

Clinical Article

Clinical Outcomes of Gamma Knife Radiosurgery for Metastatic Brain Tumors from Gynecologic Cancer : Prognostic Factors in Local Treatment Failure and Survival

Hong Kyung Shin, M.D., Jeong Hoon Kim, M.D., Ph.D., Do Heui Lee, Ph.D., Young Hyun Cho, M.D., Do Hoon Kwon, M.D., Ph.D., Sung Woo Roh, M.D., Ph.D.

Department of Neurological Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Objective : Brain metastases in gynecologic cancer (ovarian, endometrial, and cervical cancer) patients are rare, and the efficacy of Gamma Knife Radiosurgery (GKRS) to treat these had not been evaluated. We assessed the efficacy of GKRS and prognostic factors for tumor control and survival in brain metastasis from gynecologic cancers.

Methods : This retrospective study was approved by the institutional review board. From May 1995 to October 2012, 26 women (mean age 51.3 years, range 27–70 years) with metastatic brain tumors from gynecologic cancer were treated with GKRS. We reviewed their outcomes, radiological responses, and clinical status.

Results : In total 24 patients (59 lesions) were available for follow-up imaging. The median follow-up time was 9 months. The mean treated tumor volume at the time of GKRS was 8185 mm³ (range 10–19500 mm³), and the median dose delivered to the tumor margin was 25 Gy (range, 10–30 Gy). A local tumor control rate was 89.8% (53 of 59 tumors). The median overall survival was 9.5 months after GKRS (range, 1–102 months). Age-associated multivariate analysis indicated that the Karnofsky performance status (KPS), the recursive partitioning analysis (RPA) classification, and the number of treated lesions were significant prognostic factors for overall survival (HR=0.162, *p*=0.008, HR=0.107, *p*=0.038, and HR=2.897, *p*=0.045, respectively).

Conclusion : GKRS is safe and effective for the management of brain metastasis from gynecologic cancers. The clinical status of the patient is important in determining the overall survival time.

Key Words : Gynecologic cancer · Brain metastases · Gamma Knife Radiosurgery · Prognostic factor · Survival.

INTRODUCTION

Brain metastases occur in 20–40% of patients with systemic cancer, but very rarely from gynecologic cancer^{8,29-31}. The incidences of brain metastasis from ovarian, endometrial, and cervical cancer have been reported to be 0.3–2.2%, 0.4–1.2%, and 0.3–0.9%, respectively²⁵. However, the occurrence of brain metastasis from gynecologic cancer appears to have increased in recent years^{14,17,23,25}. The cause of this increase might be due to lengthening of survival times and early diagnosis^{1,14,27}. Therefore, effective and appropriate treatment is essential for these patients.

It is well known that Gamma Knife Radiosurgery (GKRS) is effective to treat metastatic brain tumors³⁶. And for brain metas-

tasis from gynecologic cancers, many different treatments have been used, including surgery, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) including GKRS, and chemotherapy. Proper multimodal therapy has improved survival in patients with brain metastasis from gynecologic cancers^{6,18,23,25}. However, in the majority of patients, treatment of brain metastasis from gynecologic cancers is palliative because the primary disease is advanced and the general condition of these patients is poor²³. Therefore, SRS has recently emerged as the preferred treatment option for these types of metastasis^{16,21,34}.

• Received : December 2, 2015 • Revised : February 21, 2016 • Accepted : April 7, 2016

• Address for reprints : Do Hoon Kwon, M.D., Ph.D.

Department of Neurological Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel : +82-2-3010-3550, Fax : +82-2-476-6738, E-mail : ykwon@amc.seoul.kr

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MATERIALS AND METHODS

Patients

This retrospective study was approved by the institutional review board, and the requirement to obtain written informed consent was waived. From May 1995 to October 2012, 26 patients with metastatic brain tumors from gynecologic cancers underwent GKRS. Gynecologic cancers include ovarian, endometrial, and cervical cancer, and these diagnoses were confirmed in our patients by pathologic examination of specimens from a biopsy or surgical resection. The diagnosis of brain metastasis was confirmed by magnetic resonance imaging (MRI).

Our series of 26 patients treated by GKRS comprised 67 lesions. However, two patients were not available for follow-up imaging. The mean age of the patients was 51.3 years (range 27–70 years). Primary cancers included ovarian cancer (14 patients, 58.3%), endometrial cancer (6 patients, 25.0%), and cervical cancer (4 patients, 16.7%). Initial symptoms of metastasis were a headache (11 patients, 45.8%), motor weakness (10 patients, 41.7%), seizure (2 patients, 8.3%), and an incidental finding (1 patient, 4.2%). The mean number of metastases was 2.46 (range 1–8). All patients were classified according to the recursive partitioning analysis (RPA) classification system of the Radiation Therapy Oncology Group (RTOG)³⁷. The mean Karnofsky performance status (KPS) score was 68.1 (range 50–90), and the RPA classification of the RTOG categorized 5 patients (20.8%) as RPA Class 1, 9 patients (37.5%) as RPA Class 2, and 10 patients (41.7%) as RPA Class 3. The mean interval from the primary site diagnosis to the brain metastasis was 42 months (range 1–168 months). The patient characteristics are summarized in Table 1.

GKRS methodology and follow-up protocol

For the GKRS, we used Leksell Gamma-Plan software. After positioning of a Leksell stereotactic frame, an MRI was performed to localize the tumor. T1-weighted MR images with gadolinium contrast enhancement were obtained from slices in the axial plane at 2-mm intervals. During the study period, dose planning was accomplished using a Leksell Gamma knife C-model from 1995 to December 2010 and using a Leksell Gamma knife Perfexion™ (ELEKTA, Stockholm, Sweden) model after January 2011. After dose planning, GKRS was performed, and the mean treated tumor volume at the time of this procedure was 8185 mm³ (range 10–19500 mm³). In addition, the median dose delivered to the tumor margin was 25 Gy (range 10–30 Gy) with a median isodose line of 50% (range 40–75%).

We performed two GKRS treatments in eight patients who had a local recurrence of tumor or multiple new metastases. At the first session, the mean treated tumor volume and the median radiation dose were 6783 mm³ (range 10–14500 mm³) and 23 Gy (range 15–28 Gy), respectively. The median interval time between the two sessions was 4.5 months (range 1–18 months). At the second session, the mean treated tumor volume and the median radiation dose were 4248 mm³ (range 180–12600 mm³) and

20 Gy (range 14–25 Gy), respectively. All patients received methylprednisolone for up to 7 days to prevent acute brain swelling after GKRS. Follow-up imaging was performed 1–3 months after

Table 1. Patient characteristics

Characteristics	No. of patients/lesions (%)
Age	
<40 years	4 (16.7)
≥40 years	20 (83.3)
Initial symptom	
Headache	11 (45.8)
Motor weakness	10 (41.7)
Seizure	2 (8.3)
Incidental finding	1 (4.2)
Pathology of the tumor	
Ovarian cancer	
Serous adenocarcinoma	9
Micropapillary serous carcinoma	1
Transitional cell carcinoma	1
Poorly differentiated carcinoma	1
Carcinosarcoma	1
Malignant mixed mullerian tumor	1
Endometrial cancer	
Endometrioid adenocarcinoma	5
Small cell carcinoma	1
Cervical cancer	
Invasive squamous cell carcinoma	2
Small cell carcinoma	2
Location of the tumor	
Frontal	4 (16.7)
Temporal	2 (8.3)
Parietal	7 (29.1)
Multiple	11 (45.8)
No. of metastases	
1	13 (54.2)
2	3 (12.5)
3	2 (8.3)
Multiple (≥4)	6 (25.0)
Extracranial metastases	
Lung	1 (4.1)
Liver	3 (12.5)
Lymph node	5 (20.8)
Bone	2 (8.3)
Multiple	7 (29.1)
None	4 (16.7)
Primary cancer treatment	
Resection+chemotherapy+RT	4 (16.7)
Resection+chemotherapy	18 (75)
Resection only	2 (8.3)
Pre-GKRS cerebral therapy	
WBRT	6
Resection	3
Ommaya reservoir insertion	7

Table 1. Patient characteristics (continued)

Characteristics	No. of patients/lesions (%)
Treated volume (mm ³)	
<5000	10 (41.6)
5000–10000	6 (25)
>10000	8 (33.3)
Radiation dose (Gy)	
<20	5 (20.8)
≥20	19 (79.2)
KPS score	
<80	15 (62.5)
≥80	9 (37.5)
RPA classification	
Class 3	10 (41.7)
Class 2	9 (37.5)
Class 1	5 (20.8)

RT : radiation therapy, GKRS : Gamma Knife Radiosurgery, WBRT : whole brain radiation therapy, KPS : Karnofsky performance status, RPA : recursive partitioning analysis

GKRS and every 3 months thereafter, depending on the patient’s medical condition.

Radiological outcome evaluation

Tumor control was evaluated by measuring the tumor volume on MRI and comparing between pre-GKRS and follow-up MRI scans. The follow-up MRI was taken at 2–3 months after GKRS, and the response was classified as a complete response (CR, tumor disappearance), partial response (PR, ≥20% tumor volume reduction), stable disease (tumor volume reduction or enlargement <20%), or tumor progression (≥20% volume enlargement). A complete response, partial response, and stable disease were indicative of tumor control. To verify that an increase in the volume of the enhancing lesions on the 2nd follow-up MRI was due to a local recurrence, we performed methionine PET and/or perfusion MRI to discriminate tumor recurrence from radiation necrosis^{38,39}. Local recurrence was defined as any secondary increase in tumor volume that had initially responded to the GKRS, and distant recurrences were defined as any newly developed metastatic lesions remotely located from previously treated lesions. Overall survival time was defined as the interval between the first GKRS and death or the last follow-up examination.

Statistical analysis

Prognostic factors affecting local tumor control and survival were estimated using Kaplan-Meier survival plots. Univariate and multivariate predictors of survival were assessed via a Cox proportional hazards model. A *p* value<0.05 was considered statistically significant. Independent variables were tested categorically and included age (cutoff value of 40 years), KPS scores (cutoff value of 80), RTOG RPA class (III vs. II or I), number of brain metastases (cutoff value of 4), presence of pre-GKRS WBRT, presence of pre-GKRS tumor resection, presence of pre-GKRS

cyst aspiration, total volume of the brain metastasis (<5000 mm³ or 5000–10000 mm³ vs. >10000 mm³), and radiation dose (cutoff value of 20 Gy). All statistical analyses were conducted using Statistical Product and Service Solution software version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

Local tumor control

Of the 26 patients who were treated with GKRS during the study period, 24 cases (59 lesions) were available for a follow-up MRI, with two patients dying prior to follow-up due to systemic disease. The mean follow-up period for all patients was 21 months (range 1–102 months). The radiological response to GKRS was classified as one of four classes depending on the tumor volume between the pre-GKRS and follow-up MRI. On MRI, a complete response occurred in 39 lesions (66.1%), a partial response in 11 lesions (18.6%), and stable disease in 3 lesions (5.1%). These three groups were classified as controlled tumors (53 lesions with 89.8%). Another six lesions (10.2%) showed tumor progression with a 4-month median time to tumor progression. This indicates that the local tumor control rate was 89.8% (53 of 59 tumors).

Five patients who had six lesions with tumor progression all expired, with the causes of death including hydrocephalus due to cerebellar metastasis (4 months after GKRS), progression of leptomeningeal seeding (29 months after GKRS), multiple brain metastasis (3 months after GKRS), and respiratory failure due to a lung metastasis (2 and 5 months after GKRS).

Local and distant recurrences

A local recurrence was confirmed to have occurred in six patients with eight lesions (18.6%), with a median time of 11 months (range 2–29 months). Five of these patients (comprising six lesions) received an additional GKRS as a local treatment. The other patient could not receive further treatment owing to a generally poor condition. A distant recurrence occurred in five patients, with a median time of 9 months (range 2–28 months). In this group, four patients received an additional GKRS. The remaining patient could not due to a poor general condition. In this group of six local recurrences and five distant recurrences, one patient had both types of recurrence. There was no radiation necrosis in these patients. In summary, within the study period, eight patients underwent multiple GKRSs for local recurrence, distant recurrence, or both. The median interval between these GKRS treatments was 4.5 months. The median overall survival of these patients was 21 months (range 5–101 months) after the 1st GKRS, which was superior to the survival outcomes in our total study population [9.5 months (range 1–102 months)] after GKRS. The mean treated tumor volume in our cohort was 6782.5 cm³ at the 1st GKRS and 4247.5 cm³ at the 2nd GKRS. The median radiation dose was 22.6 Gy at the 1st GKRS and 20 Gy at the 2nd GKRS. In these patients, there was no side effect

of repeated radiosurgery, such as radiation necrosis.

Overall survival and prognostic factors

Of the 24 patients included in our current series, six were alive at the end of the study. The overall survival rates were 82.1%, 34.7%, 13.0%, and 6.9% at 1, 6, 12, and 24 months after GKRS, respectively (Fig. 1). The median overall survival was 9.5 months after GKRS (range 1–102 months). The median overall survival

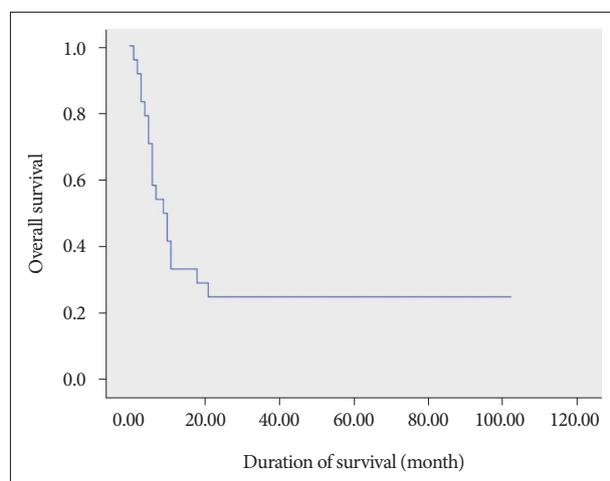


Fig. 1. Kaplan-Meier curve of overall survival outcomes after GKRS. The median survival time after GKRS was 9.5 months. The survival rates were 82.1%, 34.7%, 13.0%, and 6.9% at 1, 6, 12, and 24 months after GKRS, respectively.

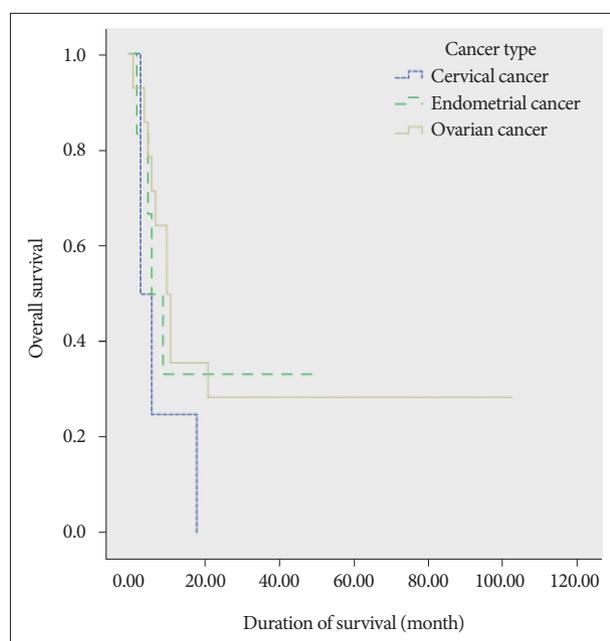


Fig. 2. Kaplan-Meier curve of overall survival after treatment of ovarian, endometrial and cervical cancer brain metastasis with GKRS. Patients with ovarian cancer had a median survival of 12 months. Patients with endometrial cancer had a median survival of 7.5 months, and patients with cervical cancer had a median survival of 3.5 months. There was no statistical significance between the groups (ovarian cancer vs. endometrial cancer, $p=0.801$, endometrial cancer vs. cervical cancer, $p=0.387$, cervical cancer vs. ovarian cancer, $p=0.129$).

for specific cancers after GKRS was 12 months (range 1–102 months) for ovarian cancer, 7.5 months (range 2–51 months) for endometrial cancer, and 3.5 months (range 1–18 months) for cervical cancer. That the cancer type is an important factor for overall survival was evident, but not statistically significant by univariate analysis [ovarian vs. endometrial, hazard risk (HR)=0.86, $p=0.801$; endometrial vs. cervical, HR=0.54, $p=0.387$; ovarian vs. cervical, HR=0.63, $p=0.129$] (Fig. 2).

By univariate analysis, we found that age (≥ 40 years), KPS score (≥ 80), and the RPA class (class 1) were significant prognostic factors for overall survival (HR=0.176, $p=0.008$, HR=0.161, $p=0.005$, and HR=0.104, $p=0.033$, respectively) and the number of treated lesions (<4) was positively associated with overall survival (HR=2.752, $p=0.052$). Age-associated multivariate analysis indicated that the KPS score (≥ 80), the RPA class (class 1), and the number of treated lesions (<4) were significant prognostic factors for overall survival (HR=0.162, $p=0.008$, HR=0.107, $p=0.038$, and HR=2.897, $p=0.045$, respectively) (Table 2, Fig. 3).

DISCUSSION

Brain metastases from gynecologic cancers

Brain metastases represent the most common type of intracranial malignancy³³. Lung cancer, renal cell carcinoma, breast cancer, and melanoma represent the majority of cases of metastatic brain tumors, and their surgical and adjuvant treatments are well described^{2,5,10}. Brain metastases from gynecologic cancers are very rare, but appear to have increased in incidence in recent years due to improved survival^{14,17,23,25}. Increased survival may be due to improved treatment modalities; 39% of patients with brain metastases are heavily treated with three or more lines of chemotherapy¹⁵, and increased diagnostic sensitivity resulting from improved cerebral imaging technology has made detecting small intracranial lesions at an earlier stage of disease recurrence possible¹³. The prognosis of brain metastasis from gynecologic cancers is generally poor. Cohen et al.⁷ reported 72 cases of brain metastases from ovarian and endometrial cancer with median survival of 6–7 months and 1–2 months after the diagnosis of brain metastases, respectively^{21,23}. Nasu et al.²³ reported a median survival of 5 months following the diagnosis of intracranial metastatic cervical cancer.

GKRS as novel alternative to surgery

In our current cases, a total of 24 patients with gynecologic cancer underwent GKRS for a brain metastasis. Fourteen of these patients had brain metastases from ovarian cancer with a median survival of 14.5 months, and six patients had brain metastases from endometrial cancer with a 7.5-month median survival and four patients had brain metastases from cervical cancer with a median survival of 5.5 months after the diagnosis of brain metastasis. And the median survival after GKRS was 12 months for ovarian cancer, 7.5 months for endometrial cancer, and 3.5 months for cervical cancer. This suggests that GKRS is an effec-

tive treatment modality for a brain metastasis from a gynecologic cancer. Differences in survival may be related to several factors. First, early detection and early treatment may affect the overall survival; with advances in MRI, small lesions can be detected and treated early which may improve survival outcomes⁴). In addition, the development of treatment modalities

with multidisciplinary approaches may contribute to an improved overall survival¹⁶). Traditionally, WBRT has been a widely used treatment for brain metastasis. At this time, however, GKRS is also a suitable alternative to surgery combined with WBRT^{3,4}). The current management of advanced stage ovarian cancer includes cytoreductive surgery followed by adjuvant chemothera-

Table 2. Prognostic factors for patient survival

Clinical characteristics	Death			
	Univariate analysis		Age-related multivariate analysis	
	Hazard ratio	p-value	Hazard ratio	p-value
Age (years)				
<40	1			
≥40	0.176	0.008		
KPS				
<80	1		1	
≥80	0.161	0.005	0.162	0.008
RPA score				
3	1	0.090	1	0.076
2	0.635	0.359	0.508	0.178
1	0.104	0.033	0.107	0.038
No. of treated lesions				
n<4	1		1	
n≥4	2.752	0.052	2.897	0.045
Pre-GKRS WBRT	1.271	0.707	1.277	0.701
Pre-GKRS resection	0.649	0.676	0.889	0.910
Pre-GKRS cyst aspiration	1.222	0.726	1.624	0.412
Treated volume (mm ³)				
<5000	1	0.749	1	0.684
5000–10000	1.454	0.551	1.744	0.389
>10000	1.442	0.495	1.132	0.818
Radiation dose (Gy)				
<20	1		1	
≥20	0.563	0.320	0.964	0.954

KPS : Karnofsky performance status, RPA : recursive partitioning analysis, GKRS : Gamma Knife radiosurgery, WBRT : whole brain radiation therapy

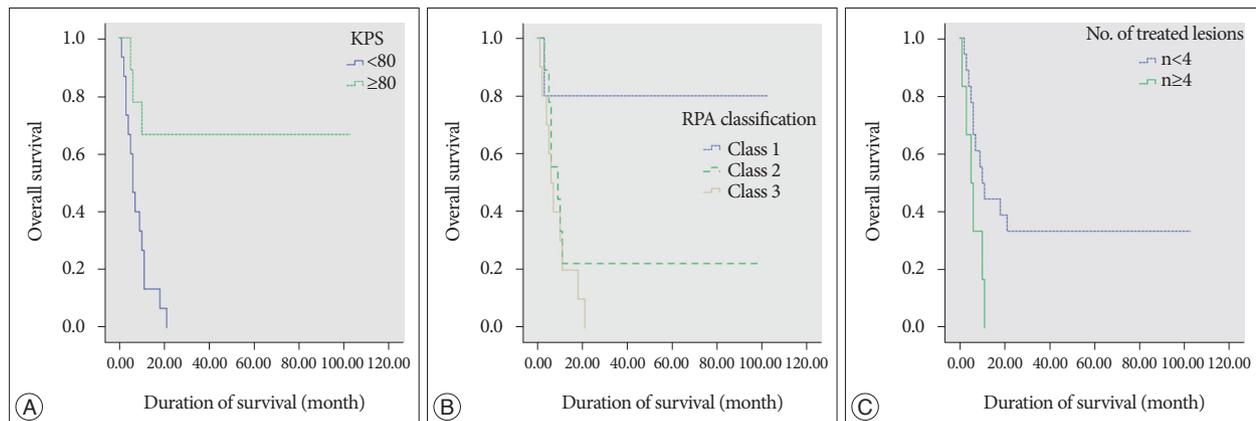


Fig. 3. A : Age-associated multivariate analysis indicated that the KPS score (≥80) was a significant prognostic factor for overall survival (HR=0.162, p=0.008). B : RPA Kaplan-Meier survival curve showed significant difference between the three classes (Class 2, HR=0.508, p=0.178, Class 1, HR=0.107, p=0.038). C : Age-associated multivariate analysis showed that the number of treated lesions (<4) was a significant prognostic factor for overall survival (HR=2.897, p=0.045).

py³). Some reports have shown that radiation therapy combined with surgery or chemotherapy is superior to radiation alone^{7,12}. Since radiation therapy can be applied instead of surgery to most patients with poor health conditions and inaccessible or multiple lesions, it has been the standard intervention for brain metastases for several decades¹⁶. Recently, stereotactic radiosurgery including GKRS has been reported to be as effective as open surgery for local tumor control^{22,35}. As a result, GKRS is being considered as an alternative to surgical resection for small metastases without a mass effect. GKRS can be used for patients with tumors in or near the eloquent cortex, with deep lesions, or at high risk from anesthesia⁴⁰.

Advantage of GKRS

GKRS has proven to be an effective therapeutic modality for the treatment of smaller solitary and multiple brain metastases because of its reduced invasiveness and its ability to target surgically inaccessible lesions and achieve local tumor control²¹. Furthermore, although there have been no direct randomized clinical comparisons of GKRS with other surgical-radiation protocols, the results we obtained in our current patients with GKRS were similar or superior to those obtained using other methods^{11,22,28}. Some earlier studies have reported the utility of GKRS for the treatment of brain metastases from gynecologic cancers (Table 3)^{3,16,19,21,24,26,32,34}. The median survival time after GKRS for patients with a brain metastasis from a gynecologic cancer ranged from 5–13 months in those studies, which is similar to the median survival time of 9.5 months in our current patients. These data collectively confirm the utility of GKRS as a treatment modality for a brain metastasis from a gynecologic cancer. Additionally, Corn et al.⁹, have reported that GKRS produced more frequent complete radiographic responses in brain metastases from ovarian cancer (40% vs. 29%) and higher 2-year survival

rates (60% vs. 15%) compared with WBRT. Therefore, novel procedures like GKRS have been employed in an attempt to improve survival.

Prognostic factors for the GKRS

However, the follow-up period after GKRS remains relatively short, and the number of patients who have undergone this procedure is still low. Understanding the prognostic indicators for GKRS for the gynecologic cancers is therefore important. Previous studies have reported that an improved performance status, single brain metastasis, and the absence of extracranial disease are associated with improved outcomes for patients with brain metastasis from gynecologic malignancies²³. With regards to endometrial cancer, three factors—high tumor grade, advanced stage of disease, and the presence of lymphovascular invasion—have been reported to be correlated with the future development of a brain metastasis²¹. In our present analysis, an older age (≥ 40 years), elevated KPS score (≥ 80), low RPA class (class 1), and small number of treated lesions (< 4) were found to be associated with improved survival outcomes in our patients with brain metastasis from a gynecologic cancer. In particular, we found that older patients may have better survival because younger patients with a brain metastasis appear have a more aggressive primary cancer. Although cancer type is generally an important factor influencing overall survival^{14,23}, we found no statistical differences between the different gynecologic cancer types in our current study, perhaps because the number of patients in our series was insufficient. We speculate therefore that the differences in survival between different primary cancers after GKRS are due to variations in the clinical course of the primary disease.

Follow-up after GKRS

MRI was used for routine follow-up in our series. However,

Table 3. Literature review of brain metastases from gynecologic cancer

Author	Number	Disease	Pre GKRS KPS score	Median margin dose (Gy)	Median tumor volume (cm ³)	Radiographic tumor control (%) (CR+PR/total number of tumors)	Survival after diagnosis of brain metastasis (months)	Survival after GKRS (months)
Ogino et al. ²⁶	16	Ovarian	80	20	9.0 (0.6–42.6)	86.4	12.5 (4–34)	9.5 (3–29)
Menendez et al. ¹⁹	9	Ovarian	-	17	4.4 (1.1–19.4)	-	-	13
Lee et al. ¹⁶	7	Ovarian	80	-	-	-	29	-
Monaco et al. ²¹	21	Ovarian	90	-	-	93.3	7	5
	6	Endometrial						
Brown et al. ³	3	Ovarian	-	20	-	-	26	-
Ratner et al. ³²	4	Ovarian	-	20	-	-	12	-
Navarro-Martín et al. ²⁴	3	Ovarian	-	15	-	-	23	-
Shepard et al. ³⁴	8	Ovarian	-	20	7.2 (0.3–17.0)	-	22 (8–41)	-
	6	Endometrial			5.3 (0.5–42.4)	-	8.3(4–16)	-
	1	Cervical						
	1	Leiomyosarcoma						

GKRS : Gamma Knife Radiosurgery, KPS : Karnofsky performance status, CR : complete response, PR : partial response

when the interpretation between radiation necrosis and tumor recurrence was difficult on the MRI scan, a methionine PET scan was used to differentiate tumor recurrence from radiation necrosis. Methionine PET proved to be an effective method to discriminate a tumor recurrence from radiation necrosis²⁰, but defined cut-off values remain to be determined and vary among previous studies. Further research is needed to utilize methionine PET as an efficient tool for differentiation. When a follow-up image showed a local recurrence or distant metastases, an additional GKRS was considered as part of the treatment for our patients. In our present study cohort, eight patients received repeated GKRS treatments due to a local recurrence, distant recurrence, or both. None of our current study patients developed a radiation-induced morbidity.

Limitation of the study

The major limitations of this study included its retrospective nature and the relatively small number of patients we examined. An uncharacterized chemotherapy regimen and heterogeneity of systemic conditions were also potential limitations of our analysis. However, our findings indicate that GKRS is a good choice of treatment for a metastatic brain tumor from a gynecologic cancer, and our findings warrant further verification.

CONCLUSION

Metastatic brain tumors from gynecologic cancers are rare but have increased in frequency in recent years. GKRS has proven to be an effective and safe treatment modality. In these cases with an older age (≥ 40 years), high KPS score (≥ 80), low RPA class (class 1), and a lower number of treated lesions (< 4) associated with better survival.

Acknowledgements

This research was supported by the Pioneer Research Center Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT, & Future Planning (NRF-2010-0019351).

References

1. Bindal RK, Sawaya R, Leavens ME, Lee JJ : Surgical treatment of multiple brain metastases. *J Neurosurg* 79 : 210-216, 1993
2. Bradley JD, Paulus R, Graham MV, Ettinger DS, Johnstone DW, Pilepich MV, et al. : Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer : promising long-term results of the Radiation Therapy Oncology Group--RTOG 9705. *J Clin Oncol* 23 : 3480-3487, 2005
3. Brown JV 3rd, Goldstein BH, Duma CM, Rettenmaier MA, Micha JP : Gamma-knife radiosurgery for the treatment of ovarian cancer metastatic to the brain. *Gynecol Oncol* 97 : 858-861, 2005
4. Chen PG, Lee SY, Barnett GH, Vogelbaum MA, Saxton JP, Fleming PA, 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* 104 : 2174-2180, 2005
5. Chi A, Komaki R : Treatment of brain metastasis from lung cancer. *Cancers (Basel)* 2 : 2100-2137, 2010

6. Chura JC, Marushin R, Boyd A, Ghebre R, Geller MA, Argenta PA : Multimodal therapy improves survival in patients with CNS metastasis from uterine cancer : a retrospective analysis and literature review. *Gynecol Oncol* 107 : 79-85, 2007
7. Cohen ZR, Suki D, Weinberg JS, Marmor E, Lang FF, Gershenson DM, et al. : Brain metastases in patients with ovarian carcinoma : prognostic factors and outcome. *J Neurooncol* 66 : 313-325, 2004
8. Cormio G, Lissoni A, Losa G, Zanetta G, Pellegrino A, Mangioni C : Brain metastases from endometrial carcinoma. *Gynecol Oncol* 61 : 40-43, 1996
9. Corn BW, Mehta MP, Buatti JM, Wolfson AH, Greven KM, Kim RY, et al. : Stereotactic irradiation : potential new treatment method for brain metastases resulting from ovarian cancer. *Am J Clin Oncol* 22 : 143-146, 1999
10. Eccles SA, Welch DR : Metastasis : recent discoveries and novel treatment strategies. *Lancet* 369 : 1742-1757, 2007
11. Flickinger JC : Radiotherapy and radiosurgical management of brain metastases. *Curr Oncol Rep* 3 : 484-489, 2001
12. Geisler JP, Geisler HE : Brain metastases in epithelial ovarian carcinoma. *Gynecol Oncol* 57 : 246-249, 1995
13. Kim TJ, Song S, Kim CK, Kim WY, Choi CH, Lee JH, et al. : Prognostic factors associated with brain metastases from epithelial ovarian carcinoma. *Int J Gynecol Cancer* 17 : 1252-1257, 2007
14. Kim YZ, Kwon JH, Lim S : A clinical analysis of brain metastasis in gynecologic cancer : a retrospective multi-institute analysis. *J Korean Med Sci* 30 : 66-73, 2015
15. Kolomainen DF, Larkin JM, Badran M, A'Hern RP, King DM, Fisher C, et al. : Epithelial ovarian cancer metastasizing to the brain : a late manifestation of the disease with an increasing incidence. *J Clin Oncol* 20 : 982-986, 2002
16. Lee YK, Park NH, Kim JW, Song YS, Kang SB, Lee HP : Gamma-knife radiosurgery as an optimal treatment modality for brain metastases from epithelial ovarian cancer. *Gynecol Oncol* 108 : 505-509, 2008
17. Mayer RJ, Berkowitz RS, Griffiths CT : Central nervous system involvement by ovarian carcinoma : a complication of prolonged survival with metastatic disease. *Cancer* 41 : 776-783, 1978
18. McMeekin DS, Kamelle SA, Vasilev SA, Tillmanns TD, Gould NS, Scribner DR, et al. : Ovarian cancer metastatic to the brain : what is the optimal management? *J Surg Oncol* 78 : 194-200; discussion 200-201, 2001
19. Menendez JY, Bauer DE, Shannon CN, Fiveash J, Markert JM : Stereotactic radiosurgical treatment of brain metastasis of primary tumors that rarely metastasize to the central nervous system. *J Neurooncol* 109 : 513-519, 2012
20. Momose T, Nariai T, Kawabe T, Inaji M, Tanaka Y, Watanabe S, et al. : Clinical benefit of 11C methionine PET imaging as a planning modality for radiosurgery of previously irradiated recurrent brain metastases. *Clin Nucl Med* 39 : 939-943, 2014
21. Monaco E 3rd, Kondziolka D, Mongia S, Niranjana A, Flickinger JC, Lunsford LD : Management of brain metastases from ovarian and endometrial carcinoma with stereotactic radiosurgery. *Cancer* 113 : 2610-2614, 2008
22. Muacevic A, Kreth FW, Horstmann GA, Schmid-Elsaesser R, Wowra B, Steiger HJ, et al. : Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. *J Neurosurg* 91 : 35-43, 1999
23. 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* 128 : 198-203, 2013
24. Navarro-Martin A, Maitz A, Manders M, Ducharme E, Chen P, Grills I : Gamma Knife radiosurgery as a primary treatment option for solitary

- brain metastases from ovarian carcinoma. *Clin Transl Oncol* 11 : 326-328, 2009
25. 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)* 48 : 57-62; discussion 62-63, 2008
 26. Ogino A, Hirai T, Fukushima T, Serizawa T, Watanabe T, Yoshino A, et al. : Gamma knife surgery for brain metastases from ovarian cancer. *Acta Neurochir (Wien)* 154 : 1669-1677, 2012
 27. Patchell RA : Brain metastases. *Neurol Clin* 9 : 817-824, 1991
 28. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. : A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 322 : 494-500, 1990
 29. Piura E, Piura B : Brain metastases from cervical carcinoma : overview of pertinent literature. *Eur J Gynaecol Oncol* 33 : 567-573, 2012
 30. Piura E, Piura B : Brain metastases from endometrial carcinoma. *ISRN Oncol* 2012 : 581749, 2012
 31. Piura E, Piura B : Brain metastases from ovarian carcinoma. *ISRN Oncol* 2011 : 527453, 2011
 32. Ratner ES, Toy E, O'Malley DM, McAlpine J, Rutherford TJ, Azodi M, et al. : Brain metastases in epithelial ovarian and primary peritoneal carcinoma. *Int J Gynecol Cancer* 19 : 856-859, 2009
 33. Schouten LJ, Rutten J, Huvneers HA, Twijnstra A : Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* 94 : 2698-2705, 2002
 34. Shepard MJ, Fezeu F, Lee CC, Sheehan JP : Gamma knife radiosurgery for the treatment of gynecologic malignancies metastasizing to the brain : clinical article. *J Neurooncol* 120 : 515-522, 2014
 35. Simonová G, Liscák R, Novotný J Jr, Novotný J : Solitary brain metastases treated with the Leksell gamma knife : prognostic factors for patients. *Radiother Oncol* 57 : 207-213, 2000
 36. Sohn MJ, Kwon Y, Kim JH, Jeon SR, Lee DJ, Kim CJ, et al. : Clinical analysis of gamma knife radiosurgery for brain metastases. *J Korean Neurosurg Soc* 28 : 649-657, 1999
 37. Tendulkar RD, Liu SW, Barnett GH, Vogelbaum MA, Toms SA, Jin T, et al. : RPA classification has prognostic significance for surgically resected single brain metastasis. *Int J Radiat Oncol Biol Phys* 66 : 810-817, 2006
 38. Terakawa Y, Tsuyuguchi N, Iwai Y, Yamanaka K, Higashiyama S, Takami T, et al. : Diagnostic accuracy of 11C-methionine PET for differentiation of recurrent brain tumors from radiation necrosis after radiotherapy. *J Nucl Med* 49 : 694-699, 2008
 39. Tsuyuguchi N, Sunada I, Iwai Y, Yamanaka K, Tanaka K, Takami T, et al. : Methionine positron emission tomography of recurrent metastatic brain tumor and radiation necrosis after stereotactic radiosurgery : is a differential diagnosis possible? *J Neurosurg* 98 : 1056-1064, 2003
 40. Vogelbaum MA, Angelov L, Lee SY, Li L, Barnett GH, Suh JH : Local control of brain metastases by stereotactic radiosurgery in relation to dose to the tumor margin. *J Neurosurg* 104 : 907-912, 2006