online © ML Comm
www.jkns.or.kr http://dx.doi.org/10.3340/jkns.2011.50.3.179
Print ISSN 2005-3711 On-line ISSN 1598-7876
J Korean Neurosurg Soc 50 : 179-184, 2011

Clinical Article

Therapeutic Effect of Gamma Knife Radiosurgery for Multiple Brain Metastases

Chul-Kyu Lee, M.D.,* Sang Ryul Lee, M.S.,* Jin Mo Cho, M.D., Kyung Ah Yang, R.N., Se-Hyuk Kim, M.D., Ph.D.
Department of Neurosurgery, Gamma Knife Center, Ajou University School of Medicine, Suwon, Korea

Objective : The aim of this study is to evaluate the therapeutic effects of gamma knife radiosurgery (GKRS) in patients with multiple brain metastases and to investigate prognostic factors related to treatment outcome.
Methods : We retrospectively reviewed clinico-radiological and dosimetric data of 36 patients with 4-14 brain metastases who underwent GKRS for 264 lesions between August 2008 and April 2011. The most common primary tumor site was the lung (n=22), followed by breast (n=7). At GKRS, the median Karnofsky performance scale score was 90 and the mean tumor volume was 1.2 cc (0.002-12.6). The mean prescription dose of 17.8 Gy was delivered to the mean 61.1% isodose line. Among 264 metastases, 175 lesions were assessed for treatment response by at least one imaging follow-up.
Results : The overall median survival after GKRS was 9.1±1.7 months. Among various factors, primary tumor control was a significant prognostic factor (11.1±1.3 months vs. 3.3±2.4 months, p=0.031). The calculated local tumor control rate at 6 and 9 months after GKRS were 87.9% and 84.2%, respectively. Paddick's conformity index (>0.75) was significantly related to local tumor control. The actuarial peritumoral edema reduction rate was 22.4% at 6 months.
Conclusion : According to our results, GKRS can provide beneficial effect for the patients with multiple (4 or more) brain metastases, when systemic cancer is controlled. And, careful dosimetry is essential for local tumor control. Therefore, GKRS can be considered as one of the treatment modalities for multiple brain metastase.

Key Words : Gamma knife radiosurgery · Metastases · Cerebral edema.

INTRODUCTION

Until now, 3 randomized controlled studies have proved the beneficial effects of stereotactic radiosurgery (SRS) in the treatment of oligometastatic brain tumors[1,2,9]. The Pittsburgh group and Radiation Therapy Oncology Group showed improved local tumor control in the SRS with whole brain radiation therapy (WBRT) group, compared to the WBRT only group, and prolonged survival in a subset of patients with a single lesion[1]. Aoyama et al.[2] reported that there was no significant difference in overall survival time and neurological deterioration between WBRT combined with SRS and SRS only. These results suggest that WBRT may be deferred until development of multiple new metastases after SRS.

However, until the present time, relatively little has been published regarding the therapeutic efficacy of SRS in the patients with multiple brain metastases[8]. Therefore, we aimed to study the therapeutic effects of SRS in patients with multiple (4 or more) brain metastases, and to investigate prognostic factors related to treatment outcomes.

• Received : June 8, 2011 • Revised : July 14, 2011
• Accepted : September 8, 2011
• Address for reprints : Se-Hyuk Kim, M.D., Ph.D.
Department of Neurosurgery, Ajou University School of Medicine
San 5, Woncheon-dong, Yeongtong-gu, Suwon 443-721, Korea
Tel : +82-31-219-5236, Fax : +82-31-219-5238
E-mail : nsksh@ajou.ac.kr
* Chul-Kyu Lee and Sang Ryul Lee are equally contributed to this paper.

MATERIALS AND METHODS

Patient characteristics

Thirty-six patients with 4 or more brain metastases underwent gamma knife radiosurgery (GKRS) for 264 lesions in our department between August 2008 and April 2011. We retrospectively reviewed the clinical records, radiological studies and dosimetric data of those patients. The mean age at the time of GKRS was 60 years (range, 36-76 years) and the mean number of brain metastases was 7 (range, 4-14). There were 18 men and 18 women. The median Karnofsky performance scale (KPS) score were 90 (range, 60-100). The primary tumor sites were the lung (n=22), breast (n=7), gastrointestinal tract (n=3), liver (n=2), kidney (n=1) and unknown (n=1). The mode of onset was synchronous in 16 (44.4%) and metachronous in 20 (55.6%). The median interval between diagnosis of brain metastases and

diagnosis of systemic cancer was 16.1 months in the metachronous type (range, 3.1-66.7). Extracranial metastases existed in 27 patients at the time of GKRS. WBRT was given in 3 patients before GKRS, and the median interval between GKRS and WBRT was 4.4 months (range, 0.9-21.3) (Table 1).

We defined "controlled primary tumor" as stable status of primary tumor without new extracranial metastases in the metachronous type, and no extracranial metastases in the synchronous type. According to our criteria, 11 patients were categorized as "controlled primary tumor" at the time of GKRS. When all patients were classified according to recursive partitioning analysis (RPA) classification[3,5], there were 3 (8.3%) of class I, 32 (88.9%) of class II and 1 (2.8%) of class III.

Among 264 brain metastases, 235 lesions were located in the supratentorial area and 29 in the infratentorial area. There was no brain stem metastasis.

Radiosurgical treatment

GKRS was performed using a Leksell Gamma Knife (Elekta Instrument, Stockholm, Sweden) model C. The planning system was a Leksell Gamma Plan version 8.3.1 (Elekta Instruments AB). For magnetic resonance (MR) imaging of radiosurgery planning, T1-weighted axial images with contrast and T2-weighted axial images were obtained with 2 mm slice thickness without gaps. Forty-five GKRS were performed in 36 patients including 9 patients who were treated with 2nd GKRS for new brain metastases. The mean lesion volume was 1.2 cc (range, 0.002-12.6). A mean prescription dose of 17.8 Gy (range, 12-22) was delivered to the mean 61.1% (range, 45-90) isodose line. The prescribed dose was planned according to the tumor volume. Tumors with a volume of less than 1 cc, 1-5 cc, 5-10 cc and more than 10 cc were treated with 20-22 Gy, 17-19 Gy, 15-16 Gy and 12-15 Gy, respectively. The dosage was reduced to 70% in the patients treated WBRT (less than 2 years) previously. The radiosurgical prescription parameters evaluated were Paddick's conformity index (CI), Shaw's CI, and gradient index[11,19].

Table 1. Demographic characteristics of 36 patients with ≥4 metastases

Characteristics	No. of patients (%)
Age	
≤60 years	18 (50.0)
>60 years	18 (50.0)
Sex	
Male	18 (50.0)
Female	18 (50.0)
Primary tumor site	
Lung (NSCLC)	22 (61.1)
Breast	7 (19.4)
Gastrointestinal tract	3 (8.3)
Liver	2 (5.6)
Genitourinary tract	1 (2.8)
Unknown	1 (2.8)
Primary tumor control	
Controlled	10 (27.8)
Uncontrolled	26 (72.2)
RPA classification	
Class I	3 (8.3)
Class II	32 (88.9)
Class III	1 (2.8)
Extracranial metastasis	
Present	27 (75.0)
Absent	9 (25)
Additional WBRT	
No	29 (80.6)
Yes	7 (19.4)
Median KPS score	90 (range, 60-80)
Mean number of lesions	7 (range, 4-14)

NSCLC : non-small cell lung cancer, RPA : recursive partitioning analysis, WBRT : whole brain radiotherapy, KPS : Karnofsky performance status

Local tumor control and peritumoral edema reduction

MR imaging was performed every 3 months, including continuous thin cut T1 enhanced images, the same technique as MR imaging for GKRS. Tumor volume was calculated as enhancing lesions in T1 enhanced images, and peritumoral edema volume was calculated as T2 abnormal signal volume minus the tumor volume. Volume measurement of tumors and peritumoral edema was performed using the co-registration program (Leksell Gamma Plan®, version 8.3.1). Local tumor control and peritumoral edema reduction was assessed according to the Macdonald's criteria[7,10]. Complete response (CR) was defined as complete disappearance of all the lesions, partial response (PR) : ≥50% decrease in enhancing tumor volume, progressive disease (PD) : ≥25% increase in the lesions, and stable disease (SD) : <50% decrease or <25% increase in enhancing tumor volume. We defined local tumor control and peritumoral edema reduction as CR and PR.

Statistical analysis

Statistical analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Survival time was calculated from the time of GKRS. To investigate prognostic factors, Kaplan-Meier analysis was used for categorical variables, and Cox regression model was used for continuous variables and multivariate analysis. Results were regarded as significant for $p<0.05$.

RESULTS

Survival time

The median follow-up duration was 4.5 months and the overall median survival time was 9.1±1.7 months (Fig. 1). At the last follow-up, 17 out of 36 patients died. The causes of death were systemic cancer progression in 16 (94.1%) and unknown in 1. Median progression-free survival after treatment was 8.0±1.4

months. The primary tumor status (controlled vs. uncontrolled), the number of lesions, the presence of extracranial metastases (absent vs. present), patient's age (≤60 vs. >60), KPS score (≤90 vs. >90) (Fig. 2), primary tumor site (lung vs. others), WBRT pre-GKRS (yes vs. no) and addifional WBRT (yes vs. no) were assessed for survival factors.

In univariate analysis, controlled primary tumor (p=0.008) was a significant factor related to survival. And this factor remained significant in multivariate analysis (p=0.031, odds ratio=0.266, 95% confidence interval : 0.080-0.884 using the forward stepwise method) (Table 2, Fig. 2).

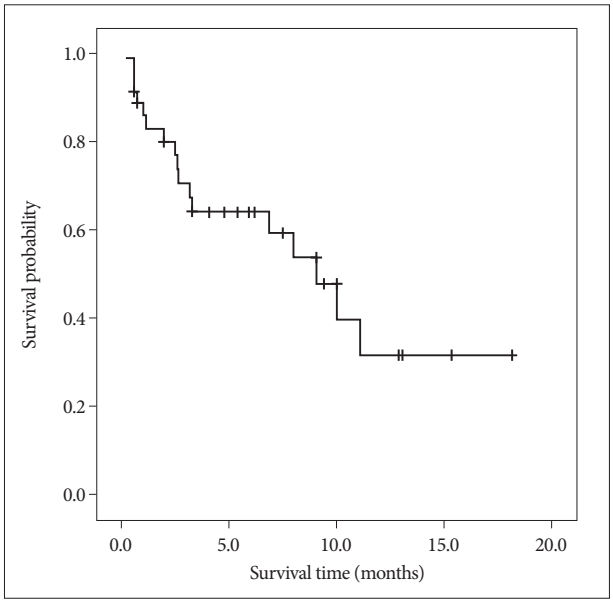

Fig. 1. Kaplan-Meier survival curves for patients with 4 or more brain metastases after gamma knife radiosurgery.

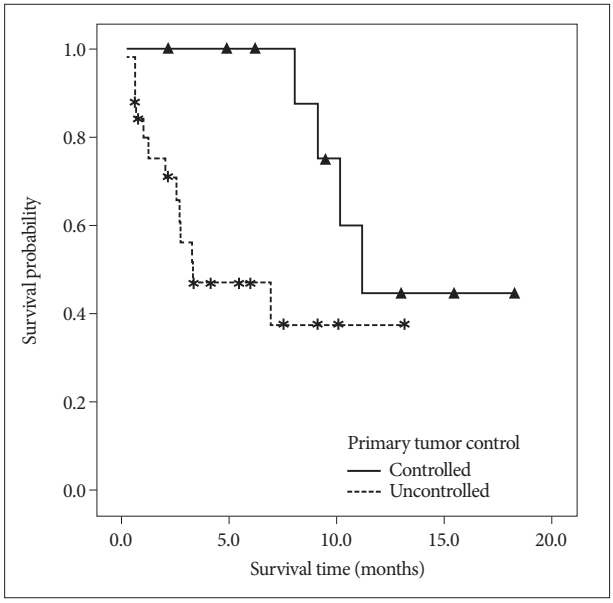

Fig. 2. Kaplan-Meier survival curves for patients with 4 or more brain metastases after gamma knife radiosurgery according to the primary tumor conditions (controlled vs. uncontrolled).

Local tumor control

One-hundred and seventy-five metastases were assessed by at least one imaging follow-up with a mean imaging follow-up duration of 4.2 months (range, 1.2-18.2). Results of local tumor control at the time of last follow-up were CR in 52 (29.7%), PR in 82 (46.9%), SD in 17 (9.7%) and PD in 14 (13.7%). The calculated local tumor control rates at 3, 6 and 9 months after GKRS were 92.5%, 87.9% and 84.2%, respectively. Paddick's CI (≤0.75 vs. >0.75), Shaw's CI (≤2 vs. >2), primary tumor site (lung vs. others), volume cover (≤97 vs. >97%), marginal dose (≤17 vs. >17 Gy), maximum dose (≤30 vs. >30 Gy), target volume (≤1 vs. >1 cc), additional WBRT (yes vs. no), and KPS score (≤90 vs. >90) were assessed for factors related to local tumor control. Paddick's CI >0.75 (p=0.0010) was a significant factor related to local tumor control in univariate analysis, and it remained significant in multivariate analysis (p= 0.005, odds ratio=7.969, 95% confidence interval : 1.860-34.150 using the forward stepwise method). Local tumor control rates of metastases treated with Paddick's CI ≤0.75 or >0.75 were 80.8% and 98.2% at 6 months, respectively (Table 3).

Among the CR patients, target volume ≤1 cc (p=0.020) and maximum dose >30 Gy (p=0.003) were significant factors related to CR in both univariate and multivariate analysis. The median time to CR was 5.7±0.8 months (range, 1.2-18.2). The calculated CR rate at 6 months was 100% for lesions of 1 cc or less in volume, and 68.3% for lesions larger than 1 cc. And the calculated CR rate at 6 months was 86.0% for lesions treated with more than 30 Gy of maximal dose, and 62.6% for lesions treated with 30 Gy or less.

New brain metastases and intratumoral necrosis

During the follow-up period, new brain metastases developed in 9 (22.2%) out of 36 patients. Among them, 9 patients were treated with 2nd GKRS. The median interval time between development of new metastases and GKRS was 4.0±0.8 months (range, 1.8-14.8).

Twenty-three lesions (13.1%) showed new or aggravated intratumoral necro-

Table 2. Prognostic factors related to survival time

Factors	Survival time (mean±SE, months)	p value*
Primary tumor status	controlled vs. uncontrolled (11.1±1.3 vs. 3.3±2.4)	0.031
Number of lesions	≤7 vs. >7 (10.1±1.5 vs. 6.9±2.5)	NS
Extracranial metastases	Present vs. Absent (9.1±1.7 vs. 12.5±2.6)	NS
Age	≤60 vs. >60 (6.9±3.0 vs. 10.1±2.0)	NS
KPS score	≤90 vs. >90 (9.1±2.2 vs. 8.0±5.6)	NS
Primary tumor site	Lung vs. others (11.1±5.2 vs. 6.9±2.6)	NS
Additional WBRT	Yes vs. No (10.1±3.8 vs. 9.1±1.6)	NS

*p value in multivariate analysis (Cox regression model). NS : not significant, KPS : Karnofsky performance status, WBRT : whole brain radiotherapy

Table 3. Prognostic factors related to local tumor control

Factors	Local tumor control (rate at 6 months)	*p* value*
Paddick's CI	≤0.75 vs. >0.75 (80.8 vs. 98.2)	0.005
Shaw's CI	≤2 vs. >2 (88.9 vs. 86.8)	NS
Gradient index	≤3.5 vs. >3.5 (92.5 vs. 79.9)	NS
Primary tumor site	Lung vs. others (91.4 vs. 83.3)	NS
Volume coverage (%)	≤97 vs. >97 (94.1 vs. 85.9)	NS
Marginal dose (Gy)	≤17 vs. >17 (82.3 vs. 90.7)	NS
Maximum dose (Gy)	≤30 vs. >30 (78.9 vs. 96.5)	NS
Target volume (cc)	≤1 vs. >1 (86.6 vs. 93.1)	NS
Additional WBRT	Yes vs. No (85.2 vs. 88.5)	NS

**p* value in multivariate analysis (Cox regression model). CI : conformity index, NS : not significant, WBRT : whole brain radiotherapy

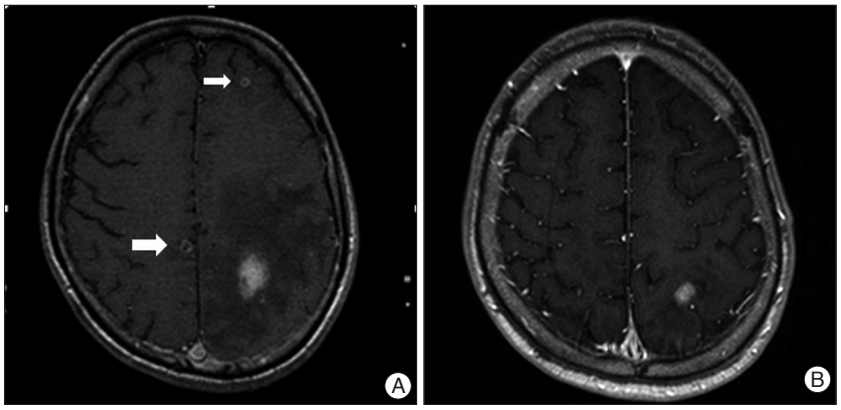

Fig. 3. Illustrative case of a 64-year-old male patient, non-small cell lung cancer, with multiple brain metastases (9 lesions). A : T1 weighted MR image after contrast injection shows enhancing lesions with marked peritumoral edema on the left parietal area and two small lesions in the left frontal and right parietal area (arrow). He got radiosurgery with 15 Gy at 50% isodose line. B : T1 weighted MR image after contrast injection, 3 months after GKRS, shows decreased mass and marked improvement of peritumoral edema in the left parietal area and disappearance of two small lesions. MR : magnetic resence, GKRS : gamma knife radiosurgery.

sis, and Paddick's CI ≤0.75 and marginal dose >17 Gy were significantly related to development of intratumoral necrosis (p<0.05). However, all intratumoral necrosis were asymptomatic or mildly symptomatic, and could be managed successfully with oral steroid administration.

Peritumoral edema reduction

Peritumoral edema was observed in 69 (39.4%) out of 175 lesions with a mean volume of 14.8 cc (range, 0.06-112.1) at the time of GKRS (Fig. 3). Twenty-one patients had peritumoral edema and were treated with steroids after GKRS only when the edema caused symptoms such as motor weakness or severe headache. The results of peritumoral edema status at the time of the last follow-up were CR in 24 (34.8%), PR in 28 (40.6%), SD in 12 (17.4%) and PD in 5 (7.2%). The actuarial peritumoral edema reduction rate was 22.4% at 6 months. Among various factors, maximal dose >30 (p=0.0313) and gradient index ≤3.5 (p=0.0336) were significantly related to peritumoral edema reduction in univariate analysis, and maximal dose >30 Gy remained significant in multivariate analysis (p=0.013, odds ratio=3.533, 95% confidence interval : 1.303-9.582 using the forward stepwise method). Peritumoral edema reduction was achieved in 55.1% of the lesions treated with maximal dose >30 Gy, while 9% of the lesions treated with maximal dose ≤30 Gy.

DISCUSSION

Optimal treatment option for the patients with brain metastasis is still controversial. Although WBRT was considered as a standard treatment for brain metastasis, historical studies have shown poor survivals regardless of the number of metastases and treatment modalities[4]. Many neurosurgeons still hesitate to provide WBRT because of the neurotoxicity of radiation, which eventually causes decreasing cognitive dysfunction and radiation induced brain atrophy. Recently, many authors have reported that single or small number of metastatic brain tumors (usually 1-3) may be well controlled by SRS[2,9,16].

Aoyama et al.[2] reported that there was no significant difference in overall survival time and neurological deterioration between WBRT+SRS and SRS only. This results was presented that SRS was effective tool for oligometastatic tumor and WBRT may be deferred until development of multiple new metastases after SRS.

Nevertheless some authors still doubt necessity of SRS for brain metastasis. Because there has been only small number of prospective randomized studies and lack of evidence. Similarly, the role of SRS for multiple (4 or more) metastatic brain tumor is still uncertain.

Many authors have attempted to add additional WBRT because traditional results of WBRT for patients with brain metastases were generally poor[1,9,13]. Surgical excision followed by WBRT has been reported to be an effective treatment for patients with single brain metastatic brain tumors. Patchell et al.[12] reported that 95 patients were treated by surgical resection for single brain metastasis, and classified two groups (with or without additional WBRT). They reported that the radiotherapy group had a significantly lower recurrence rate than the observation group (18% vs. 70%, p<0.001). Furthermore, patients who received additional WBRT after resection were found to be less likely to die of neurological causes than patients in the resection-alone group. However, there was no statistical difference in neurological death between the above two groups.

After GKRS was introduced for patients with brain metastases, GKRS with or without surgical excision became an alternative treatment for metastatic brain tumors. The main advantage of GKRS is the preservation of cognitive function, which is one of the main complications of WBRT[6,14,17,18]. GKRS with WBRT is another emerging treatment modality for metastatic brain tumors, especially multiple lesions. Kondziolka et al.[9] reported the results of 2-3 metastases treated by SRS plus WBRT or WBRT alone. They reported that the local failure rate at 1 year was 100% in the WBRT alone group, but only 8% in the SRS combined group. They also reported that the median time to any brain failure was improved in the SRS combined group. The overall survival of the SRS combined group was slightly longer than the WBRT only group, however they did not find any statistical difference (7.5 months vs. 11 months; p=0.22). They recommend the combination of SRS with WBRT for patients with two to four brain metastases rather than WBRT alone.

Serizawa et al.[15] retrospectively compared therapeutic results between GKRS alone and WBRT alone in patients harboring up to 10 brain metastases. They showed significantly longer overall survival, neurological survival, and qualitative survival in the GKRS alone group, and suggested that GKRS without prophylactic WBRT may be a primary choice of treatment for patients with as many as 10 brain metastases from a non-small cell lung cancer.

To our knowledge, relatively little has been published with regard to the therapeutic efficacy of GKRS in patients with multiple (4 or more) brain metastases. There are many reports implying GKRS as a formidable tool for treating metastatic brain tumors (although most agree that it has its limitations), but most are studies on 1-3 lesions, and studies on lesions over 4 are relatively rare.

We attempted to ascertain the clinical importance of GKRS for patients with multiple brain metastases, regardless of WBRT. In this study, the overall median survival time was 9.1±1.7 months. Considering the poor prognosis for patients with multiple metastases, it seems that our results are not inferior to previous results. Our results also show that radiation dose, performance status, RPA class, primary tumor site and combination of WBRT have not influenced the overall survival. The primary tumor control was a statistically significant factor related to survival. In terms of tumor local control, Paddick's CI was the only significant factor. Higher Paddick's CI (more than 0.75) significantly and positively affected local tumor control. In other words, careful dosimetry is essential for local tumor control.

This study has several limitations. First, this study is not a randomized or case-control study. Therefore, a selection bias may exist, and may interfere with the interpretation of the results. Second, the follow up duration is relatively short and the number of cases is small.

CONCLUSION

Although some limitation of this study are present, authors believe that GKRS can be an affordable treatment option for patients with multiple (4 or more) metastatic brain tumors, especially in systemically well controlled patients. Careful dosimetry (higher Paddick's CI) has shown to be a significant factor to improve the tumor local control rate. Further randomized controlled studies are required to clearly verify the therapeutic effects of GKRS for patients with multiple brain metastases.

References

1. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. : Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases : phase III results of the RTOG 9508 randomised trial. **Lancet 363** : 1665-1672, 2004
2. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. : Stereotactic radiosurgery plus whole-brain radiation therapy vs. stereotactic radiosurgery alone for treatment of brain metastases : a randomized controlled trial. **JAMA 295** : 2483-2491, 2006
3. Chiou SM : Validity of the graded prognostic assessment-derived index to predict brain-metastatic patients' survival after Gamma Knife radiosurgery. **Int J Radiat Oncol Biol Phys 78** : 1156-1162, 2010
4. DiStefano A, Yong Yap Y, Hortobagyi GN, Blumenschein GR : The natural history of breast cancer patients with brain metastases. **Cancer 44** : 1913-1918, 1979
5. Gaspar LE, Scott C, Murray K, Curran W : Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. **Int J Radiat Oncol Biol Phys 47** : 1001-1006, 2000
6. Grosshans DR, Meyers CA, Allen PK, Davenport SD, Komaki R : Neurocognitive function in patients with small cell lung cancer : effect of prophylactic cranial irradiation. **Cancer 112** : 589-595, 2008
7. Henson JW, Ulmer S, Harris GJ : Brain tumor imaging in clinical trials. **AJNR Am J Neuroradiol 29** : 419-424, 2008
8. Kim CH, Im YS, Nam DH, Park K, Kim JH, Lee JI : Gamma knife radiosurgery for ten or more brain metastases. **J Korean Neurosurg Soc 44** : 358-363, 2008
9. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC : Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. **Int J Radiat Oncol Biol Phys 45** : 427-434, 1999
10. Molenaar R, Wiggenraad R, Verbeek-de Kanter A, Walchenbach R, Vecht C : Relationship between volume, dose and local control in stereotactic radiosurgery of brain metastasis. **Br J Neurosurg 23** : 170-178, 2009
11. Paddick I : A simple scoring ratio to index the conformity of radiosurgical treatment plans. Technical note. **J Neurosurg 93 Suppl 3** : 219-222, 2000
12. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. : Postoperative radiotherapy in the treatment of single metastases to the brain : a randomized trial. **JAMA 280** : 1485-1489, 1998
13. Patil CG, Pricola K, Garg SK, Bryant A, Black KL : Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. **Cochrane Database Syst Rev** : CD006121, 2010
14. Ricard D, Taillia H, Renard JL : Brain damage from anticancer treatments in adults. **Curr Opin Oncol 21** : 559-565, 2009
15. Serizawa T, Iuchi T, Ono J, Saeki N, Osato K, Odaki M, et al. : Gamma knife treatment for multiple metastatic brain tumors compared with whole-brain radiation therapy. **J Neurosurg 93 Suppl 3** : 32-36, 2000
16. Smith ML, Lee JY : Stereotactic radiosurgery in the management of brain metastasis. **Neurosurg Focus 22** : E5, 2007
17. Vogelbaum MA, Asher AL, Kondziolka D, Boulis NM, Selden NR, Hoh BL, et al. : Modern treatment of cerebral metastases : Integrated Medical

Learning (SM) at CNS 2007. **J Neurooncol 93** : 89-105, 2009
18. Welzel G, Fleckenstein K, Schaefer J, Hermann B, Kraus-Tiefenbacher U, Mai SK, et al. : Memory function before and after whole brain radiotherapy in patients with and without brain metastases. **Int J Radiat Oncol Biol Phys 72** : 1311-1318, 2008
19. Woo HJ, Hwang SK, Park SH, Hwang JH, Hamm IS : Factors related to the local treatment failure of gamma knife surgery for metastatic brain tumors. **Acta Neurochir (Wien) 152** : 1909-1914, 2010