

Outcomes in 20 Gynecologic Cancer Patient with Brain Metastasis: A Single Institution Retrospective Study

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Background The incidence of brain metastasis (BM) in gynecologic cancers has risen recently, due to prolonged survival times and an early diagnosis. We analyzed treatment outcomes of patients with BM from gynecologic cancers.

Methods Among 951 patients with BM who were treated in neurosurgical department from July 2003 to February 2016, a total of 20 (2%) patients were from gynecologic cancers. The patients' clinical characteristics were collected by using medical records. There were 14 (66.7%) ovarian cancers, 4 (19.0%) uterine cancers, and 2 (9.5%) cervical cancers. As a primary treatment modality, 11 patients were treated with Gamma Knife surgery (GKS), 6 with surgical resection followed by whole brain radiation therapy (WBRT), and 3 with WBRT only. Overall and progression-free survival according to the primary origin and the primary treatment were analyzed.

Results Median overall survival time was 28 months, and progression-free survival was 15 months. In patients with ovarian cancer, median overall survival did not reach during the follow-up periods and progression-free survival time was 15 months. Median overall survival time in patients who received GKS as the primary treatment was 17 months and that in patients who underwent surgical resection followed by WBRT was 37.3 months ($p=0.16$). The median value of progression-free survival time in patients who received GKS as the primary treatment was 12 months and that in patients who underwent surgical resection with WBRT was 42 months ($p=0.042$). Median follow up period of over all patients was 13 months.

Conclusion BM from gynecologic cancer is rare (2%), but our findings suggest that the prognosis might not always be poor. In our small series, surgical resection with WBRT was a treatment modality significantly associated with a longer progression-free survival. Additional studies with more cases and multi-institutional cooperation are needed to determine which treatment modality leads to better outcomes.

Key Words Brain; Metastasis; Gynecology.

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INTRODUCTION

Brain metastasis (BM) develops in approximately 10% to 30% of all cancer patients and it is a common neurologic complication of lung cancer, breast cancer, and melanoma [1-3]. As for gynecologic cancer, the most common metastatic sites are

liver, lung, bones, and lymph nodes [4]. However, BM originating from gynecologic cancer is extremely rare, with the exception of choriocarcinoma, and considered as a late manifestation [5]. The incidence of BM from ovarian, endometrial, and cervical cancer has been reported to be 0.3–2.2%, 0.4–1.2%, and 0.3–0.9%, respectively [1,2]. However, the occurrence of BM in gynecologic malignancies appears to have increased in recent years, due to advances in neuroimaging such as computed tomography (CT) and magnetic resonance imaging (MRI), together with the prolonged survival of patients [1,2,6].

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Because of its rarity, only a few papers about outcome and prognostic factors of gynecologic cancer have been published, and a consensus on therapeutic guidelines has not been established [6]. Although the prognosis of BM differs according to primary tumor, general treatment principle has been alike regardless of primary cancer. Therefore, the treatment options for BM from gynecologic cancer include surgery, radiosurgery, or whole brain radiation therapy (WBRT) depending on the condition of the patients. However, the increasing incidence of BM of gynecologic cancer calls for special attention since the treatment strategy clearly affects patient prognosis [7-9]. In this study, we reviewed our experience with 20 patients who underwent treatment for BM from gynecologic cancer. We reviewed the clinical characteristics of patients, and analyzed their outcomes by primary origin and primary treatment.

MATERIALS AND METHODS

Patient populations

A retrospective review of the medical records of 951 BM patients who were treated at the Neurosurgical Department of our institution from July 2003 to February 2016 (patients who underwent treatment or management in other departments were not included) identified 20 (2%) patients originating from gynecologic cancer. BM patients with primary choriocarcinoma were excluded to create a more uniform patient population.

The medical and radiological records of those 20 patients were reviewed. Clinical variables were the type of primary cancer, therapeutic modalities, overall survival time, progression-free survival time, and the Karnofsky Performance Status (KPS) score. Each case of gynecologic cancer was staged based on the International Federation of Obstetricians and Gynecologists Staging System [10]. Outcomes according to the therapeutic modalities for the BM, that is, Gamma Knife surgery (GKS), surgical resection followed by WBRT, or WBRT only were analyzed. The study was approved by the Institutional Review Boards of Bundang Seoul National University Hospital (B-1708-417-108). The informed consent was obtained from all patients for collection of clinical data.

Selection of therapeutic modalities

Among a total of 20 patients, 6 (30%) patients underwent surgical resection followed by WBRT at initial diagnosis of BM, 11 (55%) patients received GKS, and the remaining 3 (15%) patients had WBRT only.

Clinical indications for surgery followed by WBRT in this study included single lesion, non-eloquent location of the lesion, and symptoms and signs of intractable intracranial hy-

pertension, intractable seizures, a reduced level of consciousness, or progressive neurologic deficit. Basically, neurosurgical candidates were expected to survive more than 6 months.

When the location of the lesion was critical for surgical resection (located in eloquent area) or the patient's general condition was too poor to undergo major surgery, and the number of lesions was less than 10, GKS was selected as the treatment modality. When the lesion recurred after initial treatment, and if the patient previously underwent WBRT so that the patient was unable to take another WBRT, GKS was the only treatment of choice as the second therapy.

When there were more than 10 lesions or the general condition of the patient was too poor, WBRT was selected as the initial treatment modality. And even if the number of the lesions were less than 10, when the size of the lesion was too large to take GKS (larger than 3 cm in maximum diameter), WBRT was selected for the optimal treatment modality.

Statistical analysis

Statistical analyses were conducted using SSPS 20.0 (IBM Corp., Armonk, NY, USA). The origin of the primary cancer, time interval between the diagnosis of primary cancer and BM, KPS score, and therapeutic modalities were regarded as candidate prognostic factors. The overall survival and progression-free survival were estimated using the Kaplan-Meier method and analyzed based on the log-rank test. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

The characteristics of 20 patients with a primary gynecologic malignancy and BM are summarized in Table 1. The mean age at time of BM diagnosis was 54.4 years (range from 28 to 76 years). The median interval time from the diagnosis of the primary gynecologic cancer to the development of BM was 28 months (range from 0 to 99 months). Fourteen (70%) patients had primary ovarian cancer, 4 (20%) had uterine cancer, and 2 (10%) patients had cervical cancer. Median follow up period of over all patients was 13 months.

Those patients who underwent surgical resection followed by WBRT were all alive during the follow-up periods. The maximal size of the lesions ranged 2.7 cm to 5.3 cm, and the average was 4.8 cm in this group. There were no major, but only minor complications such as headache or vomiting. However, 2 out of 6 patients experienced local recurrences, and the second treatments for recurred BM were also surgical resection in both cases, as there was no evidence of systemic progression.

In those patients who underwent GKS as initial treatment, the number of lesion was up to 8. Two out of 11 patients had lesions involving the eloquent areas. The maximal size of the

Table 1. Characteristics of patients with brain metastases from gynecologic cancers

No.	Age	Primary origin	Intervals to BM	Systemic status at BM diagnosis	Location	Eloquent area	Number of lesions	KPS score	1st treatment	Dose-fractionation (Gy/Fx)	Recur	Intervals to recur (months)	2nd treatment	Follow-up durations (months)	Patient status	Post treatment complications
1	50	Ovary	24	Stable	Temporoparietal	No	1	80	OP+WBRT	NA	Yes	38	OP	40.6	Alive	None
2	67	Ovary	26	Stable	Parietal	No	1	70	OP+WBRT	30 Gy/10 Fx	No	NA	NA	42	Alive	Nausea, vomiting
3	38	Cervix	99	Stable	Temporal	No	1	70	OP+WBRT	36 Gy/12 Fx	Yes	42	OP+Re-RTx	47	Alive	None
4	59	Ovary	91	Stable	Frontal	No	1	70	OP+WBRT	35 Gy/14 Fr	No	NA	NA	37	Alive	None
5	56	Ovary	22	Stable	Frontal	No	1	80	OP+WBRT	40 Gy/16 Fr	No	NA	NA	6	Alive	Nausea
6	28	Ovary	24	Stable	Frontal	No	1	80	OP+WBRT	35 Gy/10 Fr	No	NA	NA	6	Alive	Scalp pain, alopecia
7	43	Cervix	75	Progressive	Parietal	No	4	80	GKS	14 Gy, 20 Gy, 20 Gy, 24 Gy Mean: 19.5	No	NA	NA	5	F/U loss	None
8	55	Uterus	71	Progressive	Parietal	No	8	50	GKS	19 Gy, 22 Gy, 15 Gy, 19 Gy, 22 Gy, 15 Gy, 22 Gy, 22 Gy Mean: 19.5	No	NA	NA	6	F/U loss	Confusion
9	63	Ovary	35	Progressive	Cerebellum	No	3	60	GKS	20 Gy, 16 Gy, 22 Gy Mean: 19.3	Yes	4	GKS	17.3	Dead (systemic cause)	Dysmetria, headache
10	54	Uterus	0	Progressive	Frontal	No	8	80	GKS*	22 Gy, 22 Gy, 22 Gy, 20 Gy, 22 Gy, 22 Gy, 15 Gy Mean: 20.9	Yes	1	WBRT	1	Dead (systemic cause)	None
11	40	Uterus	60	Progressive	Parietal	No	6	50	GKS	15 Gy, 15 Gy, 20 Gy, 15 Gy, 20 Gy, 20 Gy Mean: 17.5	No	NA	NA	13	Dead (systemic cause)	Seizure
12	51	Ovary	51	Stable	Cerebellum	No	2	90	GKS	20 Gy, 22 Gy Mean: 21	Yes	3	GKS	20	Alive	None
13	64	Ovary	25	Stable	Temporoparietal	No	1	70	GKS	17 Gy	Yes	5	WBRT	6.5	Alive	None
14	71	Ovary	32	Stable	Parietal	No	1	70	GKS	17 Gy	Yes	12	OP+WBRT	30	Alive	None

Table 1. Characteristics of patients with brain metastases from gynecologic cancers (continued)

No.	Age	Primary origin	Intervals to BM diagnosis	Systemic status at BM diagnosis	Location	Eloquent area	Number of lesions	KPS score	1st Treatment	Dose-fractionation (Gy/Fx)	Recur	Intervals to recur (months)	2nd Treatment	Follow-up durations (months)	Patient status	Post treatment complications
15	66	Ovary	28	Stable	Basal ganglia	Yes	2	80	GKS	20 Gy; 24 Gy Mean: 22	Yes	16	GKS	2.8	Alive	None
16	60	Ovary	28	Stable	Pons	No	2	90	GKS	12 Gy; 18 Gy Mean: 14	No	NA	NA	8	Alive	None
17	76	Ovary	28	Stable	Basal ganglia	Yes	1	80	GKS	17 Gy	No	NA	NA	16	Alive	None
18	45	Ovary	54	Progressive	Frontal	Yes	2	60	WBRT	24 Gy/10 Fr	Yes	36	GKS	F/U loss	Alive	No record
19	35	Uterus	20	Progressive	Frontal	Yes	2	60	WBRT	30 Gy/10 Fr	Yes	11	GKS	28	F/U loss	Nausea, scalp pain
20	67	Ovary	22	Progressive	Frontal	Yes	10	70	WBRT	30 Gy/10 Fr	Yes	16	GKS	12	Dead	(unknown cause)

*The patient was treated by GKS in other hospital. One month after GKS, the patient was transferred to our institute and underwent palliative WBRT, because BM progressed. BM, brain metastasis; KPS, Karnofsky performance status; Gy, gray; Fx, fractionation; NA, not applicable; GKS, Gamma Knife surgery; OP, operation; Re-RTx, re-radiotherapy; WBRT, whole brain radiation therapy; F/U, follow-up

lesions ranged 0.9 cm to 4 cm, and the average was 3 cm in this group. The prescription doses of each lesion are listed in Table 1, and average of all doses was 19.2 Gy. The clinical manifestations after GKS were minor and transient: confusion, headache, dysmetria, or seizure. During the follow-up periods after GKS, 6 out of 11 patients had local recurrences, and repeated GKS were performed in 3 cases, surgical resection followed by WBRT in one, and WBRT in two, depending on the number of lesions and clinical manifestations. Two patients were lost to follow up, and 3 patients died during the follow-up periods. The causes of death were systemic aggravation (one patient with pulmonary effusion and the other with hepatic failure due to the progression of primary cancer) rather than intracranial problems.

Out of 3 patients who had WBRT only as the primary treatment, two patients had 2 lesions involving the eloquent area, and one patient had more than 10 lesions at the time of BM diagnosis and some of the lesions were near the eloquent area. The former 2 patients initially treated WBRT rather than taking GKS despite the number of lesions was only 2, because the patients decided WBRT considering their poor general condition and economic problem. In this group, all 3 patients had local recurrences eventually, and they all underwent GKS as the second treatment. One patient was lost to follow up and another patient died during follow up periods.

The information about prescribed radiation doses and fractionation is summarized in Table 1, and there were two groups-postoperative radiation group (6 patients) and WBRT only group (3 patients). Overall doses seemed higher in postoperative radiation group, but the radiation doses in that group included boost radiation to the operation site. The radiation doses which cover whole brains were almost similar between two groups.

The median overall survival time after the diagnosis of brain metastases was 28 months, and the progression-free survival time was 15 months (Fig. 1). For patients with ovarian cancer, median overall survival time did not reach during follow-up periods and the progression-free survival time was 15 months (Fig. 2). For uterus and cervix cancer patients, the number of patients was too small to analyze statistically.

According to therapeutic modality, the median overall survival time of the 11 patients who received GKS as the initial treatment was 17 months and that of the 6 patients who underwent surgical resection followed by WBRT was 37.3 months ($p=0.16$). The median progression-free survival time for patients who received GKS as the primary treatment was 12 months and that for patients who underwent surgical resection along with WBRT was 42 months ($p=0.042$) (Fig. 3). The number of patient who underwent WBRT only as the initial treatment (3 patients) was too small to analyze statistically.

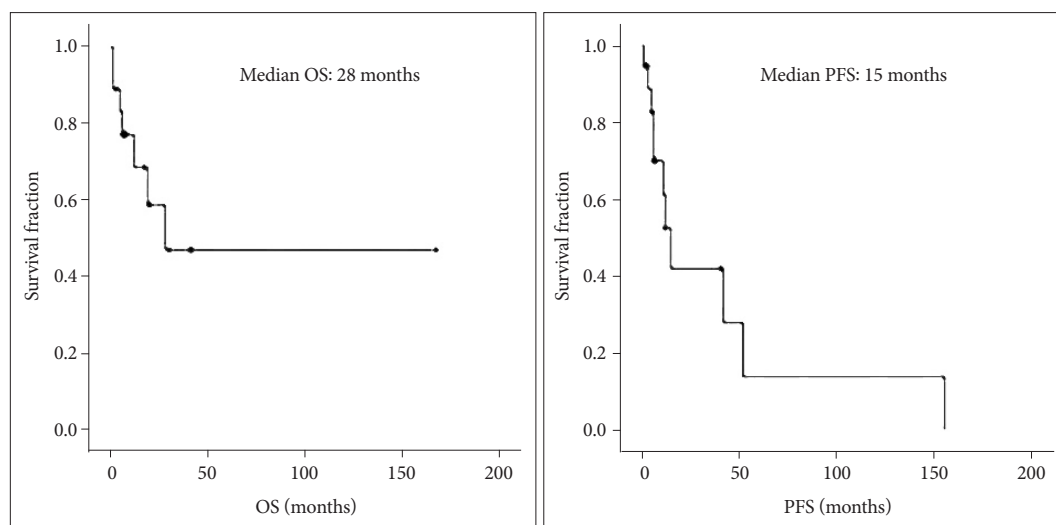


Fig. 1. The OS and PFS curve of patients with brain metastasis patients from all gynecologic cancers based on Kaplan-Meier survival estimates. OS, overall survival; PFS, progression-free survival.

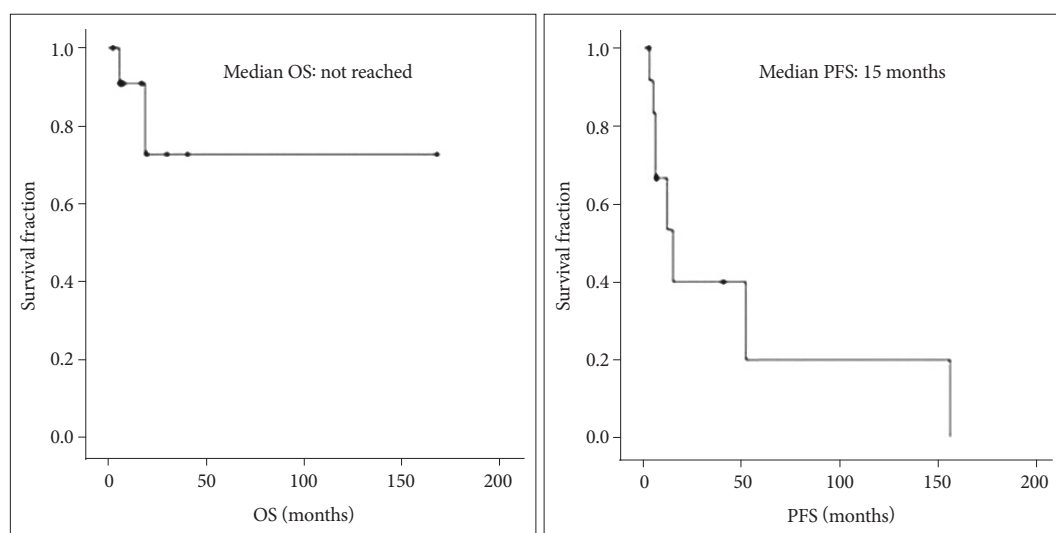


Fig. 2. The OS and PFS curve of patients with brain metastasis from ovarian cancer based on Kaplan-Meier survival estimates. OS, overall survival; PFS, progression-free survival.

DISCUSSION

BM originating from gynecologic cancer has been described as being rare in the literature. In our study, we also found the rarity: twenty out of 951 (2%) BM patients had gynecological cancer as their primary cancer. However, with increased survival times and regular screening programs, it has in fact become relatively more common than a decade ago [11].

According to the previous reports, the median overall survival time after a diagnosis of BM from ovarian cancer was 6 to 7 months [10,12,13], that from endometrial cancer was 1 to 2 months [8], and that from cervical cancer was 9.9 months [4]. However, in our study, the median overall survival time after BM diagnosis from all gynecologic cancer was 28 months.

Our study showed relatively good outcomes compared with the published reports. It might be due to the use of effective chemotherapeutics and the improvement of surgical techniques, but there was also patient selection bias [11]. Increased diagnostic sensitivity resulting from improved cerebral imaging technologies also made it possible to detect small intracranial lesions and early diagnosis during the course of disease recurrence [4,6]. In our study, surgical resection followed by WBRT is a treatment modality significantly associated with improved survivals. This finding is consistent with a previous study that aggressive and multimodality treatment methods such as neurosurgery and combination chemoradiotherapy increased the survival time for patients with gynecologic cancer and BMs.

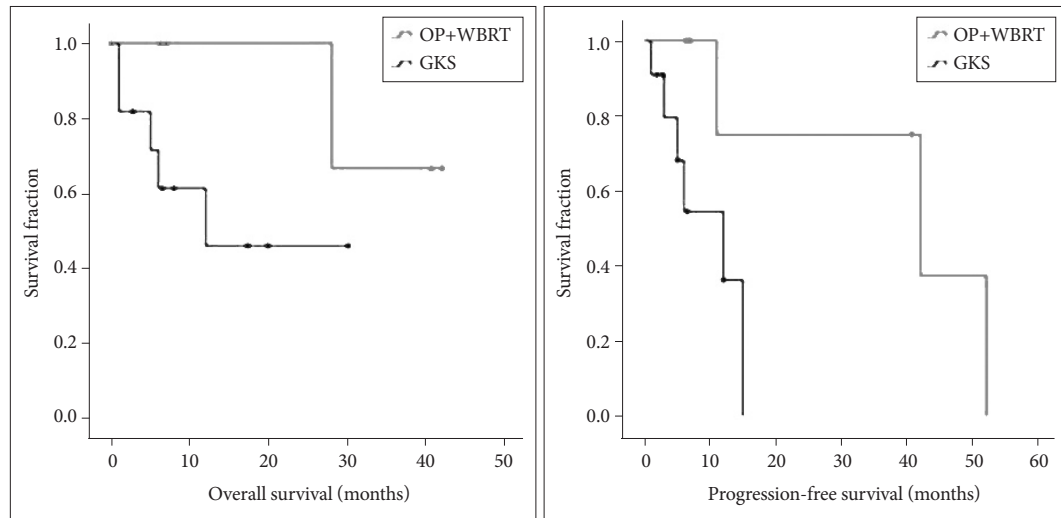


Fig. 3. A comparison of survival curves of patients with brain metastasis from all gynecologic cancers by treatment modalities. The green curve represents the patients who received surgical resection followed by WBRT and the blue curve represents the patients who received GKS as the primary treatment. WBRT, whole brain radiation therapy; GKS, Gamma Knife surgery; OP, operation.

However, these results must be interpreted carefully, because the characteristics of the patients are different among the groups by treatment modalities (Table 1). In most cases, the number and the location of the lesions determined the choice of primary treatment modality. If there were too many lesions or the location of the lesions was risky to be surgically resected (e.g., the basal ganglia, pons, and so on), GKS or WBRT were considered as the initial treatment modality.

In case of old patient, oligometastases, or critical location of the lesion, surgical resection is not usually indicated and GKS could be an alternative treatment option. The outcome of GKS treatment in our study (median overall survival time of 17 months) was better than that of a previous study. In most recent study, the median overall survival time after GKS for gynecological cancer BM patients was 9.5 months [3,5]. Moreover, in our data, there were no severe complications after GKS.

Preoperative performance status (which measured in KPS score) was also related to treatment outcome. As shown in Table 1, in mortality cases, patients showed lower KPS score (which ranged 50 to 80 and the average was 65) when brain metastases were diagnosed. When the performance status of the patients at the time of diagnosis of brain metastases were not poor, that is KPS scores are 70 or more, we could choose more aggressive treatment like surgery, which led good outcomes.

There are several limitations to consider when interpreting our findings. First, there were biases in the selection of patient and primary treatment modality for BM, given the retrospective nature of this study. Second, the extracranial metastases were not considered, which could influence the outcomes.

Lastly, small number of patients is not appropriate to make a generalized consensus.

Despite these limitations, our study is worthwhile considering the rarity of BM patient from gynecologic cancer. Our study revealed that prognosis of brain metastases from gynecologic cancer is not always poor. Surgical resection followed by WBRT might be a treatment modality significantly associated with a longer survival when indicated. Further studies with a larger sample size at the multi-center or national level are necessary to provide a more comprehensive and comparative analysis.

Conflicts of Interest

The authors have no financial conflicts of interest.

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