Efficacy and Safety of Fractionated Stereotactic Radiosurgery for Large Brain Metastases

Won Joo Jeong, M.D., Jae Hong Park, Ph.D., Eun Jung Lee, M.D., Jeong Hoon Kim, M.D., Ph.D., Chang Jin Kim, M.D., Ph.D.,
Young Hyun Cho, M.D., Ph.D.

Department of Neurosurgery, Radiosurgery Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Objective: To investigate the efficacy and safety of fractionated stereotactic radiosurgery for large brain metastases (BMs).

Methods: Between June 2011 and December 2013, a total of 38 large BMs >3.0 cm in 37 patients were treated with fractionated Cyberknife radiosurgery. These patients comprised 16 men (43.2%) and 21 women, with a median age of 60 years (range, 38–75 years). BMs originated from the lung (n=19, 51.4%), the gastrointestinal tract (n=10, 27.0%), the breast (n=5, 13.5%), and other tissues (n=3, 8.1%). The median tumor volume was 17.6 cc (range, 9.4–49.6 cc). For Cyberknife treatment, a median peripheral dose of 35 Gy (range, 30–41 Gy) was delivered in 3 to 5 fractions.

Results: With a median follow-up of 10 months (range, 1–37 months), the crude local tumor control (LTC) rate was 86.8% and the estimated LTC rates at 12 and 24 months were 87.0% and 65.2%, respectively. The median overall survival (OS) and progression-free survival (PFS) rates were 16 and 11 months, respectively. The estimated OS and PFS rates at 6, 12, and 18 months were 81.1% and 65.5%, 56.8% and 44.9%, and 40.7% and 25.7%, respectively. Patient performance status and preoperative focal neurologic deficits improved in 20 of 35 (57.1%) and 12 of 17 (70.6%), respectively. Radiation necrosis with a toxicity grade of 2 or 3 occurred in 6 lesions (15.8%).

Conclusion: These results suggest a promising role of fractionated stereotactic radiosurgery in treating large BMs in terms of both efficacy and safety.

Key Words: Fractionated stereotactic radiosurgery · Brain metastases · Cyberknife.

INTRODUCTION

Brain metastases (BMs) have been reported in up to 40% of patients with systemic cancer1(2), and the incidence of BMs is increasing due to the routine brain magnetic resonance imaging (MRI) screening and an improved outcome of systemic therapy against primary cancers. Management of BMs depends on their size, number, and location together with patient factors such as age, performance status, and primary disease status3(4). Stereotactic radiosurgery (SRS), typically delivered in a single fraction, has been shown to be effective and safe in treating BMs and, is generally indicated for a single or oligometastases <3 cm in diameter. However, the toxicity of SRS given in a single fraction is considered to outweigh the benefits of local tumor control (LTC) for large BMs >3 cm and leads to increased risks of neurological morbidity from radiation necrosis (RN)5(6,7). Although large lesions are often amenable to microsurgical resection, surgery is infeasible in cases of critical location and/or poor patient medical status.

Recently, the concept of fractionated stereotactic radiosurgery (FSRS) has emerged, and it is reportedly an effective and safe way to treat BMs, especially large lesions. Since June 2011, we adopted this approach in treating large BMs. Treatment outcomes were evaluated by the objective tumor response on MRI, patient survival and functional improvement, and radiation necrosis. Prognostic factors were also analyzed.

MATERIALS AND METHODS

Eligibility

This study was approved by the institutional review board of the Asan Medical Center. Between June 2011 and December 2013, a total of 37 patients with large BMs were enrolled according to the inclusion and exclusion criteria indicated below.

Inclusion criteria

1) Age of ≥18 years, with histologically proven solid cancer and fewer than 6 brain metastases, one of which is >3 cm in
pressure for which surgical decompression is indicated
2) Received any form of prior cranial irradiation
3) Received prior surgical resection of the targeted lesion
4) Primary hematologic malignancy, such as lymphoma or leukemia
5) Pregnant or breast-feeding patients

**Exclusion criteria**
1) Suffering from significant mass effect or raised intracranial

**Table 1. Summary of baseline patient characteristics**

| Characteristics          | No. |
|--------------------------|-----|
| No. of patients          | 37  |
| Age, median              | 60 years (range, 38–75) |
| Gender                   |     |
| Men                      | 16 (43.2%) |
| Women                    | 21 (56.8%) |
| Number of metastases     |     |
| Total                    | 79 (including 41 treated by a single fraction) |
| Median (range)           | 2 (1–6) |
| Tumor volume (cc), median (range) | 17.6 (9.4–49.6) |
| Location of metastases   |     |
| Cerebral hemisphere      | 26 (68.4%) |
| Cerebellum               | 9 (23.7%) |
| BG & diencephalon        | 3 (7.9%) |
| Primary cancers          |     |
| Lung                     | 19 (51.4%) |
| GI tract                 | 10 (27.0%) |
| Breast                   | 5 (13.5%) |
| Others                   | 3 (8.1%) |
| Status of primary cancer |     |
| Controlled               | 21 (56.8%) |
| Uncontrolled             | 7 (18.9%) |
| Newly diagnosed          | 9 (24.3%) |
| Extracranial metastases  |     |
| Present                  | 26 (70.3%) |
| Absent                   | 11 (29.7%) |
| KPS score                |     |
| ≥70                      | 30 (81.1%) |
| <70                      | 7 (18.9%) |
| RTOG-RPA class           |     |
| I                        | 7 (18.9%) |
| II                       | 23 (62.2%) |
| III                      | 7 (18.9%) |
| DS-GPA score             |     |
| ≤1.0                     | 14 (37.8%) |
| 1.5–2.5                  | 18 (48.6%) |
| ≥3.0                     | 5 (13.5%) |

BG : basal ganglia, GI : gastrointestinal, KPS : Karnofsky performance status, RTOG-RPA : Radiation Therapy Oncology Group-Recursive Partitioning Analysis, DS-GPA : Diagnosis-Specific Graded Prognostic Assessment
was applied to approximately 80% of the maximum dose with a
conformity index (CI, defined as the prescribed isodose volume
divided by the volume of tumor encompassed by the prescription
isodose volume) <1.2 and GTV coverage >99%. The median
prescription dose was 35 Gy (range, 30–41 Gy). Doses were
administered in 3 to 5 daily fractions depending on the size of
lesions; lesions <3.5 cm were treated in 3 fractions and lesions
≥3.5 cm in 5 fractions.

**Follow-up, outcome measures, and statistics**

Follow-up clinical examination and MRI were performed at
3-month intervals after treatment.

Tumor size was defined as the largest cross-sectional area at
follow-up MRI. Each lesion was measured to evaluate local tu-
mor response and graded using the MacDonald criteria.

Complete response was indicated by a complete disappearance
of all enhancing lesions on MRI, no corticosteroid use, and
clinical stability or improvement. Partial response was indicated by
>50% decrease from the baseline in perpendicular diameter
product sums of all measurable enhancing lesions on MRI,
elimination or reduction in corticosteroid dose, and clinical sta-
ility or improvement. Progressive disease was indicated by >25%
increase in perpendicular diameter product sums of all enhancing
lesions on MRI, appearance of a new lesion, or clinical deterio-
ration. Patients were considered to have stable disease if they
did not meet the qualifications for complete response, partial
response, or progression. LTC was defined as complete re-
response, partial response, or stable disease. Local failure was de-
defined as radiographic progression at the treatment site. Distant
failure was defined by the development of new BMs outside the
treatment site.

RN was assessed objectively using MRI or confirmed patho-
logically after surgical resection. The following criteria were
considered for RN: 1) increased T1 contrast enhancement lo-
cated in the irradiated area with central hypointensity and in-
creased peripheral edema, 2) substantial regression or stability
(for at least 3 months) of enhancing areas on serial follow-up
MRIs without additional treatment, or 3) absence of perfusion
within the contrast-enhancing lesion on dynamic susceptibility
contrast perfusion MRI.

All radiation toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE Version 4.0).

LTC, overall survival (OS), progression-free survival (PFS),
and RN were estimated using the Kaplan-Meier method calcu-
lated from the treatment start date to the date of events or the
last follow-up. Factors possibly affecting the outcome were test-
ed using the log-rank test for univariate analysis and the Cox
proportional hazards models with variable selection, which in-
cluded age (≥65 years vs. <65 years), gender, primary cancer
type, tumor location, tumor volume (<22 cc vs. ≥22 cc), single
vs. multiple BMs, status of primary cancer, presence of extra-
cranial metastases, pretreatment KPS score (≥70 vs. <70), ROTG-
RPA class, DS-GPA score, and prescription dose. All statistical
tests were conducted using SPSS version 21.0 (SPSS Inc., Chica-
go, IL, USA). Statistical significance was set at p<0.05.

**RESULTS**

**Objective tumor response and local tumor control**

The maximum tumor response was evaluated for 36 lesions
after exclusion of two lesions for which no follow-up images
were available. The rates of complete response, partial response,
stable disease, and progressive disease were 11.1%, 44.4%,
30.6%, and 13.9%, respectively. With a median follow-up of 10
months (range, 1–37 months), the crude LTC rate was 86.8%
and the estimated LTC rates at 12 and 24 months were 87.0%
and 65.2%, respectively (Fig. 1). Prescription dose was the only
factor affecting the LTC on univariate and multivariate analysis.

Both of the lesions treated with a prescription dose of 31 Gy de-
veloped local failure, whereas only 3 of 36 lesions with a prescrip-
tion dose of ≥35 Gy developed local failure (hazard ratio, 49.26;
95% confidence interval, 6.897–352.128; p<0.001) (Table 2).

**Survival**

The Kaplan-Meier curve for OS is shown in Fig. 2. The me-
dian OS was 16 months, and the estimated OS rates at 6, 12 and
18 months were 81.1%, 56.8%, and 40.7%, respectively. Of 21
patients who died, 10 (47.6%) died from the progression of extracranial disease, 6 (28.6%) from brain failure, and 5 (23.8%) from unknown causes. On univariate analysis, KPS score <70 (hazard ratio, 3.389; 95% confidence interval, 1.317–8.721; p = 0.011) and RTOG-RPA class III (hazard ratio, 5.26; 95% confidence interval, 1.328–20.886; p=0.018) indicated poor patient survival (Table 3, Fig. 3), although only RTOG-RPA class remained significant on multivariate analysis.

Twenty-one patients (56.8%) showed progression including distant failure in 20 patients, local failure in 5 patients, and both distant and local failure in 4 patients. The median PFS was 11 months and the estimated PFS rates at 6, 12, and 18 months were 65.5%, 44.9%, and 25.7%, respectively. The cumulative incidence function (CIF) for progression is shown in Fig. 4. Multiple BMs were associated with poor PFS (hazard ratio, 2.603; 95% confidence interval, 1.027–6.598; p=0.044) (Table 3), as 14 of

Fig. 2. Probability for overall survival.

Table 3. Prognostic factors for overall survival and progression-free survival (log-rank test)

| Prognostic factors                              | OS Hazard ratio (95% CI) | OS p value | PFS Hazard ratio (95% CI) | PFS p value |
|------------------------------------------------|--------------------------|------------|---------------------------|-------------|
| Age                                            |                          |            |                           |             |
| ≥65 years                                      | 1.015 (0.930–1.109)      | 0.732      | 1.059 (0.456–2.456)       | 0.893       |
| <65 years                                      |                          |            |                           |             |
| Gender                                         |                          |            |                           |             |
| Male                                           | 0.714 (0.302–1.690)      | 0.443      | 1.69 (0.764–3.736)        | 0.194       |
| Female                                         |                          |            |                           |             |
| Tumor volume                                   |                          |            |                           |             |
| <22 cc                                         | 1.915 (0.779–4.706)      | 0.157      | 0.687 (0.242–1.953)       | 0.482       |
| ≥22 cc                                         |                          |            |                           |             |
| Prescription dose                              |                          |            |                           |             |
| 31 Gy                                          | 0.462 (0.105–2.045)      | 0.309      | 0.322 (0.117–0.883)       | 0.026       |
| ≥35 Gy                                         |                          |            |                           |             |
| Number of metastases                           |                          |            |                           |             |
| Single                                         | 1.064 (0.447–2.533)      | 0.889      | 2.603 (1.027–6.598)       | 0.044       |
| Multiple                                       |                          |            |                           |             |
| State of primary cancer                        |                          |            |                           |             |
| Controlled                                     | 0.429 (0.149–1.235)      | 0.117      | 1.413 (0.470–4.244)       | 0.538       |
| Uncontrolled                                   |                          |            |                           |             |
| Newly diagnosed                                | 3.130 (0.975–10.051)     | 0.055      | 0.522 (0.208–1.307)       | 0.165       |
| Extracranial metastases                        |                          |            |                           |             |
| Presence                                       | 0.565 (0.206–1.552)      | 0.268      | 2.062 (0.860–4.941)       | 0.104       |
| Absence                                        |                          |            |                           |             |
| KPS score                                      |                          |            |                           |             |
| ≥70                                            | 3.389 (1.317–8.721)      | 0.011      | 0.546 (0.165–1.805)       | 0.321       |
| <70                                            |                          |            |                           |             |
| RTOG-PRA class                                 |                          |            |                           |             |
| I                                              | 1.848 (0.506–6.747)      | 0.353      | 0.799 (0.322–1.985)       | 0.629       |
| II                                             |                          |            |                           |             |
| III                                            | 5.260 (1.328–20.886)     | 0.018      | 0.462 (0.118–1.797)       | 0.265       |
| DS-GPA score                                   |                          |            |                           |             |
| ≤1                                             | 0.534 (0.220–1.300)      | 0.167      | 1.236 (0.515–2.965)       | 0.635       |
| 1.5–2.5                                        | 0.134 (0.017–1.052)      | 0.056      | 1.052 (0.274–4.031)       | 0.941       |
| ≥3                                             |                          |            |                           |             |

OS : overall survival, PFS : progression-free survival, CI : confidence interval, KPS : Karnofsky performance status, RTOG-RPA : Radiation Therapy Oncology Group-Recursive Partitioning Analysis, DS-GPA : Diagnosis-Specific Graded Prognostic Assessment
19 patients (73.7%) with multiple BMs developed progression vs. 7 of 18 (38.8%) with a single BM.

**Neurological and functional outcomes**

Preoperative focal neurologic deficits such as motor weakness and cerebellar dysfunction, improved in 12 of 17 patients (70.6%) 3 months after treatment. The KPS score improved in 20 of 35 patients (57.1%), with a mean preoperative KPS score of 74 (median, 70; range, 50–100) vs. a mean KPS score of 80.6 (median, 80; range, 50–100) 3 months after treatment ($p=0.001$) (Fig. 5).

**Radiation necrosis**

RN occurred in 6 of 38 lesions (15.8%). CIF for RN is shown in Fig. 6. The median time to RN was 10.5 months (range, 6–18 months). Five patients with RN of toxicity grade 2 were controlled with corticosteroid medication and 1 patient with toxicity grade 3 was salvaged by surgery. No factors were identified that affected the occurrence of RN.

**DISCUSSION**

Although SRS typically delivered in a single fraction has been proven to be effective and safe in treating BMs, it is not feasible for large lesions, especially those >3.0 cm, due to increased toxicity and local treatment failure. Microsurgical resection is usually indicated for large BMs, immediately decompressing the mass effect and alleviating neurological symptoms. However, not all patients with large BMs are eligible for surgery when considering surgical accessibility, the number of lesions, and patient medical status. Moreover, systemic therapy against...
primary cancers should be withheld during perioperative periods, which can be further confounded by surgical morbidity in certain cases. Alternatively, whole-brain radiotherapy (WBRT) remains palliative in nature and may influence cognitive function. Currently, the first-line treatment for large BMs has not been established and is usually determined by considering various factors, including tumor volume, number, location, and overall condition of patient.

Theoretically, fractionated administration of radiation dose potentially minimizes toxicity to late-responding healthy tissues, with a low α/β ratio compared to a single acute dose of radiation for a given level of tumor damage, according to the linear quadratic model of cellular survival. In addition, reoxygenation and redistribution of the cell cycle between dose fractions renders hypoxic tumor cells, which are abundant in large BMs compared to small tumors, more radiosensitive. As expected, recently published studies on FSRS for large BMs have demonstrated high LTC rates, ranging from 63–100%, at 1 year follow-up, with acceptable risks of toxicity.

Consistent with these results, our present LTC rates were 87.0% and 65.2% at 1- and 2-years follow-up, respectively, and the median OS was 16 months, which also compares well with the outcomes of single-fraction SRS for small BMs. Furthermore, patient performance status and neurological function improved significantly, presumably benefitting the quality of life in these cases.

The optimal dose fractionation protocol for FSRS in BMs has not yet been established. In a recent systematic review on stereotactic radiotherapy dose and LTC probability, Wiggernaad et al. reported that a biological effective dose, using an α/β ratio of 12 (BED12), of at least 40 Gy, which correspond to a single fraction dose of 20 Gy, was associated with a 1-year LTC rate of 70% or more. The high LTC rate at 1-year follow-up in our present study appears to accord with this observation. Lower LTC rates have been also associated with large BMs, with large BMs having a BED of 15 Gy. In our present analyses, which included only large BMs, the overall LTC rates observed were comparable to historic single fraction SRS for small BMs.

The LTC rates of even larger lesions in our current series (≥3.5 cm) treated with more fractions were not inferior to those of lesions <3.5 cm, indicating a promising role of FSRS in treating large BMs. Recently, Murai et al. reported that dose fractionation of 27–30 Gy in 3 fractions and 31–35 Gy in 5 fractions on consecutive days was tolerable and effective in treating large BMs. Further studies are needed to determine the optimal dose fractionation protocol, especially in relation to tumor size.

RN has been reported at a rate of 2–15% after FSRS. In our current study, RN occurred in 6 out of the 38 lesions we examined (15.8%), which falls at the upper margin of this range. This can be explained in part by a slightly higher prescription dose employed for our present cases and lack of uniform criteria for RN in different studies. Meanwhile, most of our patients with RN were controlled with corticosteroid medication, except for one instance salvaged by surgery. As the incidence of brain necrosis after SRS increases with the size of the target volume, the volume of normal brain receiving a certain threshold dose has been implicated in the development of RN, with

![Fig. 6. Cumulative incidence function for radiation necrosis.](image)

**Table 4. Recent studies on fractionated stereotactic radiosurgery for brain metastases**

| Author (year) | No. of patients | Tumor volume (cc), median | Dose/fractions | LTC rate (%) at 1 year | OS (months), median |
|---------------|----------------|--------------------------|----------------|-----------------------|-------------------|
| Higuchi et al. (2009) | 43 | 17.6 (mean) | 30 Gy/3 | 75.9 | 8.8 |
| Giubilei et al. (2009) | 30 | 4.8 | 18–32 Gy/3–4 | 86.1 | 9.2 |
| Kim et al. (2011) | 40 | 5.0 | 32–40 Gy/6 | 71.0 | 8 |
| Jiang et al. (2012) | 40 | 17.5 | 20–53 Gy/4–15 | 94.2 | 15 |
| Feuvret et al. (2014) | 12 | 29.4 | 33 Gy/3 | 100 | 16.8 |
| Minniti et al. (2014) | 135 | 10.1 | 27–36 Gy/3 | 88.0 | 14.8 |
| Murai et al. (2014) | 54 | 8–33 (range) | 27–35 Gy/3–5 | 69.0 | 6 |
| Wegner et al. (2015) | 36 | 15.6 | 12–27 Gy/2–5 | 63.0 | 3 |
| The present study | 37 | 17.6 | 30–41 Gy/3–5 | 87.0 | 16 |

LTC: local tumor control, OS: overall survival
smaller volumes having a lower risk of RN.

In line with previous studies, our multivariate analysis showed that good patient performance (KPS score ≥70) and lower RTOG-RPA class significantly predicted a better survival outcome. Gaspar et al. reported that RTOG-RPA class I cases had the best survival outcomes (median 7.1 months), whereas those of RTOG-RPA class III had the poorest survival results (median 2.3 months). Kim et al. reported that good KPS (≥70), controlled primary cancer, no extracranial metastases, lower RTOG-RPA class, higher DS-GPA score, single brain metastasis, and absence of previous WBRT were significant predictors of longer survival. Of these variables, only the number of extracranial metastatic organs was found to be a only significant predictor in our multivariate analysis. Minniti et al. previously that stable extracranial disease and a good KPS (>70) were associated with the most significant survival benefit.

FSRS is now emerging, yet controversial and not a current standard of practice in treating large BMs. This study presents additional clinical data that support the application of this approach as valid modality in terms of efficacy and safety.

CONCLUSION

FSRS is promising in treating large BMs in terms of both efficacy and safety. Further studies are needed to determine the optimal dose fractionation protocol in relation to tumor size and identify reliable prognostic factors for large BMs.

• Acknowledgements

This paper was presented at the 54th annual meeting of the Korean Neurosurgical Society, held from Oct 17 to 19, 2014.

References

1. Aoyama H, Shirato H, Onimaru R, Kagei K, Ikeda Y, Ishii N, et al.: Hypofractionated stereotactic radiotherapy alone without whole-brain irradiation for patients with solitary and oligo brain metastases using noninvasive fixation of the skull. Int J Radiat Oncol Biol Phys 56: 793-800, 2003
2. Bir SC, Ambekar S, Nanda A: Long term outcome of Gamma Knife radiosurgery for metastatic brain tumors. J Clin Neurosci 21: 2122-2128, 2014
3. Blonigen BJ, Steinmetz RD, Levin L, Lamb MA, Warnick RE, Brennan JC: Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 77: 996-1001, 2010
4. Fabrig A, Ganslandt O, Lambrechts U, Grubenbauer G, Kleint G, Sauer R, et al.: Hypofractionated stereotactic radiotherapy for brain metastases - results from three different dose concepts. Strahlenther Onkol 183: 625-630, 2007
5. Feuvret L, Vinchon S, Martin V, Lamproglou I, Halley A, Calugaru V, et al.: Stereotactic radiotherapy for large solitary brain metastases. Cancer Radiother 18: 97-106, 2014
6. Flickinger JC, Kondziolka D, Lunsford LD, Coffey RJ, Goodman ML, Shaw EG, et al.: A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. Int J Radiat Oncol Biol Phys 28: 797-802, 1994
7. Gaspar L, Scott C, Rothman M, Ashell S, Phillips T, Wasserman T, et al.: Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 37: 745-751, 1997
8. Giubilei C, Ingrasso G, D'Andrea M, Benassi M, Santoni R: Hypofractionated stereotactic radiotherapy in combination with whole brain radiotherapy for brain metastases. J Neurooncol 91: 207-212, 2009
9. Higuchi Y, Serizawa T, Naganag O, Matsuda S, Ono J, Sato M, et al.: Three-staged stereotactic radiotherapy without whole brain irradiation for large metastatic brain tumors. Int J Radiat Oncol Biol Phys 74: 1543-1548, 2009
10. Jiang XS, Xiao JP, Zhang Y, Xu YJ, Li XP, Chen XJ, et al.: Hypofractionated stereotactic radiotherapy for brain metastases larger than three centimeters. Radiat Oncol 7: 36, 2012
11. Jo KI, Im YH, Kong DS, Seol HJ, Nam DH, Lee IT: Gamma Knife radiosurgery for brain metastases from breast cancer. J Korean Neurosurg Soc 54: 399-404, 2013
12. Kalkanis SN, Kondziolka D, Gaspar LE, Burri SH, Asher AL, Colbs CS, et al.: The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 96: 33-43, 2010
13. Kim H, Jung TY, Kim JY, Jung S, Moon KS, Park SJ: The usefulness of stereotactic radiosurgery for radiosensitive brain metastases. J Korean Neurosurg Soc 54: 107-111, 2013
14. Kim YJ, Cho KH, Kim JY, Lim YK, Min HS, Lee SH, et al.: Single-dose versus fractionated stereotactic radiotherapy for brain metastases. Int J Radiat Oncol Biol Phys 81: 483-489, 2011
15. Kwon AK, Dibase SJ, Wang B, Hughes SL, Milcarek B, Zhu Y: Hypofractionated stereotactic radiotherapy for the treatment of brain metastases. Cancer 115: 890-898, 2009
16. Lee CC, Yen CP, Xu Z, Schlesinger D, Sheehan J: Large intracranial metastatic tumors treated by Gamma Knife surgery: outcomes and prognostic factors. J Neurosurg 120: 52-59, 2014
17. Mehta MP, Tsao MN, Whelan TJ, Morris DE, Hayman JA, Flickinger JC, et al.: The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys 63: 37-46, 2005
18. Minniti G, Clarke E, Lanzaetta G, Osti ME, Trasimenni G, Bozzao A, et al.: Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. Radiat Oncol 6: 48, 2011
19. Minniti G, D’Angelillo RM, Scarinci C, Trodella LE, Clarke E, Matteucci P, et al.: Fractionated stereotactic radiosurgery for patients with brain metastases. J Neurooncol 117: 295-301, 2014
20. Mow N, Ogin H, Banabe Y, Iwabuchi M, Okumura T, Matsushita Y, et al.: Stereotactic radiosurgery of 468 brain metastases ≤ 2 cm: implications for SRS dose and whole brain radiation therapy. Int J Radiat Oncol Biol Phys 81: 207-212, 2009
21. Patchell RA: The management of brain metastases. Cancer Treat Rev 29: 533-540, 2003
22. Rampino R, Crucicchihank G, Lewis AD, Fitzsimmons SA, Workman P: Direct measurement of pO2 distribution and bioreductive enzymes in human malignant brain tumors. Int J Radiat Oncol Biol Phys 29: 427-431, 1994
23. Shaw EG, Scott C, Souhami L, Dinapoli R, Klein R, Loeffler J, et al.: Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys 47: 291-298, 2000
24. Shehata MK, Young B, Reid B, Patchell RA, St Clair W, Sims J, et al.: Stereotactic radiosurgery of 468 brain metastases < or =2 cm: implications for SRS dose and whole brain radiation therapy. Int J Radiat Oncol Biol Phys 59: 87-93, 2004
25. Shibamoto Y, Yutaka Y, Tsutsui K, Takahashi M, Abe M: Variation in
the hypoxic fraction among mouse tumors of different types, sizes, and sites. Jpn J Cancer Res 77 : 908-915, 1986
26. Tomé WA : Universal survival curve and single fraction equivalent dose : useful tools in understanding potency of ablative radiotherapy : in regard to Parks et al. (Int J Radiat Oncol Biol Phys 2008;72 : 1620-1621). Int J Radiat Oncol Biol Phys 73 : 1286, 2009
27. 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
28. Wegner RE, Leeman JE, Kabolizadeh P, Rwigema JC, Mintz AH, Burton SA, et al. : Fractionated stereotactic radiosurgery for large brain metastases. Am J Clin Oncol 38 : 135-139, 2015
29. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. : Updated response assessment criteria for high-grade gliomas : response assessment in neuro-oncology working group. J Clin Oncol 28 : 1963-1972, 2010
30. Wiggenraad R, Verbeek-de Kanter A, Kal HB, Taphoorn M, Vissers T, Struijksma H : Dose-effect relation in stereotactic radiotherapy for brain metastases. A systematic review. Radiother Oncol 98 : 292-297, 2011
31. Wiggenraad R, Verbeek-de Kanter A, Mast M, Molenaar R, Kal HB, Lycklama à Nijeholt G, et al. : Local progression and pseudo progression after single fraction or fractionated stereotactic radiotherapy for large brain metastases. A single centre study. Strahlenther Onkol 188 : 696-701, 2012
32. Yang HC, Kano H, Lunsford LD, Niranjan A, Flickinger JC, Kondziolka D : What factors predict the response of larger brain metastases to radiosurgery? Neurosurgery 68 : 682-690, discussion 690, 2011
33. Yoo H, Kim YZ, Nam BH, Shin SH, Yang HS, Lee JS, et al. : Reduced local recurrence of a single brain metastasis through microscopic total resection. J Neurosurg 110 : 730-736, 2009