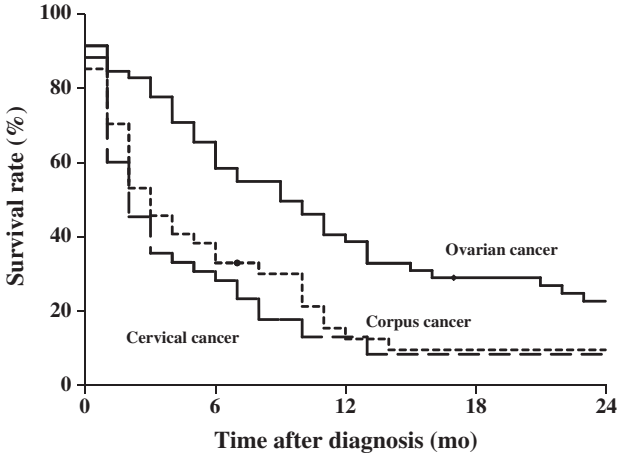

Fig. 1. Two-year overall survival curve of ovarian, corpus, and cervical cancer analyzed by Kaplan–Meier method. Brain metastases from ovarian cancer revealed better prognosis than that from corpus cancer and cervical cancer ($p<0.001$, log-rank test).

brain metastasis from ovarian cancer had a statistically better prognosis than those from corpus cancer and cervical cancer ($p<0.001$, log-rank test). Ninety percent of the patients died of their disease. When the patient died of brain stem dysfunction, cerebral herniation and/or increased intracranial pressure caused by advanced brain metastases, we classified the cause of death as brain metastases. Only 41.5% of the patients died of the brain metastases (Supplementary Table 2). Multivariate analysis for evaluating the prognostic factors associated with overall survival revealed ovarian/tubal/peritoneal origin, KPS > 70, single brain metastasis, absence of extracranial disease, cranial surgery, cranial radiotherapy, and chemotherapy to be the independent favorable prognostic factors (Table 5).

Discussion

The incidences of brain metastases from gynecologic malignancies have been reported to be 0.5–2.2% for ovarian cancer [14,18], 0.3–0.9% for corpus cancer [15,17,23,24], and 0.4–1.2% for cervical cancer [23,25]. The reported incidence of ovarian cancer with brain metastasis after introduction of platinum-containing chemotherapy is higher, at 2–12% [9,10,16,19,26,27]. The incidence of brain metastases from corpus and cervical cancer has been increasing in recent years [28]. Prolongation of the survival of patients with gynecologic malignancies due to improved surgical techniques and chemotherapies has been attributed as the main reason for the rising incidence of brain metastasis from these malignancies [28,29]. Interestingly, 39% of the patients with brain metastases were heavily treated with three or more lines of chemotherapy [16]. Increased diagnostic sensitivity resulting from improved cerebral imaging technology has made it possible to detect small intra-cranial lesions at an earlier stage during the course of disease recurrence [10].

The present study has some notable features for the evaluation of the clinicopathologic characteristics and prognostic factors of patients with brain metastases from gynecologic malignancies. We retrospectively collected 139 patients with brain metastases from gynecologic malignancies in a multi-institutional study. Thus, the present study contained the largest number of such patients to date, which made it possible to compare clinicopathologic characteristics and prognostic factors in detail. Although 9% of the patients revealed apparent brain metastases at initial diagnosis, most of the patients were diagnosed to have brain metastases over 2 years after initial diagnosis. Previous reports have demonstrated that the median interval from diagnosis to CNS involvement is 19–46 months for ovarian cancer [14,16,18,19], 2–26 months for corpus cancer [13,15,17,23], and 12–28 months for cervical cancer [15,23–25]; these intervals were significantly associated with the overall survival rate after the

Table 4
Treatment of brain metastases of ovarian, corpus, and cervical cancer groups.

Treatment modality	Ovarian (n = 56)	Corpus (n = 39)	Cervical (n = 42)
Surgery	1 (1.8%)	1 (2.6%)	2 (4.8%)
Surgery + radiation	8 (14.3%)	7 (17.9%)	5 (11.9%)
Surgery + chemotherapy	1 (1.8%)	1 (2.6%)	1 (2.4%)
Surgery + radiation + chemotherapy	5 (8.9%)	0 (0%)	2 (4.8%)
Radiation	21 (37.5%)	18 (46.2%)	21 (50.0%)
Radiation + chemotherapy	11 (19.6%)	2 (5.1%)	2 (4.8%)
Chemotherapy	3 (5.4%)	3 (7.7%)	3 (7.1%)
Palliative care only	6 (10.7%)	7 (17.9%)	6 (14.3%)

Table 5
Multivariate analysis assessing independent prognostic factors associated with overall survival.

Variable	n	Odds ratio	95% CI	p value
Disease origin				
Ovary/fallopian tube/peritoneum	52	1		
Other	73	2.144	1.406–3.269	<0.01
KPS				
70≤	69	1		
<70	56	1.521	1.022–2.264	0.005
Number of brain metastases				
Single	55	1		
Multiple	70	2.21	1.434–3.406	<0.01
Presence of extracranial disease at diagnosis of brain metastases				
Absent	34	1		
Present	91	1.905	1.171–3.098	0.002
Surgery for brain metastases				
Performed	32	1		
Not performed	93	1.791	1.072–2.992	<0.01
Radiotherapy for brain metastases				
Performed	94	1		
Not performed	31	2.681	1.626–4.423	0.002
Chemotherapy for brain metastases				
Performed	32	1		
Not performed	93	2.356	1.391–3.991	0.039

CI, confidence interval.
The data were analyzed by log-rank test.

diagnosis of these malignancies. Further, these intervals are much longer than those for hematogenous spread to other sites, such as the liver and lung, where the median time to metastasis is approximately 6 months [16].

The diagnosis of brain metastases has become easier with modern diagnostic modalities; however, 92% of the patients in the present study were symptomatic at the diagnosis of brain metastases. These findings were consistent with a previous report on corpus cancer [23]. It is speculated that, because of its low incidence, brain metastasis was not foreseen by the gynecologic oncologists, and cranial radiographic evaluation was not carried out without evident symptoms. Efforts to find asymptomatic, small, and solitary brain metastasis, may lead the better prognosis after treatment. A significant number of patients had a solitary brain metastasis (44.5%), small size brain metastases (<2 cm) (21.2%), no pulmonary disease (56.2%), no extracranial disease (24.1%), and had good performance status: findings consistent with previous reports [13,14,16,18,30]. The patients with these favorable clinical factors were considered to be good candidates for aggressive treatment of brain metastases.

Most of the patients were treated with cranial surgery, radiotherapy, chemotherapy, and combinations of these, which are consistent with previous reports on brain metastases from gynecologic malignancies [13,15,18,24,31–33]. The relatively small numbers of cases with brain metastasis from gynecologic malignancies described until now in the literature have precluded any conclusions being drawn about the optimal therapeutic management of these patients. It has been considered that the surgical removal and/or cranial radiotherapy are good options in patients with brain metastases when the systemic disease is controlled [13,15]. Stereotactic radiosurgery as well as the whole-brain radiotherapy has been used for treating these patients [10,34,35]. Whereas, brain metastases from ovarian cancer are responsive to chemotherapy [27,33]. Therefore, multimodal treatments may provide better results in the selected patients who may profit from effective local tumor control in the brain [19,31,33].

The prognoses of brain metastasis from gynecologic malignancies are very poor. Previous studies have reported the median survival after diagnosis of brain metastases from ovarian cancer was 6 to 7 months, and only a few patients survive for more than 1 year [26,27,30,31,36]. Cohen et al. [31] reported that the survival rates of patients at 1 and 5 years of follow-up were 31% and 5%, respectively. However, recent reports have demonstrated a longer median survival time up to 23 months for patients with brain metastases from ovarian cancer [10,18,31,37], findings compatible with the results of the present study. Multivariate analysis revealed KPS >70, single brain metastasis, absence of extracranial disease, and treatment by cranial surgery, cranial radiotherapy, and chemotherapy to be independent favorable prognostic factors for overall survival. RPA has served as the traditional means to determine prognosis for patients [38], focusing on the important prognostic variables of age, performance status, control of the primary site, and presence of other extracranial metastases. However, we could find no correlation between RPA score and prognosis of brain metastases from gynecologic malignancies. Meanwhile, it has been demonstrated that aggressive treatment with SRS, total radiation dose, single brain metastasis, presence of extracranial disease, sensitivity to platinum, clinical presentation, age, performance status, KPS score, and RPA score are significant prognostic factors for brain metastasis from ovarian cancer [10,13,14,18,20,32,36,37,39]. Most interestingly, statistical analysis also demonstrated that brain metastases from ovarian cancer had a better prognosis than that from corpus cancer and cervical cancer.

In the present study, all histologic sub-types in each group of patients were included for the analysis. It is considered that the natural course of disease and its spread varies among these histologic sub-types and raises the possibility of bias due to potentially different responses to therapy. Further detailed study with sub-division by histology is necessary to elucidate this point.

In conclusion, this multi-institutional retrospective study was undertaken to evaluate the clinicophathological characteristics of brain metastases from gynecologic malignancies. Using multivariate analysis to evaluate the prognostic factors associated with overall survival, we found that KPS >70, single brain metastasis, absence of extracranial disease, and treatment by cranial surgery, cranial radiotherapy, and chemotherapy were independent favorable prognostic factors. It is considered that aggressive multimodal therapy is warranted in the treatment of brain metastases from gynecologic malignancies in carefully selected patients [24]. The present study may provide a platform for the discussion of management strategies in these rare clinical scenarios.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2012.11.001.

Conflict of interest statement

The authors have declared no conflicts of interest.

Acknowledgments

We are indebted to Dr. Yoshiaki Yamamoto, Department of Obstetrics and Gynecology, Takeda General Hospital, Dr. Atsushi Arakawa, Department of Obstetrics and Gynecology, Nagoya City University, Graduate School of Medicine, Dr. Nobuko Nishioka, Department of Obstetrics and Gynecology, Koshigaya Municipal Hospital, Dr. Naoto Furukawa, Department of Obstetrics and Gynecology, Nara Medical University, Dr. Fumitaka Numa, Department of Obstetrics and Gynecology, Tokuyama Central Hospital, Dr. Hiroshi Tsubamoto, Department of Obstetrics and Gynecology, Hyogo College of Medicine, Dr. Kyoko Shirota, Department of Obstetrics and Gynecology, Faculty of Medicine, Fukuoka University, Dr. Hideo Fujimoto, Department of Obstetrics and Gynecology, JA Hiroshima General Hospital, Dr. Hiroko Nakamura, Department of Obstetrics and Gynecology, Kure Medical Center, Dr. Kyoko Kasahara, Department of Obstetrics and Gynecology, Takeda General Hospital, Dr. Yoshio Itani, Department of Obstetrics and Gynecology, Nara Prefectural Nara Hospital, Dr. Masumi Okada, Department of Obstetrics and Gynecology, Naruto Hospital, and Dr. Kazuhiko Ogawa, Department of Radiology, University of Ryukyus School of Medicine, for the registration of patients and Dr. Kentaro Kai, Department of Obstetrics and Gynecology, Faculty of Medicine, Oita University for the statistical analysis.

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