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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

Gregory M. Gressel, MD, Lisbet S. Lundsberg, PhD, Gary Altwerger, MD, Tasleem Katchi, MD, Masoud Azodi, MD, Peter E. Schwartz, MD, and Elena S. Ratner, MD

Objective: The reported incidence of brain metastasis from epithelial ovarian cancer (EOC), endometrial cancer (EC), and cervical cancer (CC) is exceedingly rare. As the long-term survival for patients with gynecologic cancer increases, there has been a corresponding increase in the number of diagnosed intracranial metastases. We seek to report our experience with managing brain metastatic disease (BMD) in patients with gynecologic cancer.
Methods: A retrospective review of all patients with EOC, EC, and CC at our institution revealed 47 patients with concurrent BMD between 2000 and 2013. Demographic data, risk factors, treatment modalities, progression-free data, and overall survival data were collected.
Results: Median survival time in patients with brain metastasis from EOC, EC, and CC was 9.0, 4.5, and 3.0 months, respectively. Two-year overall survival rates were 31.6%, 13.6%, and 0%, respectively. Patients received surgery, radiation therapy alone, palliative care, or radiation plus surgery. Radiation combined with surgical resection resulted in a significant hazards ratio of 0.36 (95% confidence interval, 0.15–0.86), compared with radiation alone.
Conclusions: Our report provides a large single-institution experience of brain metastases from gynecologic cancer. Patients with BMD have poor prognoses; however, treatment with multimodal therapy including surgical resection and radiation may prolong overall survival.

Key Words: Gynecologic cancer, Ovarian cancer, Endometrial cancer, Cervical cancer, Brain metastasis

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Brain metastases from gynecologic malignancies are very rare occurrences. However, as long-term survival from gynecologic cancer improves with better chemotherapy and therapeutic modalities, there has been a corresponding increase in the incidence of diagnosed brain metastases from these diseases.[1,2] The observed increase can be attributed better treatment regimens, improvement in survival, and better imaging modalities.[3–6]

Once the diagnosis of brain metastatic disease (BMD) is made, the reported prognosis of these patients is poor. Without

Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven CT.

Address correspondence and reprint requests to Gregory M. Gressel, MD, Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, PO Box 208063, New Haven, CT 06520–8063. E-mail: gregory.gressel@gmail.com.

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treatment, survival has been described to be 0.5 to 2 months.[7–9] Multimodal approach with whole-brain radiation therapy (WBRT), chemotherapy, and surgical resection is associated with improved survival, particularly in the setting of solitary lesions and controlled extracranial disease.[7–9] Stereotactic radiosurgery including γ-knife radiosurgery (GKRS) has emerged as a promising treatment option. However, data regarding optimal treatment strategy for BMD was limited. In addition, the influence of prognostic factors such as age, grade, histology, and the period of latency between detection of the primary cancer and brain metastases on optimal treatment plan and its outcome remains unclear. The present study was undertaken to evaluate prognostic factors and treatment strategies that will improve overall survival of patients with BMD from pelvic cancer.

MATERIALS AND METHODS

Patients enrolled in our study were diagnosed with brain metastases from gynecologic malignancy at Yale New Haven Hospital between January 2000 and December 2013. A retrospective review of the Yale Tumor Registry was performed to identify appropriate patients. To identify appropriate patients, *International Classification of Diseases, Ninth Revision* codes for endometrial, cervical, and ovarian cancer were cross-matched with the *International Classification of Diseases, Ninth Revision* code for brain metastasis. Inclusion criteria included tissue-confirmed diagnosis of epithelial ovarian cancer (EOC), endometrial cancer (EC), or cervical cancer (CC) with concomitant evidence of brain metastases as diagnosed by computed tomography, magnetic resonance imaging, or positron emission tomography-computed tomography. Exclusion criteria included presence of peritoneal, vulvar or vaginal cancer, and dual primary or uncertain primary cancer. The medical records of these patients were reviewed under approval from the Yale University institutional review board.

A retrospective chart review was performed to obtain significant deidentified patient data including age at initial diagnosis, patient race, cancer stage, tumor histology, number of brain lesions, latency of diagnosis of brain metastases from initial cancer diagnosis, symptoms present at diagnosis, presence or absence of extracranial disease, and treatment modality. Treatment was categorized as surgery only, radiation only, surgery combined with postoperative radiation, or palliative care alone (no treatment). Survival was calculated from time of initial diagnosis of BMD until date of death or last contact.

Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC). Descriptive data are presented as median (SD), and median survival times are presented for cancer type and treatment. Kaplan-Meier survival curves were generated to evaluate survival functions and corresponding log-rank and Wilcoxon tests for homogeneity over data strata for treatment, type of cancer, and prognostic variables of interest. Cox proportional hazards modeling was performed to generate both unadjusted and adjusted hazards ratios (HRs) for treatment and corresponding 95% confidence intervals (CIs). *P* values less than 0.05 were considered to indicate statistical significance.

RESULTS

Forty-seven patients met the aforementioned criteria and were included in the analysis. Most patients had EC (46.8%) followed by EOC (40.4%) and CC (12.8%). The mean age at diagnosis for EC was 56.6 (8.5) years, for EOC was 61.2 (10.0) years, and for CC was 52.2 (15.4) years. Most patients were white (Table 1).

More than half of patients presented with stage IV cancer, regardless of primary tumor location (Table 1). The predominant histology for EOC was serous adenocarcinoma (78.9%), for EC was endometrioid adenocarcinoma (59.0%), and for CC was squamous cell carcinoma (50.0%; Table 1). Patients with CC presented with BMD later than patients with EOC or EC. Time from initial cancer diagnosis to brain metastases was 22.7 (20.7) months for the EOC group, 9.5 (14.6) months for the EC group, and 42.5 (44.4) months for the CC group. Most patients had multiple brain lesions at diagnosis; however, survival was not significantly greater with patients who had single lesions compared with multiple lesions (Table 2).

Eighty-nine percent of patients in all groups presented with symptoms. The most common presenting symptoms were headaches, slurred speech, ataxia, weakness, and seizures. Most patients presented with significant extracranial disease rather than isolated brain metastases (68.4%, 77.2%, and 100% for

TABLE 1. Demographics, stage of disease, and tumor histology of patients with BMD classified by primary tumor location

	EOC	EC	CC
Total no. patients, n (%)	19 (40.4)	22 (46.8)	6 (12.8)
Race, n (%)			
White	17 (89.5)	14 (63.6)	6 (100)
Asian	0	4 (18.2)	0
Hispanic	1 (5.3)	2 (9.1)	0
Black	1 (5.3)	2 (9.1)	0
Stage, n (%)			
I	1 (5.3)	1 (4.5)	1 (16.7)
II	2 (10.5)	2 (9.1)	1 (16.7)
III	6 (31.6)	6 (27.3)	0
IV	10 (52.6)	12 (54.5)	3 (50)
Not described	0	1 (4.5)	1 (16.7)
Tumor histology			
Serous adenocarcinoma	15 (78.9)	4 (18.2)	
Clear cell adenocarcinoma	2 (10.5)		
Endometrioid adenocarcinoma		13 (59.0)	
Endocervical adenocarcinoma			1 (16.7)
Squamous cell carcinoma		1 (4.5)	3 (50)
Adenosquamous carcinoma		1 (4.5)	2 (33.3)
Leiomyosarcoma		1 (4.5)	
Carcinosarcoma		2 (9.1)	
Not described	2 (10.5)		

TABLE 2. Clinical characteristics of patients with brain metastases

	EOC	EC	CC
Age at diagnosis, mean (SD), range, y	61.2 (10.0), 43–78	56.6 (8.5), 43–72	52.2 (15.4 (47–77)
Latency from initial diagnosis to BMD, mean (SD), range, mo	22.7 (20.7), 0–80	9.5 (14.6), 0–80	42.5 (44.4), 1–116
Symptoms present at diagnosis, n (%)	18 (94.7)	19 (86.4)	5 (83.3)
Multiple lesions, n (%)	11 (57.8)	14 (63.6)	5 (83.3)
Single lesions, n (%)	8 (42.1)	8 (36.3)	1 (16.6)
Extracranial disease, n (%)	13 (68.4)	17 (77.2)	6 (100)
Isolated brain metastases, n (%)	6 (31.6)	5 (22.8)	0
Site of extracranial disease, n (%)			
Lung	11 (84.6)	11 (64.7)	4 (66.7)
Bone	1 (7.7)	6 (35.3)	2 (33.3)
Liver	6 (46.2)	3 (17.6)	3 (50.0)
Head and neck	0	3 (17.6)	1 (16.7)
Survival from diagnosis of BMD (range), mo	9 (0–83)	4.0 (0–123)	3 (1–22)
Survival time with single lesion (range), mo	9.5 (1–81)	4.0 (0–45)	4.0 (4–4)
Survival time with multiple lesions (range), mo	6.0 (0–83)	5.0 (0–10)	2.0 (2–22)
Survival time with advanced disease (range), mo	9.0 (1–81)	6.0 (0–123)	3 (1–22)
Survival with isolated BMD (range), mo	9.0 (0–83)	3.0 (1–30)	N/A

N/A, not applicable.

EOC, EC, and CC, respectively). Most patients in all groups had pulmonary metastases (53.1%) followed by metastases to the liver (25.5%), bone (12.8%), and head and neck (8.5%). There was no statistically significant difference in survival in patients with isolated intracranial metastases compared with those with advanced extracranial disease.

The median survival time from diagnosis of brain metastasis was 9 months for the EOC group, 4 months for the EC group, and 3 months for the CC group. Kaplan-Meier survival curves for type of cancer and survival months are presented in Figure 1; log-rank test for cancer group and survival was not significant ($P = 0.124$). Two-year overall survival was low for all groups (31.6%, 13.6%, and 0% for EOC, EC, and CC, respectively). Combined 2-year overall survival was 21.3% for all groups. With respect to treatment, 3 patients received surgery alone, 25 patients received radiation therapy alone, 12 patients underwent surgery in addition to radiation, and 7 patients received palliative care alone (no treatment; Table 3). The median survival time for treatment was 30.0 months for patients receiving surgery alone, 4.0 months for radiation therapy alone, 10.5 months for surgery + postoperative radiation, and 1.0 months for palliative care alone. Given only 3 patients received surgery alone, these data were censored and not included in the analysis, thus providing 44 observations for proportional hazards modeling. Kaplan-Meier analysis demonstrates a significant log-rank test between treatment and survival from brain metastases ($P = 0.002$; Fig. 2). After examination of all covariates and prognostic factors, only history of prior treatment with chemotherapy resulted in statistically significant effect on survival ($P = 0.0003$).

Proportional hazards modeling unadjusted for potential confounding variables and risk factors demonstrated a significant reduction in mortality for radiation combined with surgical resection compared with radiation therapy alone (HR, 0.32; 95% CI, 0.14–0.76), whereas palliative care demonstrate an increased, albeit nonsignificant, risk of mortality compared with radiation alone (HR, 1.62; 95% CI, 0.70–3.82). After controlling for prior treatment with chemotherapy, Cox proportional hazards model for radiation combined with surgical resection resulted in a 64% reduced rate of mortality when compared with radiation therapy alone (HR, 0.36; 95% CI, 0.15–0.86). Palliative care resulted in a 66% increase in mortality compared with radiation therapy alone (HR, 1.66; 95% CI, 0.70–3.92; Fig. 2). History of chemotherapy was also shown

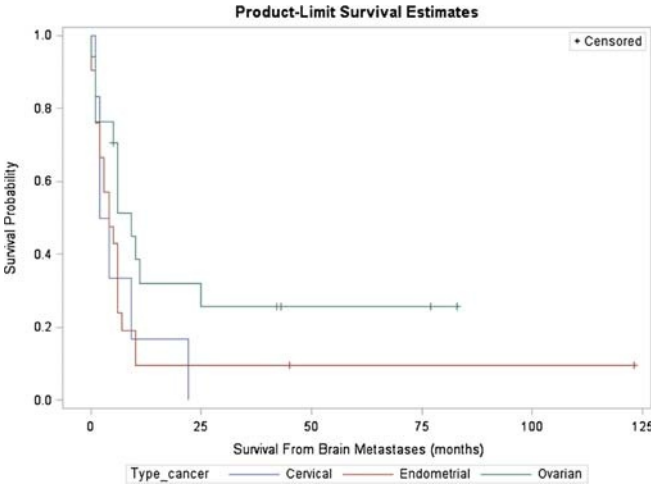

FIGURE 1. Survival curve of ovarian, uterine, and CC analyzed by Kaplan-Meier method.

TABLE 3. Treatment modality with associated survival from diagnosis of brain metastases

	EOC	EC	CC	Total
Surgical resection, n (%)*	2 (10.5)*	1 (4.5)*	0*	3 (6.4)*
Survival (range), mo*	47.0 (13–81)*	30 (30–30)*	N/A*	30.0 (13–81)*
Radiation alone, n (%)	6 (31.6)	15 (68.1)	4 (66.7)	25 (53.2)
Survival (range), mo	5.5 (0–83)	4.0 (0–123)	6.5 (2–22)	4.0 (0–123)
Surgical resection + radiation, n (%)	9 (47.4)	2 (9.1)	1 (16.7)	12 (25.5)
Survival (range), mo	11 (5–83)	26 (7–45)	2.0 (2–2)	10.5 (2–83)
Palliative care, n (%)	2 (10.5)	4 (18.2)	1 (16.7)	7 (14.9)
Survival (range), mo	1.0 (1–1)	4.0 (2–10)	1.0 (1–1)	1.0 (1–10)

*Data were censored given the few number of events.

to be an independent significant predictor of survival (HR, 0.27; 95% CI, 0.10–0.73).

DISCUSSION

Brain metastases are overall much more common than primary brain lesions and constitute the most common intracranial neoplasm in adults. Brain metastatic disease most commonly originates from the lung (50%–60%) followed by breast cancer (15%–20%) and melanoma (5%–10%).[10] Conversely, brain metastases from gynecologic cancer (other than choriocarcinoma) are exceedingly rare with incidences of 0.3% to 2.2%, 0.4% to 1.2%, and 0.3% to 0.9% for EOC, EC, and CC, respectively.[3]

Data from the present study corroborate findings presented by other studies. Ovarian cancer is known to be more likely to metastasize to the brain, followed by EC and CC.[11] Most patients present with advanced disease (stage III or IV) from EOC, EC, or CC. Patients with EOC are more likely to have serous histology, whereas data on most prominent histology for EC and CC are lacking.[12] Approximately 65% of patients will have extracranial disease and 50% will have multiple lesions.[13]

In our cohort of patients, brain metastases from EOC were more common than from EC or CC. Epithelial ovarian cancer tumors were more likely to be serous histology (78.9%), which is comparable to findings from other authors.[10,14] Most patients in all groups presented with advanced stage (stage III or stage IV) and significant extracranial disease, which is typical of BMD from pelvic cancer. Our study did not analyze performance status; however, Karnofsky Performance Status (KPS) greater than 70 has been shown by several studies to impart improved survival.[3,5,10,15–17]

Factors predictive of improved survival in BMD from gynecologic cancer include early age at diagnosis, optimal primary debulking surgery, presence of single brain lesions, absence of extracranial disease, treatment with adjuvant chemotherapy, treatment with multimodal therapy, KPS greater than 70, early-stage or low-grade tumors, and aggressive treatment.[3,7,10,15,17,18] Interestingly, our findings did not demonstrate improved survival from single brain lesions compared with multiple brain lesions. In addition, unlike other studies,[3,7,10,12,16,19,20] we did not show improved survival for patients with isolated brain metastases compared with patients with advanced extracranial disease. The discrepancy between these findings and available literature is likely related to small sample size.

Treatment options for BMD include systemic chemotherapy, WBRT, SRS with GKRS, surgical resection, corticosteroids, antiepileptics, and palliation of symptoms alone. The treatment option to be chosen by the physician should be based on tumor location, number of lesions, size of the lesions, presence of extracranial disease, and the patient's performance status.[21] Our study demonstrated that treatment with radiosurgery in addition to whole-brain radiation or craniotomy with postoperative radiation is more likely to result in significantly improved survival compared with radiation therapy alone.

Most studies resoundingly agree that aggressive treatment (surgical resection or GKRS combined with adjuvant whole-brain radiation and/or adjuvant chemotherapy) improves overall survival.[3,5,7,10,11,19,21–29] Patients with favorable characteristics (KPS >70 and age <65 years with controlled primary cancer and no extracranial metastases) are more likely to have better outcomes and are thus better dispositioned to

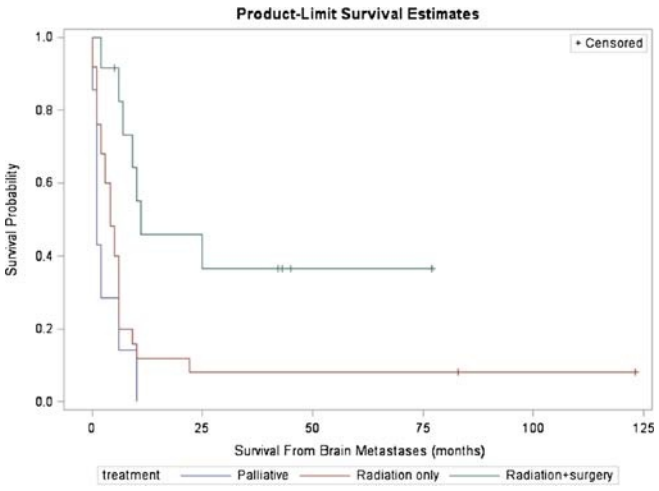

FIGURE 2. Survival curve of brain metastases treated with different treatment modalities analyzed by Kaplan-Meier method.

receive aggressive therapy such as surgical resection and adjunctive radiation.[15] This is likely the case in our cohort as well.

Although we present one of the largest retrospective series in the literature, our study is also limited by small sample size, making it difficult to draw statistically significant conclusions regarding prognostic factors. The retrospective nature of the data inherently introduces a selection bias: patients with excellent performance status are more likely to be offered aggressive treatment and therefore do better overall. This underscores the need for larger prospective randomized trials, looking at specific treatment modalities for patients with BMD from gynecologic cancer.

CONCLUSIONS

We almost have all the data regarding prognosis of patients with BMD from pelvic cancer stem from small retrospective studies. However, the reports of gynecologic cancer metastatic to the brain are increasing, likely related to improved overall survival with platinum- and taxane-based chemotherapy regimens and better imaging modalities, which pick up brain metastases in asymptomatic patients who previously may not have lived long enough to develop them. The existing data, corroborated by findings of this study, give us an idea of how to identify appropriate patients for aggressive treatment based on their stratified risk factors.

Tumor location, number of lesions, size of lesions, extracranial disease, and the patient's overall performance status should play a role in determination of appropriate therapy. Patients with small, single lesions, no extracranial disease, and excellent performance status may be candidates for surgical resection followed by postoperative radiation. Patients with multiple lesions may be better candidates for GKRS, which can target multiple lesions at once. Alternatively, patients with advanced extracranial disease or poor performance status may benefit most from WBRT alone or palliation of symptoms. Despite ominous prognosis for all patients with BMD from pelvic cancer, these retrospective data provide us with the ability to appropriately counsel patients and identify appropriate treatment strategies to prolong survival.

REFERENCES

1. Sewak S, Muggia FM, Zagzag D. Endometrial carcinoma with cerebellar metastasis: a case report and review of the literature. *J Neurooncol*. 2002;58:137–140.
2. Bruzzone M, Campora E, Chiara S, et al. Cerebral metastases secondary to ovarian cancer: still an unusual event. *Gynecol Oncol*. 1993;49:37–40.
3. Ogawa K, Yoshii Y, Aoki Y, et al. Treatment and prognosis of brain metastases from gynecological cancers. *Neurol Med Chir (Tokyo)*. 2008;48:57–62.
4. Kastritis E, Efstathiou E, Gika D, et al. Brain metastases as isolated site of relapse in patients with epithelial ovarian cancer previously treated with platinum and paclitaxel-based chemotherapy. *Int J Gynecol Cancer*. 2006;16:994–999.
5. Kim TJ, Song S, Kim CK, et al. Prognostic factors associated with brain metastases from epithelial ovarian carcinoma. *Int J Gynecol Cancer*. 2007;17:1252–1257.
6. Tay SK, Rajesh H. Brain metastases from epithelial ovarian cancer. *Int J Gynecol Cancer*. 2005;15:824–829.
7. Anupol N, Ghamande S, Odunsi K, et al. Evaluation of prognostic factors and treatment modalities in ovarian cancer patients with brain metastases. *Gynecol Oncol*. 2002;85:487–492.
8. McMeekin DS, Kamelle SA, Vasilev SA, et al. Ovarian cancer metastatic to the brain: what is the optimal management? *J Surg Oncol*. 2001;78:194–200.
9. Rodriguez GC, Soper JT, Berchuck A, et al. Improved palliation of cerebral metastases in epithelial ovarian cancer using a combined modality approach including radiation therapy, chemotherapy, and surgery. *J Clin Oncol*. 1992;10:1553–1560.
10. Nasu K, Satoh T, Nishio S, 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.
11. Monaco E 3rd, Kondziolka D, Mongia S, et al. Management of brain metastases from ovarian and endometrial carcinoma with stereotactic radiosurgery. *Cancer*. 2008;113:2610–2614.
12. Growdon WB, Lopez-Varela E, Littell R, 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;18:262–268.
13. Atallah D, Chahine G, Voutsadakis IA. Brain metastasis from ovarian cancer. *J Clin Oncol*. 2003;21:2996–2998.
14. Ratner ES, Toy E, O'Malley DM, et al. Brain metastases in epithelial ovarian and primary peritoneal carcinoma. *Int J Gynecol Cancer*. 2009;19:856–859.
15. Chen PG, Lee SY, Barnett GH, et al. Use of the Radiation Therapy Oncology Group recursive partitioning analysis classification system and predictors of survival in 19 women with brain metastases from ovarian carcinoma. *Cancer*. 2005;104:2174–2180.
16. Rades D, Fischer D, Veninga T, et al. Prognostic factors for survival and intracerebral control after irradiation for brain metastases from gynecological cancer. *Gynecol Oncol*. 2009;114:506–508.
17. Sehouli J, Pietzner K, Harter P, et al. Prognostic role of platinum sensitivity in patients with brain metastases from ovarian cancer: results of a German multicenter study. *Ann Oncol*. 2010;21:2201–2205.
18. Kumar L, Barge S, Mahapatra AK, et al. Central nervous system metastases from primary epithelial ovarian cancer. *Cancer Control*. 2003;10:244–253.
19. Cohen ZR, Suki D, Weinberg JS, et al. Brain metastases in patients with ovarian carcinoma: prognostic factors and outcome. *J Neurooncol*. 2004;66:313–325.
20. Cormio G, Maneo A, Colamaria A, et al. Surgical resection of solitary brain metastasis from ovarian carcinoma: an analysis of 22 cases. *Gynecol Oncol*. 2003;89:116–119.
21. Chung SB, Jo KI, Seol HJ, et al. Radiosurgery to palliate symptoms in brain metastases from uterine cervix cancer. *Acta Neurochir (Wien)*. 2013;155:399–405.
22. Chura JC, Shukla K, Argenta PA. Brain metastasis from cervical carcinoma. *Int J Gynecol Cancer*. 2007;17:141–146.
23. Chura JC, Marushin R, Boyd A, et al. Multimodal therapy improves survival in patients with CNS metastasis from uterine cancer: a retrospective analysis and literature review. *Gynecol Oncol*. 2007;107:79–85.
24. Lee YK, Park NH, Kim JW, et al. Gamma-knife radiosurgery as an optimal treatment modality for brain metastases from epithelial ovarian cancer. *Gynecol Oncol*. 2008;108:505–509.

25. Mahmoud-Ahmed AS, Suh JH, Barnett GH, et al. Tumor distribution and survival in six patients with brain metastases from cervical carcinoma. *Gynecol Oncol*. 2001;81:196–200.
26. Mahmoud-Ahmed AS, Suh JH, Barnett GH, et al. The effect of radiation therapy on brain metastases from endometrial carcinoma: a retrospective study. *Gynecol Oncol*. 2001;83:305–309.
27. Matsuo K, Eno ML, Ahn EH, et al. Multidrug resistance gene (MDR-1) and risk of brain metastasis in epithelial ovarian, fallopian tube, and peritoneal cancer. *Am J Clin Oncol*. 2011;34:488–493.
28. Ogino A, Hirai T, Fukushima T, et al. Gamma knife surgery for brain metastases from ovarian cancer. *Acta Neurochir (Wien)*. 2012;154:1669–1677.
29. Pothuri B, Chi DS, Reid T, et al. Craniotomy for central nervous system metastases in epithelial ovarian carcinoma. *Gynecol Oncol*. 2002;87:133–137.