Bull Yamaguchi Med Sch 49(3-4):55-62, 2002

Cyberknife radiosurgery/radiotherapy for brain metastasis: prognostic factors for local control

Yasutaka Jimi, M.D.

Department of Neurosurgery, Yamaguchi University School of Medicine
(Received June 3, 2002, revised September 12, 2002)

Key words: CyberKnife, brain metastasis, local tumor control
tumor shrinkage time

Abstract **Purpose**: Homogeneous irradiation and the delivery of fractionated radiotherapy using the CyberKnife are useful treatments for brain metastases. Here we present our results of local tumor control after CyberKnife treatment. **Materials and Methods**: Local tumor control was evaluated for 107 lesions in 60 patients with radiological follow-up histories longer than 1 month (range 1.1 - 36.4 months, median 6.7 months). Also, tumor shrinkage time (TST) was assessed for 98 lesions by magnetic resonance imaging. The median and mean tumor volumes per patient were 2.8 and 6.1 cm^3 (range 0.1-38.4 cm^3), respectively, at the time of the initial CyberKnife treatment. The mean marginal dose was 20.1 Gy (range 11.6-24.9 Gy, median 20.3 Gy). Forty-two cases (70%) involved a single lesion, and 18 (30%) involved multiple lesions, ranging in number from 2 to 7. **Results**: We found no permanent symptoms resulting from radiation necrosis during the follow-up periods after CyberKnife treatment. Actuarial local control rates were 88% and 63% at 6 months and 1 year, respectively. The median time to local failure was 5.8 months, with a range of 3.0-21.9 months. TST analysis showed that large tumor volume and low marginal dose were still associated with poor tumor control. CyberKnife treatment was unable to control the tumor in 18 of 106 tumors. However, none of the patients who underwent additional radiosurgery or other surgical procedure died of brain metastasis. **Conclusion**: CyberKnife treatment is a useful modality which can be the first choice for treatment of brain metastasis.

Introduction

Stereotactic radiosurgery is widely used in the treatment of brain metastases, and has achieved better local control rates than conventional whole-brain radiation therapy (WBRT).[1-4] Recently, the CyberKnife (Accuray, Calif., USA), developed in 1997,[5-7] has been used for this purpose. It is a powerful instrument mounted on a highly maneuverable robotic manipulator which eliminates the need for skeletal fixation or rigid immobilization of the target through its use of real-time image guidance. Gamma-knife units have several limitations, including rigid target fixation and limited degrees of treatment freedom, which can be major drawbacks when treating patients with multiple, large, or non-spherical tumors. Such patients could benefit from the use of homogeneous irradiation and the delivery of fractionated CyberKnife therapy. Here we describe the results we have obtained with CyberKnife radiosurgery in patients with brain metastases, including assessment of local tumor control and tumor growth patterns during the process of tumor reduction after the treatment.

Materials and methods

Sixty patients with metastatic brain tumors (107 lesions) who underwent CyberKnife radiosurgery/radiotherapy at Kounan Saint Hill Hospital between 1997 and 2001 were included in this study. Patient age ranged from 30 to 88 years, with a median of 64 years. Thirty-four patients (57%) were male and 26 (43%) were female. The median score on the Karnofsky performance scale (KPS) at the time of the initial CyberKnife treatment was 80% (range 20-100%). Forty-two cases (70%) involved a single lesion, and 18 (30%) involved multiple lesions, ranging in number from 2 to 7. The average number of lesions per patient was 1.8. The major histologic types were carcinomas of the lung (43%), breast (28%), intestine (8%), stomach (3%), kidney (4%), and others (14%). The median and mean volumes of the 107 tumors were 2.8 and 6.1 cm^3 (range 0.1-38.4 cm^3), respectively, at the time of initial CyberKnife treatment. In our institution, the marginal dose was defined as that delivered at an isodose surface surrounding 90% of the entire volume of each tumor. In patients who received fractionated irradiation, the marginal dose was recalculated by the linear-quadratic formula using the LQ-Model [8], and the α/β ratio was defined as 2 Gy. The mean marginal dose was 20.1 Gy (range 11.6-24.9 Gy, median 20.3 Gy). Single-dose radiosurgery was performed on 74 lesions with a median tumor volume of 1.4 cm^3. Fractionated radiosurgery was basically performed if the tumor was located in an eloquent area of the brain, or was large. Fractionated radiosurgery (1.6 times per case on average) was performed on 32 lesions with a median tumor volume of 8.1 cm^3.

Local tumor control was evaluated for 107 lesions with radiological follow-up histories longer than 1 month (range 1.1 - 36.4 months, median 6.7 months). Local recurrence of treated metastases was defined as an increase of greater than 25% in the contrast of images obtained by magnetic resonance imaging (MRI), or where neurological deterioration occurred. Time to local failure was assessed for each lesion, and was measured from the date of initial CyberKnife treatment. The times to local failure were analyzed using the Kaplan-Meier method[9], by arbitrarily dividing categorized variables into two groups by changing the cutoff values. The logrank test was used to evaluate the effects of patient characteristics and treatment factors on these outcomes.[10] Factors affecting local tumor control were also determined by multivariate analysis. Parameters with p values less than or equal to 0.40 were included in the multivariate analysis, which used the Cox proportional hazard model with the backward stepwise method.[11] Differences at $p < 0.05$ were regarded as statistically significant.

To assess tumor growth patterns during the process of tumor reduction after CyberKnife treatment, we estimated tumor shrinkage time (TST) by MRI during follow-up in 98 lesions.[12] Tumors showing regrowth in the follow-up period were excluded from this analysis. We measured the diameter of a tumor in three orthogonal planes (a, b, and c) on MR images. We used the following formula, which calculates the volume of an ellipsoid: $V = (4\pi abc/3) (2^3$. TST was calculated by modifying the formula used for tumor doubling time, as follows: $TST = -t \log(2) / \log(V1/V0)$, where V0 is the initial volume of the tumor and V1 is the volume of the tumor after t days. With this formula, TST becomes high when the tumor shrinks slowly. The values for each group were compared using the Mann-Whitney or Spearman correlation tests for independence.

Results

We found no permanent symptoms resulting from radiation necrosis during any of

Table 1. Analysis of local tumor control (106 lesions)

	Univariate	Multivariate
tumor volume (<2.99 vs >2.99 cm^3)	0.0157	0.4327
marginal dose (<21.9 vs >21.9 Gy)	0.0281	0.1727
adjuvant WBRT	0.0701	0.3318
lung cancer vs others	0.4072	NI
breast cancer vs others	0.4417	NI
infratentorial location	0.0203	0.2287
recurrent tumor	0.1178	0.5458
eloquent tumor	0.0629	0.5766

NI: not included, WBRT: whole-brain radiation therapy

the follow-up periods after CyberKnife treatment. Actuarial local control rates were 88% and 63% at 6 months and 1 year, respectively. The median time to local failure was 5.8 months, with a range of 3.0-21.9 months. The possible prognostic factors for local tumor control were tumor volume, marginal dose, adjuvant WBRT, location of the primary lesion (lung or breast cancer vs others), location of the metastasis (infratentorial), tumor recurrence, and tumor location in an eloquent area of the brain such as the motor and speech areas, or brainstem. The results are shown in Table 1. A large tumor volume (greater than 2.99 cm^3), infratentorial location, and a marginal dose of radiation (21.9 Gy or less) were also associated with poor tumor control ($p<0.05$) in the Kaplan-Meier analysis (Table 1, Figs. 1-3). However, multivariate analysis by Cox proportional hazards regression modeling showed no statistical significance for any of these factors. Univariate analysis showed that adjuvant WBRT before CyberKnife treatment and tumor location in a non-eloquent brain area were associated with favorable tumor control, although with borderline significance ($p=0.0701$ and 0.0629, respectively). Univariate and multivariate analyses showed that multiplicity did not affect local tumor control.

Eighteen of 106 tumors (in 18 patients) showed failure of local control during the follow-up period (Table 2). The average marginal dose for the 18 tumors was

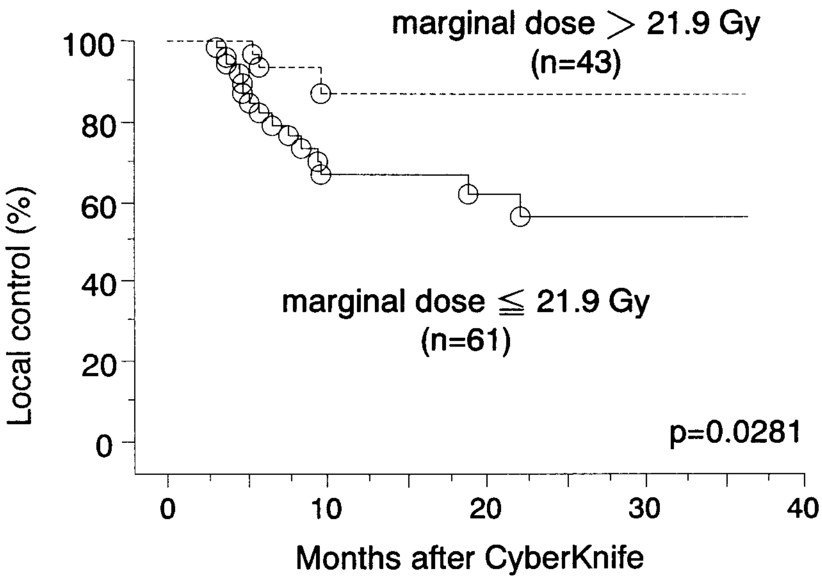

Fig. 1 The Kaplan-Meier model with long-rank test applied to each categorization demonstrated significantly longer tumor control rates in patients a marginal dose of greater than 21.9 Gy ($p < 0.05$).

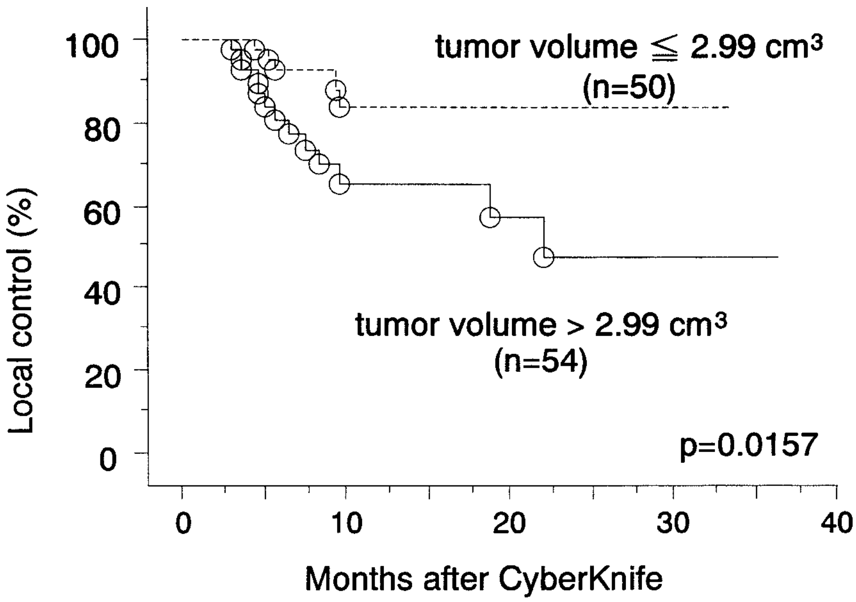

Fig. 2 The Kaplan-Meier model with long-rank test applied to each categorization demonstrated significantly longer tumor control rates in patients with a tumor volume of 2.99 cm3 or less ($p < 0.05$).

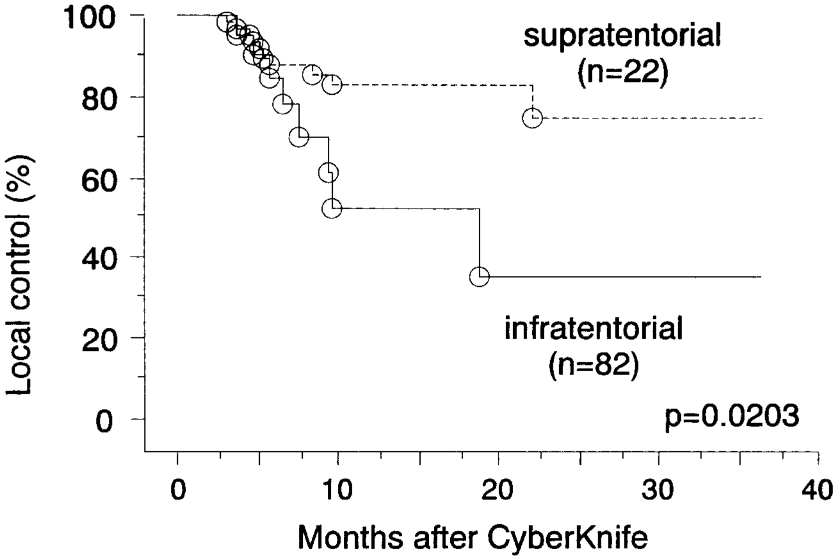

Fig. 3 The Kaplan-Meier model with long-rank test applied to each categorization demonstrated significantly longer tumor control rates in patients with supratentorial tumors ($p < 0.05$).

19.5 Gy (range 11.6-24.7 Gy, median 19.9 Gy). The median and mean volumes of the 18 tumors (responsible for the patients' neurological disorder) were 9.07 and 4.3 cm^3 (range 0.2-38.4 cm^3), respectively, at the time of initial CyberKnife treatment. Twelve patients received additional radiosurgery (CyberKnife for ten tumors and gamma knife for two) when tumor recurrence was diagnosed. After the second radiosurgery, ten of these patients had no recurrence, whereas two required additional surgical treatment during the follow-up period after the second CyberKnife treatment. Three of 18 patients underwent surgical treatment at the first recurrence to relieve the symptomatic mass effect at the site of local failure. Two of them received CyberKnife treatment immediately after surgery for the residual tumor, whereas one case was proven to be radiation necrosis by histological examination. Three patients who did not undergo either additional radiosurgery or surgical treatment died of progressive brain metastasis. Four of 14 patients who received CyberKnife treatment died of extracranial metastases other than brain metastasis. Eleven patients were still alive after a median follow-up period of 14.2 months (range 4.9-37.1 months) from the date of the initial CyberKnife treatment.

In the analysis of TST, the median time to MRI follow-up was 4.9 months, with a range of 1.4-36.4 months. The mean TST was 15.6 months after the initial CyberKnife treament (from 2.1 to 46.7 months; median 13.1 months). Possible relevant factors for TST were tumor volume, number of lesions per patient, age, sex, marginal dose, location of primary lesion (lung or breast cancer vs others), and use of adjuvant WBRT (Table 3). Among these factors, a larger tumor volume and lower marginal dose were significantly associated with a high TST (poor tumor control) (Figs. 4, 5).

Discussion

Regarding local tumor control using the gamma-knife, a smaller tumor volume has also been shown to be correlated with better tumor control[1,3], except for a few reports indicating that dose and tumor size are not significant.[4] Six-month and 1-year actuarial local tumor control rates in our series were similar to those in previous studies, i.e. 82% at 6 months[3], and 48-85% at 1 year (Table 4). In our factor analysis, we found that tumor volume affected local tumor control significantly in univariate analysis but not in multivariate analysis. When cases showing good tumor control were included in the analysis, tumor volume significantly affected the tumor shrinkage time. These results sug-

Table 2. Lesions with local control failure

Age (years) Gender	Volume (cm3)	Dose (Gy)	Second treatment	Third treatment
1) 69, male	3.2	20.4	CyberKnife	no recurrence
2) 88, male	4.3	18.8	CyberKnife	no recurrence
3) 55, female	3.8	21.4	CyberKnife	no recurrence
4) 56, female	1.4	24.3	CyberKnife	no recurrence
5) 82, male	38.4	16.1	gamma Knife	no recurrence
6) 51, male	26.2	16.1	gamma Knife	no recurrence
7) 72, male	5.5	18.0	CyberKnife	no recurrence
8) 50, female	23.5	16.1	CyberKnife	no recurrence
9) 48, male	3.0	11.6	CyberKnife	no recurrence
10) 50, female	0.9	21.7	CyberKnife	no recurrence
11) 60, male	14.8	19.6	CyberKnife	surgery (tumor)
12) 46, female	12.8	20.0	CyberKnife	surgery (tumor)
13) 69, male	2.1	19.8	surgery (tumor)	CyberKnife
14) 73, male	4.3	21.8	surgery (tumor)	CyberKnife
15) 66, male	0.2	24.8	surgery (necrosis)	no recurrence
16) 53, female	0.8	22.0	no treatment	—
17) 80, male	7.0	16.9	no treatment	—
18) 73, female	3.4	18.0	no treatment	—

gest that tumor volume is related to local tumor control. A higher dose of radiation delivered to the tumor was significantly associated with improved local tumor control.[13] Our data for tumor shrinkage time and factor analysis also showed that lower irradiation doses can be associated with poor local tumor control. Although our initial purpose of treating patients with the CyberKnife was to avoid radiation injury as much as possible, the radiation dose can be important in large tumors. In this analysis, radiation dose was reduced in large tumors (cases 5, 6, and 8 in Table 2) or tumors in eloquent areas of the brain, even if the tumor was small (cases 9 and 17 in Table 2), which necessitated repeated CyberKnife treatment. Taking this together with the fact that no permanent symptoms were observed to result from radiation necrosis during the follow-up periods, more aggressive irradiation appears to be acceptable for the treatment of larger tumors using the fractionated method. A recent report has stated that surgical excision of the tumor before radiosurgery provides better tumor control.[14] Indeed, in the present series, a single CyberKnife treatment was unable to control 18 of 104 tumors. However, our results suggest that even large tumors can be treated by fractionated CyberKnife irradiation, and that subsequent treatment by either radiosurgery or conventional surgery can be satisfactory for the management of recurrent tumors. Although CyberKnife treatment is not as effective for cystic metastases as other radiosurgery techniques, our results suggest that fractionated CyberKnife radiosurgery can be an effective first treatment for larger solid metastatic brain tumors, which can result in financial benefits associated with shorter hospital stays.

Table. 3. Analysis of factors affecting tumor shrinkage time

tumor volume	< 0.0001
no. of lesions	0.8492
age	0.6465
sex	0.1611
marginal dose	< 0.0001
lung cancer or others	0.8175
breast cancer or others	0.5207
adjuvant WBRT	0.6397

Although our analyses did not exclude elderly patients or patients with large tumors or higher pre-KPS scores, but only those with cystic tumors, our results for tumor control rates are comparable or better than those of previous series involving gamma-knife treatment. While gamma-knife units have several limitations, including

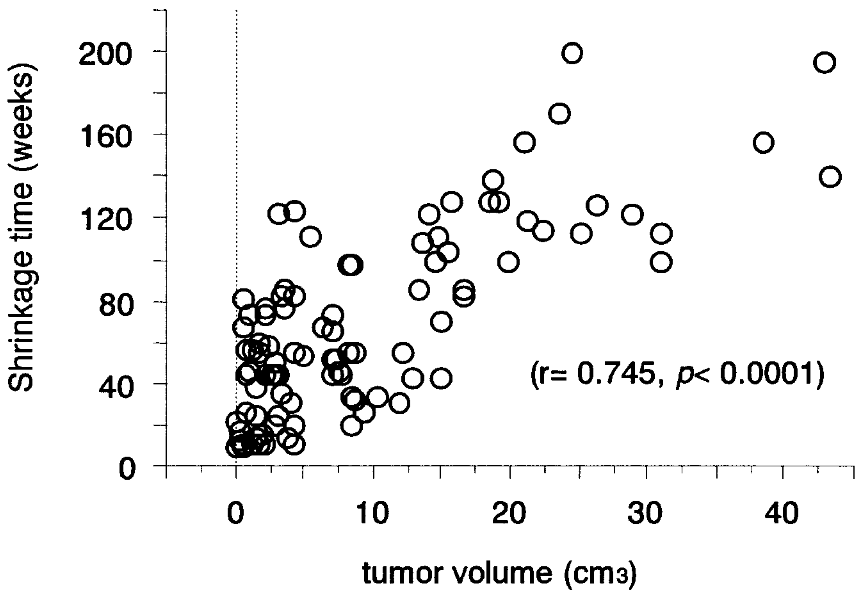

Fig. 4 Relationship between tumor volume and shrinkage time (r= 0.745, p< 0.0001)

rigid target fixation and limited degrees of treatment freedom, CyberKnife treatment provides the additional advantage of avoiding patient discomfort or pain caused by repeated skeletal fixation or rigid immobilization of the target. Thus, CyberKnife treatment is a useful modality which can be the first choice for brain metastasis, especially in elderly patients, patients with multiple intracranial metastases, and possibly patients with large metastatic lesions.

Conclusions

The CyberKnife is a useful instrument and can be the first choice for treatment for brain metastasis. More aggressive irradiation can be acceptable for the treatment of larger tumors using a fractionated approach.

Acknowledgements

I gratefully thank Professor and Chairman Michiyasu Suzuki (Department of Neurosurgery, Yamaguchi University Shool of Medicine), Dr. Kenichi Saito (Department of Neurosurgery, Kounan Saint Hill Hospital), and Dr. Takafumi Nishizaki (Department of Neurosurgery, Yamaguchi University Shool of Medicine) for helpful discussion, advice and technical support on this study.

Reference

1) Alexander, E., Moriarty, T.M., Da-

Table 4. Previous report concerning local tumor control and clinical features

	median volume (cm^3)	age (yr)	6 mo.	1 yr.
Kim, 2000	2.1 (0.02-45.5)	58	—	48%
Alexander, 1995	3.0 (0.1-53.0)	55	—	85%
Brenemna, 1997	—	55	—	(25)
Shiau, 1997	1.3 (0.02-45.5)	56	82%	77%
Shirato, 1997	>2 cm: 36%	61	93%	66%
present study	2.8 (0.1-38.4)	62	88%	63%

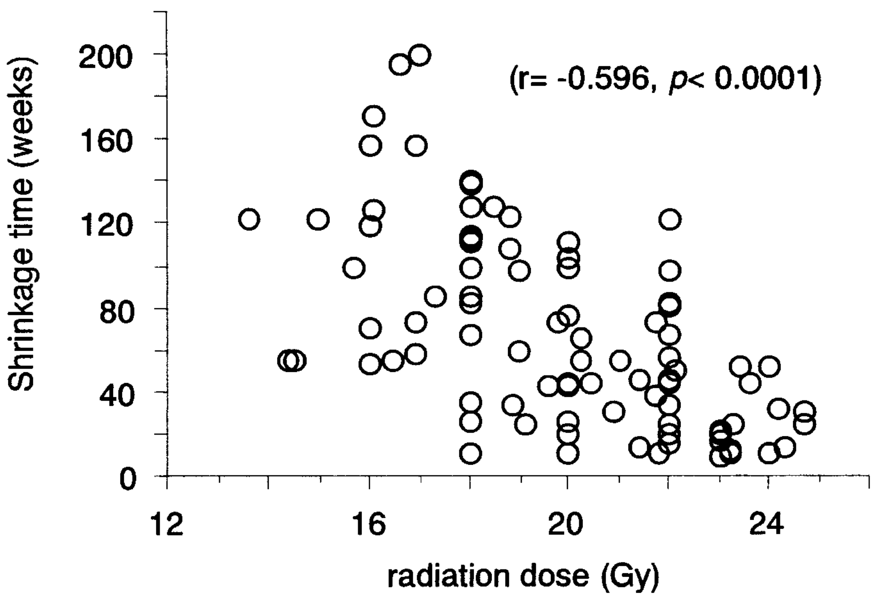

Fig. 5 Relationship between marginal dose and shrinkage time (r= -0.596, p< 0.0001)

vis, R.B., Wen, P.Y., Fine, H.A., Black, P.M., Kooy, H.M., Loeffler, J.S.: Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. *J. Natl. Cancer Inst.* **87**: 34-40, 1995.

2) Breneman, J.C., Warnick, R.E., Albright, R.E., Kukiatinant, N., Shaw, J., Armin, D., Tew, J.: Stereotactic radiosurgery for the treatment of brain metastases. Results of a single institution series. *Cancer* **79**: 551-557, 1997.

3) Kim, D.G., Chung, H.T., Gwak, H.S., Paek, S.H., Jung, H.W., Han, D.H.: Gamma knife radiosurgery for brain metastases: prognostic factors for survival and local control. *J. Neurosurg.* **93**: 23-29, 2000.

4) Flickinger, J.C., Kondziolka, D., Lunsford, L.D., Coffey, R.J., Goodman, M.L., Shaw, E.G., Hudgins, W.R., Weiner, R., Harsh, G.R., Sneed, P.K.: A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. *Int. J. Radiat. Oncol. Biol. Phys.* **28**: 797-802, 1994.

5) Adler, J.R. Jr., Cox, R.S.: Preliminary clinical experience with the CyberKnife: Image-guided stereotactic radiosurgery. Radiosurgery. Basel Karger,1996 *Kondziolka D (ed.)* Vol **1** pp316-326, 1996.

6) Adler, J.R. Jr.: The cyberknife: a frameless robotic system for radiosurgery. Stereotact-Funct-Neurosurg. **69**: 124-128, 1997.

7) Chang, S.D., Murphy, M., Geis, P., Martin, D.P., Hancock, S.L., Doty, J.R., Adler, J.R. Jr.: Clinical experience with image-guided robotic radiosurgery (the CyberKnife) in the treatment of brain and spinal cord tumors. *Neurol. Med. Chir.* **38**: 780-783, 1998.

8) Fowler, J.F.: The linear-quadratic formula and progress in fractionated radiotherapy. Brit. *J. Radiol.* **62**: 679-694, 1989.

9) Kaplan, E.L., Meier, P.: Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**: 457-481, 1958.

10) Peto, R., Peto, J.: Asymptotically efficient rank invariant test procedures. *J. R. Stat.* Soc. *Series A* **135**: Part II 185-207, 1972.

11) Cox, D.R.: Regression models and life tables. *J. R. Stat.* Soc. *Series B* **34**: 187-202, 1972.

12) Cho, K.G., Hoshino, T., Nagashima, T., Murovic, J.A., Wilson, C.B.: Prediction of tumor doubling time in recurrent meningiomas. Cell kinetics studies with bromodeoxyuridine labeling. *J. Neurosurg.* **65**: 790-794, 1986.

13) Shiau, C.Y., Sneed, P.K., Shu, H.K., Lamborn, K.R., McDermott, M.W., Chang, S., Nowak, P., Petti, P.L., Smith, V., Verhey, L,J., Ho, M., Park, E., Wara, W.M., Gutin, P.H., Larson, D.A.: Radiosurgery for brain metastases: relationship of dose and pattern of enhancement to local control. *Int. J. Radiat. Oncol. Biol. Phys.* **37**: 375-383, 1997.

14) Serizawa, T., Iuchi ,T., Ono, J., Saeki, N., Osato, K., Odaki, M., Ushikubo, O., Hirai, S., Sato, M., Matsuda, S.: Gamma knife treatment for multiple metastatic brain tumors compared with whole-brain radiation therapy. *J. Neurosurg.* **93**: 32-36, 2000.