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Clinical Article

The Usefulness of Stereotactic Radiosurgery for Radioresistant Brain Metastases

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Objective : We investigated the effectiveness of stereotactic gamma knife Radiosurgery (GKR) for radioresistant brain metastases with the impact upon histology.

Methods : Between April 2004 and May 2011, a total of 23 patients underwent GKR for 67 metastatic brain tumors from 12 renal cell cancers, 5 sarcomas and 6 melanomas. The mean age was 56 years (range, 18 to 79 years). Most of the patients were classified as the Radiation Therapy Oncology Group recursive partitioning analysis class II (91.3%). The synchronous metastasis was found in 6 patients (26.1%) and metachronous metastasis in 17 patients (73.9%). We analyzed the local control rate, intracranial progression-free survival (PFS) and overall survival (OS).

Results : The mean tumor volume for GKR was 2.24 cc and the mean prescription dose was 19.4 Gy (range, 10 to 24) to the tumor margin. Out of metachronous metastases, the median duration to intracranial metastasis was 3.3 years in renal cell cancer (RCC), 2.4 years in melanoma and 1.1 years in sarcoma (p=0.012). The total local control rate was 89.6% during the mean 12.4 months follow-up. The six-month and one-year local control rate was 90.2% and 83% respectively. Depending on the pathology, the control rate of RCC was 95.7%, sarcoma 91.3% and melanoma 80.5% during the follow-up. The common cause of local failure was the tumor bleeding in melanoma. The median PFS and OS were 5.2 and 8.4 months in RCC patients, 6.5 and 9.8 months in sarcoma, and 3.8 and 5.1 months in melanoma.

Conclusion : The GKR can be one of the effective management options for the intracranial metastatic tumors from the radioresistant tumors. The melanoma showed a poor local control rate compared to other pathologies because of the hemorrhage.

Key Words : Intracranial · Metastasis · Radioresistant · Renal cell cancer · Sarcoma · Melanoma.

INTRODUCTION

Previous studies have reported that the patients with metastatic brain tumors have the average survivals of 5 to 8 weeks in medical palliation regimens, 4 to 7 months after whole brain radiotherapy (WBRT), and 9 to 19 months only in selected groups of patients with favorable prognostic factors, treated with combined surgery and radiotherapy[4,6,7,10,11]. Gamma knife radiosurgery (GKR) gives the advantages of minimal invasiveness, a substantial reduction of hospitalization time and an excellent local rate of control[9,15].

Cancers such as renal cell carcinoma, melanoma and sarcoma have been labeled 'radioresistant' due to the fact that they do not respond to conventional fractionated radiation therapy[2]. Therefore, the value of low-dose WBRT has been questioned as the treatment for metastatic brain tumors from radioresistant histologies[17]. The unsatisfactory results with WBRT suggest that more aggressive approaches, such as surgery or radiosurgery should be applied whenever possible. Several retrospective studies have reported acceptable local control rates with radiosurgery, even in the putatively radioresistant oncotype[3,8,13,16]. Out of radioresistant tumors, the median survival from the time of radiosurgery is shorter for brain metastases from a melanoma than renal cell carcinoma and the recursive partitioning analysis (RPA) class I status and renal cell carcinoma predicts a longer survival[1,13,14].

We managed the cerebral metastases from radioresistant tumors with stereotactic radiosurgery as a primary treatment for

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local brain control. In this report, we investigated the results on local tumor control, intracranial progression free survival (PFS) and overall survival (OS) with the impact of histology, and analyzed some prognostic factors related with local tumor control, intracranial PFS and OS.

MATERIALS AND METHODS

Between April 2004 and May 2010, total of 23 patients with 67 brain metastases from sarcoma, melanoma or renal cell cancer underwent gamma knife radiosurgery (GKR) at our hospital with the Leksell gamma knife (Elekta Instruments, Inc., Norcross, GA, USA). The institutional review board of our hospital approved this study. The patient characteristics, treatment parameters, and any available clinical and neuroimaging follow-up were retrospectively analyzed. The single variables were : the detection of intracranial metastasis (synchronous, metachronous), histological diagnosis (renal cell cancer, sarcoma, and melanoma), number of tumors (five or more, one to four tumors), individual tumor volume (10 cc or more, less than 5 cc, between them), total radiation volume (10 cc or more, less than 10 cc), prescription dose (18 Gy or more, less than 18 Gy), tumor location (supratentorial, infratentorial), additional brain treatment and systemic treatment. The Radiation Therapy Oncology Group (RTOG) prognostic classes for brain metastases using a RPA which uses a three-class system for the future stratification and reporting of brain metastases was proposed; class I : patients with Karnofsky performance status (KPS) ≥70, less than 65 years of age with controlled primary and no extracranial metastases; class III : KPS <70; class II : all others[5].

The procedure began with a rigid fixation of an MRI compatible Leksell stereotactic frame (model G, Elekta Instruments, Atlanta, GA, USA) to the patient's head using local anesthetic scalp infiltration (1% lidocaine). For stereotactic targeting a 3-D volume acquisition MRI using contrast-enhanced spoiled-Gradient Recalled Acquisition in Steady State images were acquired. All patients had intracerebral tumors which showed contrast enhancement. A highly conformal and selective dose plan (Leksell Gamma Plan®) was created. Dose of 16-24 Gy to the edge of the tumor were prescribed to all lesions except one lesion on orbital apex. The tumor edge isodose lines ranged from 40% to 70%. All patients received an intravenous dose of 40 mg of methylprednisolone at the conclusion of the procedure. The patients were observed for several hours and then discharged the next day. After GKR, all patients were followed with serial contrast enhanced MRI scans, which were requested at every 3-month.

OS was calculated from the date of the patients first GKR until death or until the latest follow-up. Local and distant recurrence was calculated from the time of the initial GKR. The 'local' was defined as the recurrence of any of the brain metastasis at the same site as the original GKR-treated lesion. Local control of lesions was assessed radiologically combined with clinical data. Local progression was defined when a 25% increase in size of the maximum diameter without further treatment on the brain. The 'distant' was defined as any new brain metastasis in a location distant from the original treated tumor. The intracranial PFS was calculated from the date of the patients first GKR until the local or distant recurrence. We defined the median range as the follow-up length and determined the effects of single variables on local control, intracranial PFS and OS via univariate and/or multivariate analyses. The single variables were age, histological diagnosis, systemic disease status, the RTOG-RPA class, number of tumors, tumor location, prescription dose, tumor volume, additional brain treatment and systemic treatment. We calculated the survival probability using the Kaplan-Meier method, performing comparisons with the log-rank test. We examined variables in the proportional hazard analysis (Cox model), to identify the independent predictors of survival. All statistical analyses were performed at a significance level of $p<0.05$, using the statistical package SPSS 15.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics

A total of 23 patients underwent GKR for metastatic brain tumors from 12 renal cell cancers, 5 sarcomas and 6 melanomas. The mean age was 56 years (range, 18 to 79). The number of male patients was 18 and female patients were 5. RTOG-RPA class II was found in 21 patients (91.3%) and class III in two patients (8.7%). The number of patients with total tumor volume more than 10 cc was 17. The number of patients having more than 5 tumor was 3 and less than 5 was 20. The synchronous metastases were shown in 6 patients (26.1%); histologic renal cell cancers in three, sarcomas in two and a melanoma in one. The metachronous metastases were detected in 17 (73.9%); histological renal cell cancers in nine, sarcomas in three and melanomas in five. The median duration to metachronous metastases was 2.7 (±0.246) years. Depending on the pathologies, the median duration to metachronous metastases of renal cell cancer was 3.3 (±0.894) years, melanoma 2.4 (±0.329) years and sarcoma 1.1 (±0.735) years. There was a statistical significance between them ($p=0.012$).

Local tumor control rate

The mean duration of follow-up was 12.4 months (range, 1.6-72.9). The total number of treated metastases with GKR was 67. The mean individual tumor volume was 2.24 cc (range, 0.01 to 19.4) and the mean prescription dose was 19.4 Gy (range, 10 to 24). The local control rate was 89.6% (60 out of 67 tumors) during the follow-up. Three-month, six-month, nine-month and one-year local control percentage were 97%, 90.2%, 83% and 83%, resectively.

The control rate was analyzed. In comparison according to the individual tumor volume, the control rate of the tumors with 5

cc or less was 91.2% (52 out of 57 tumors), 10 cc or less to 5 cc was 100% (7 out of 7) and more than 10 cc was 33.3%. The control rate difference between them was statistically significant in the Kaplan-Meier method (p=0.001) (Fig. 1A).

The control rate of the tumor with the prescription dose 18 Gy or more was 90.0% (45 out of 50) and the control rate of tumors prescribed with less than 18 Gy was 88.2% (15 out of 17) (p=0.708). Depending on the location, the control rate of the tumor with supratentorial location was 88.9% (56 out of 63) and infratentorial location was 100% (4 out of 4) (p=0.499). Depending on the pathology, the control rate of renal cell carcinoma was 95.7% (22 out of 23), sarcoma was 91.3% and melanoma was 80.6% (17 out of 21) (p=0.137) (Fig. 1B). Out of 4 GKR failed cases in melanoma, three cases had tumor bleedings. Multivariate analysis with Cox's regression model showed that melanoma patients were at a higher risk of poor local control than renal cell cancer patients [hazard ratio=4.596, p=0.183, 95% confidence interval (CI) : 0.488-43.323]. The tumor volume with 10 cc or more showed poor local control as compare to that with 5 cc less (hazard ratio=17.310, p=0.005, 95% CI : 2.371-126.39).

Intracranial progression-free survival and Overall survival

The rate of intracranial recurrence after GKR was 88% (18 out of total 23 patients). The median PFS including local and distant recurrence was 5.6 (±0.841) months. The three-month PFS was 85.9%, six-month PFS 21.8% and one-year PFS 21.8%. The PFS-related variables were analyzed as a univariate analysis. There was no statistical significance related with RPA class (p=0.949), local control (p=0.081), synchronous or metachronous metastasis (p=0.740), the number of metastasis (p=0.839), the total volume of metastasis (p=0.693), the pathology (p=0.179) and the radiation dose (p=0.767). When we focused on the histologic type, there was a trend toward improved median PFS for patients with renal cell carcinoma (5.2±0.223 months) and sarcoma (6.5±0.550 months) as compared with patients with melanoma (3.8±0.438 months) (p=0.179). As the management of intracranial local and distant recurrence, the second GKR was performed for nine patients, and one patient underwent the second and third GKR during follow-up periods. WBRT (total 30 Gy) was performed in three patients. However, for the other seven patients simple palliative management was performed due to the systemic aggravation or poor general clinical condition.

The median OS was 7.8 (±1.791) months. The three-month OS was 73.9%, six-month OS 56.5% and one-year OS 37.1%. The OS-related variables were analyzed as a univariate analysis. There was no statistical significance related with RPA class (p=0.247), local control (p=0.338), intracranial recurrence (p=0.100), synchronous or metachronous metastasis (p=0.510), the number of metastasis (p=0.607), the total volume of metastasis (p=0.819), the pathology (p=0.444) and the radiation dose (p=0.194). Depending on the histologic type, the median survival for patients with renal cell carcinoma was 8.4 (±7.178) months, sarcoma 9.8 (±2.149) and melanoma 5.1 (±1.898). Additional brain treatment including repeated GKR and WBRT showed the increased overall survival (16.4±9.174 months) compared with no treatment group (4.1±1.819 months, p=0.01). Systemic chemotherapy was done in 8 patients. The patients having systemic chemotherapy showed the increased overall survival (5.8±2.502 months) compared with not treatment group (9.8±8.202 months, p=0.111) without the statistical significance. There were two patients (8.7%) with the brain-related death. One patient had the leptomeningeal dissemination of melanoma and one patient showed the aggravation of multiple metastatic lesions in sarcoma.

DISCUSSION

Secondary metastatic brain tumors from primary cancer are usually occurred in the terminal stage of the cancer and considered as the most frequent intracranial tumors and their increasing incidence in cancer patients (range from 19% to 53%) have been reported in many studies[4,10,11]. In the past, the treatment of brain metastases was extremely limited to surgical manage-

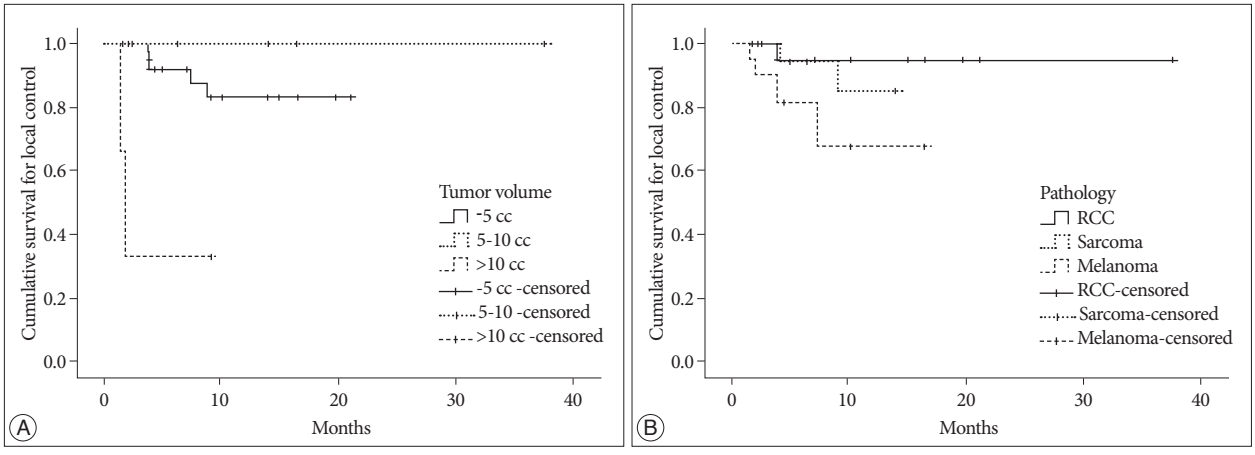

Fig. 1. A : Kaplan-Meier curve of local control rate depending on the tumor volume (p=0.001). B : Kaplan-Meier curve of local control rate depending on the pathology (p=0.137).

ment in highly selected patients only and WBRT was applied to remaining patients[12,13]. The incidence of brain metastases has been escalating with the increase in the effectiveness of systemic chemotherapy and better local/regional tumor control due to contemporary surgery and radiotherapy[12].

Once the brain metastases occur, it is considered as a negative prognostic sign with poorer systemic condition. The prognostic factors of secondary metastatic brain tumors are Karnofsky Performance Scale (KPS) score, status of systemic disease, histological diagnosis, and total intracranial tumor volume[4,5,12]. Several procedures, such as resection, WBRT, and GKR, have been applied to patients with secondary brain metastatic tumors for local tumor control. Stereotactic radiosurgery gives the advantages of minimal invasiveness, with substantial reduction of hospitalization time and excellent local control rate[9,15].

Secondary brain metastatic tumors from renal cell carcinoma, sarcoma and melanoma are considered as radioresistant tumors, due to fact that they do not respond to low-dose conventional fractionated radiation therapy[2,16]. However, clinical and radiologic results of GKR in brain metastases from radioresistant tumors, such as melanoma or renal cell carcinoma, have been reported that local tumor control rates are substantially similar to those recorded in other metastatic oncotypes, whereas actuarial survival indexes are usually lower, particularly in melanoma patients[1,13,14]. The pathology of melanoma showed the poor overall survival than renal cell carcinoma and the increased frequency of intracerebral hemorrhage.

Powell et al.[13], reported that GKR is an effective treatment option for patients with radioresistant brain metastases. Even though outcomes were generally poor in their study population, the results suggested that GKS can be considered as a proper treatment option for patients with radioresistant brain metastases. Their study revealed that the KPS score, RPA class and single metastasis, but not more than 3 metastases, to be prognostic factors of overall survival. Depending on the pathology, higher rates of local tumor control were achieved for renal cell cancer in comparison with melanoma (93.6% vs. 63.0%; p=0.001). Sin et al.[16], reported on a radioresistant series including 31 patients with renal cell carcinoma (7 patients), melanoma (14 patients) and colon carcinoma (10 patients). Their local disease control was to be 7 months, and it is far superior to the median one-month survival of untreated metastatic brain tumors. The overall survival was directly related to tumor control time and inversely to the number of metastases. A smaller tumor volume had a positive association with a prolonged intracranial PFS. Clarke et al.[3], reviewed 27 patients with single brain metastasis from radioresistant histologies (renal cell carcinoma and melanoma). The 3-, 6-, 9-, 12-, and 18-months local control rates after stereotactic radiosurgery were 82.8%, 77.9%, 69.3%, 69.3%, and 55.4%, respectively. Radiologically, 7 patients had progression, 5 patients were stable, and 15 patients had shrinkage. They suggested that GKR would be a safe and feasible strategy for treatment of patients with a single radioresistant brain metastasis. Brown et al.[1], reported a radioresistant series that included 41 consecutive patients with renal cell cancer (16 patients), melanoma (23 patients), and sarcoma (2 patients) from the Mayo Clinic. The median survival time after radiosurgery was 14.2 months. On the basis of univariate analysis, only RPA class and systemic disease status were significantly associated with survival outcomes. A multivariate analysis showed that RPA class and primary histological diagnosis were independent predictors of overall survival. The Kaplan-Meier analysis of death as a result of neurological progression as the time until the event, also showed a significant difference between those patients with melanoma and those with renal cell primary tumors and that the primary renal cell carcinoma predicted longer survival.

In our study, the local control rate was 89.6% which is very comparable to results of previous studies on GKR from various other primary cancers. The control rate was statistically related with tumor volume. Depending on the pathology, the control rate of renal cell carcinoma was 95.7% (22 out of 23), sarcoma was 91.3% and melanoma was 80.6% (17 out of 21). The melanoma pathology showed a lower tumor control rate, even in small sized tumors, which was related with the tumor hemorrhage after GKR. Also, the intracranial PFS and OS of melanoma were shorter than renal cell carcinoma and sarcoma.

CONCLUSION

The GKR can be one of the effective management options for the intracranial metastatic tumors from the radioresistant tumors. The melanoma showed a poor local control rate compared to other pathologies because of the hemorrhage.

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