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Comments

1. This paper describes an aggressive treatment strategy for two patients with disseminated ependymoma. I admire the authors' enthusiasm, but I find it difficult to recommend this treatment strategy in general.
2. The best-documented treatment of ependymoma is total tumour resection. In my opinion craniospinal radiotherapy is not indicated as part of the primary treatment, since less than 10% of ependymoma patients get dissemination. If radiotherapy is given as part of primary treatment, it should be focal.
3. Disseminated ependymoma has a dismal prognosis. Aggressive treatment of these patients with radiotherapy, chemotherapy or surgery, can at best give a short increase in patient survival with good quality of life. Most patients with disseminated ependymoma would probably not benefit from aggressive treatment.

Eirik Helseth

The authors studied and described well the efficacy of stereotactic radiosurgery for recurrent disseminated nodular ependymomas. Those tumours are apparently difficult to treat well, and stereotactic radiosurgery might be the best therapeutic option today.

Kintomo Takakura

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Clinical Article

Routine clinical adoption of magnetic resonance imaging was associated with better outcome after surgery in elderly patients with a malignant astrocytic tumour: a retrospective review

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Summary

Background. There is controversy about extensive surgical treatment for a malignant astrocytic tumour in more elderly patients who may have poorer outcomes and higher complication rates. This retrospective study investigated outcome in elderly patients with malignant astrocytic tumour before and after the adoption of routine clinical use of magnetic resonance (MR) imaging.

Methods. During 1982 through 1999, 88 patients with malignant astrocytic tumour aged 60 years or over were treated in our institute. Thirty-seven patients had an anaplastic astrocytoma and 51 had a glioblastoma. Thirty-seven patients treated from 1982 to 1988 did not have pre-operative evaluation by MR imaging (Group A), 26 patients treated from 1989 to 1995 had preoperative MR imaging evaluation (Group B), and 25 patients treated after 1996 underwent preoperative MR imaging with functional brain mapping and intra-operative navigation system monitoring (Group C).

Findings. The median survival time was 8.8 months in Group A, 12.7 months in Group B, and 17.6 months in Group C. Patients with glioblastoma in Group B (11.7 months, $n = 15$) and Group C (16.0 months, $n = 19$) had significantly longer median survival time than in Group A (6 months, $n = 17$) ($P = 0.0054$ between Groups A and B, $P = 0.0024$ between Groups A and C). Better preoperative performance status, more thorough surgical resection, and better performance status after the initial treatment was obtained after the introduction of MR imaging, and patients with the optimal indicators showed significantly longer survival time compared with the patients without these factors.

Interpretation. Pre-operative MR imaging may contribute to longer survival time by providing an earlier diagnosis in patients with better performance status, by allowing more thorough surgical resection, and resulting in better performance status after the treatment.

Keywords: Malignant astrocytoma; elderly; outcome; surgery.

Introduction

The treatment of patients with a malignant astrocytic tumour is one of the most challenging contemporary neurosurgical problems. Surgical treatment, especially for the elderly, is considered to result in a poor outcome and a high complication rate [3, 7, 8]. The median survival was only 2.2 months in patients older than 60 years with glioblastoma [9]. Craniotomy plus radiotherapy improved the median survival up to 16 weeks in elderly patients (60 years or over) who were treated during 1983 through 1989 [14]. In a series of 146 adults, 27 were older than 65 years and had a median survival of only 4.8 months [6]. These reports illustrate the poor prognosis for elderly patients with malignant astrocytic tumour.

Total surgical resection with adjuvant radiochemotherapy is considered to be optimal leading to prolonged survival time and improved neurological status in patients with a malignant astrocytic tumour [12]. However, the merits of extensive surgical resection in elderly patients with a malignant astrocytic tumour, remain controversial [8]. Extensive or repeated surgery in an elderly patient may have greater risks of surgical morbidity and death and there are several reports that radical surgery provides little benefit for elderly patients with a malignant astrocytic tumour [5, 7]. Nevertheless, in another report the optimal results in elderly patients were achieved in those in better performance status by thorough surgical resection and definitive radiation therapy [10].

The present study is based on a comprehensive analysis of the medical records in our department during 1982 through 1999 in order to assess the outcome in elderly patients with a malignant astrocytic tumour

before and after the introduction of magnetic resonance (MR) imaging. We analyzed the prognostic importance of pre- and postoperative performance status, extent of surgical resection at operation, and postoperative complications.

Methods and material

Case material

During 1982 through 1999, 281 patients with malignant astrocytic tumour were treated by surgical procedures and/or radio-chemotherapy in our department. One hundred and seven patients treated from 1982 to 1988 had no pre-operative evaluation by MR imaging (Group A), 84 patients from 1989 to 1995 underwent pre-operative MR imaging evaluation (Group B), and 90 patients after 1996 underwent preoperative MR imaging including functional brain mapping and surgery under guidance from an intra-operative navigation system (Group C). Intra-operative functional mapping was also used for patients with malignant astrocytic tumour in eloquent areas in Group C.

The present study included 88 patients who were aged 60 years or over. The 51 male and 37 female patients were aged from 60 to 78 years (mean age 66.8 ± 4.7 years). Twenty-seven patients were older than 70 years. There were 37 patients in Group A, 26 patients in Group B, and 25 patients in Group C.

Histological confirmation was required for inclusion in this study. The histological diagnosis was established using the new World Health Organization classification. The 281 patients with malignant astrocytic tumour included 154 cases of anaplastic astrocytoma and 127 cases of glioblastoma. Thirty-seven (24.0%) of the cases of anaplastic astrocytoma, and 51 (40.2%) of the cases of glioblastoma occurred in elderly patients.

Treatment

The treatment protocol was relatively uniform but not identical for all patients. Thirty patients (34.1%) underwent gross total resection, and 58 patients (65.9%) underwent partial resection or stereotactic biopsy. Nineteen patients were treated by radiation therapy. The standard radiation therapy consisted of 30 Gy in 15 fractions to the tumour and peritumoral brain and 30 Gy in 15 fractions to the whole brain before 1987, and 60 Gy in 30 fractions to the local brain thereafter. The standard radiotherapy protocol was a total dose of 60 Gy in 30 fractions of 2 Gy, 5 days per week over 6 weeks, delivered to the local brain by parallel opposed ports with megavoltage equipment. 1-(4-Amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU) was administered intravenously or intra-arterially for 58 patients.

Clinical investigation

The pre- and postoperative performance status was classified using the Eastern Co-operative Oncology Group (ECOG) scale ranging from 0 to 4. The postoperative performance status was determined between 1 and 3 months after surgery. Surgical morbidity was defined as postoperative intracranial haematoma, iatrogenic neurological deficit, and sepsis at the surgical site. Follow-up analysis was obtained by review of the patient's records or by contact with the family. Eighty-three of the 88 patients (94.3%) had died by the cut-off date for data analysis, June 30, 2001. For survival analysis, day 0 was defined as the first day of admission.

Statistical analysis

Survival rates were determined using the Kaplan-Meier method. The statistical significance between life table curves was determined using the logrank test.

Results

The median survival time of the 88 elderly patients was 11.7 months, which was significantly shorter than that of patients under the age of 60 years. Median survival times of the elderly patients with anaplastic astrocytoma and glioblastoma were significantly shorter than those of the younger patients with these tumours. The median survival time of elderly patients with anaplastic astrocytoma was significantly longer than that of elderly patients with glioblastoma (Table 1).

As shown in Table 2, median survival times of elderly patients with glioblastoma in Groups B (11.7 months, n = 15) and C (16.0 months, n = 19) were significantly longer than those in Group A (6 months, n = 17), respectively (p = 0.0054 between A and B, p = 0.0024 between A and C). Median survival time was somewhat longer after the introduction of functional brain mapping and

Table 1. *Survival in patients undergoing surgery for malignant astrocytic tumour*

Histology	No. of patients	Median survival time (months)	Probability
Total	281		
–under 60 year	193	22.6	P < 0.0001
–60 year or over	88	11.7	
Anaplastic astrocytoma	154		
–under 60 years	117	29.3	P = 0.0006
–60 years or over	37	14.7*	
Glioblastoma	127		
–under 60 years	76	16.3	P = 0.0021
–60 years or over	51	10.8*	

* P = 0.0105.

Table 2. *Survival in elderly patients undergoing surgery for malignant astrocytic tumour*

Histology	No. of patients	Median survival time (months)	Probability
Total	88		
Group A	37	8.8	
Group B	26	12.7	NS
Group C	25	17.6	
Anaplastic astrocytoma	37		
Group A	20	10.3	
Group B	11	13.8	NS
Group C	6	34.9	
Giloblastoma	51		
Group A	17	6.0	P = 0.0054*
Group B	15	11.7	P = 0.0024**
Group C	19	16.0	

* Between Group A and B, ** between Groups A and C.

intra-operative navigation system monitoring in Group C (16.0 months, n = 19) compared to B (11.7 months, n = 15), but there was not a statistical significance between the groups (p = 0.5729).

The number of patients with better pre-operative performance status of ECOG 0-2 increased after the introduction of MR imaging. The median survival time of the patients with better pre-operative performance status was significantly longer than that of the patients with lower performance status of ECOG 3-4 (Table 3).

Gross total resection was achieved in more patients after the introduction of MR imaging. The median survival time of patients with gross total resection was significantly longer than that of patients with partial resection or biopsy (Table 3).

More patients had better postoperative performance status after the introduction of MR imaging. The median survival time of patients with better postoperative performance status was significantly longer than that of patients with lower performance status (Table 3).

The overall morbidity was 30.7%. The surgical morbidity was 17.1% and the medical complication rate was 13.6%. The operative mortality was 0%. Functionally significant neurological worsening occurred in eleven patients, which was caused by cerebral vascular damage during the operation in four patients, surgical intervention extending to eloquent areas in four patients, postoperative intraparenchymal haematoma in one patient, status epilepticus following surgery in one patient, and encephalitis following cerebrospinal fluid leakage in one patient. The median survival time of the patients with or without complications was 8.5 months (n = 27) and 13.8 months (n = 61), respectively, with no statistically significant difference.

Table 3. *Effect of neuroimaging methods on outcome in elderly patients*

	No. of patients				Median survival time (months)	Probability
	Group A	Group B	Group C	Total		
Preoperative ECOG						
0–2	14	14	20	48	17.9	P = 0.0013
3–4	23	12	5	40	7.5	
Postoperative ECOG						
0–2	12	17	19	48	17.6	P = 0.0004
3–4	25	9	6	40	5.7	
Extent of removal						
Gross total	8	6	16	30	19.3	P < 0.0001
Partial or biopsy	29	20	9	58	8.5	

Discussion

The present study indicates that the adoption of pre-operative MR imaging and additional imaging modalities was accompanied by a lengthening in survival time after surgery in elderly patients with a malignant astrocytic tumour. Among the factors in this may have been an earlier diagnosis and thus better performance status at surgery, allowing more thorough surgical resection, and better performance status after the initial treatment. Our analysis found that patients with malignant astrocytic tumour aged 60 years or over could survive as long as 17.6 months using current treatment modalities such as MR imaging with functional mapping, intra-operative navigation system, and intra-operative functional mapping under "awake" craniotomy or under generalized anesthesia. Median survival times extend further after the introduction of functional brain mapping and intra-operative navigation system monitoring in patients with glioblastoma, although there was no statistical significance between Group B and C. The lack of the statistical significance may be due to the small patient population (in which patients with tumour in eloquent area are further less). Future evaluation with a larger number of patients would address this important issue. Alternatively, we do not rule out the possibility that multiple factors including the surgeon's experience, awareness of the referring physician, and development of the operative microscope also contributed, at least in part, to the better outcome.

Most previous studies have found that surgical treatment for elderly patients with malignant astrocytic tumour resulted in high mortality and morbidity as well as a high complication rate [2, 4, 13]. In a series of 207 consecutive patients (mean age 53 years), 53 patients over 65 years old had a complication rate of 30.2%, and 20 patients over 70 years old had a complication rate of 50% [4]. Both rates were much higher than the overall complication rate of 25.1%. In a series of 80 patients aged over 65 years who underwent craniotomy for intra-axial tumour, the death rate was 3.8%, and worsening of the neurological state occurred in 16.3% and medical complications in 28.8% [13]. Surgical treatment for elderly patients clearly carries the risk of a worse outcome and a high complication rate. No significant improvement of survival time was found in 40 patients aged over 65 years treated by aggressive surgery plus radiotherapy compared with 88 patients treated by stereotactic biopsy plus radiotherapy [7]. In their series, the optimal treatment with resection plus radiation for elderly patients with glioblastoma resulted in an average survival of 30 weeks. In contrast, our results demonstrate that patients treated by gross total resection had a significantly longer median survival time (19.3 months) than patients with partial resection or biopsy (8.5 months) ($P < 0.0001$). Gross total resection was obtained in more patients after the introduction of MR imaging, suggesting that pre-operative MR imaging with or without functional mapping provides more precise anatomical and/or functional information, and contributes to more thorough surgical resection.

Our study indicates that pre-operative as well as post-operative performance status is also a significant contributing factor for better prognosis. Elderly patients with better performance status ($\geq$70 Karnofsky performance status score) treated by maximal resection and definitive radiotherapy had a longer survival time than those treated by palliative radiation and biopsy [10]. Median survival was found to be longer in elderly patients who were more functional [1]. Patients older than 70 years with Karnofsky performance status score of more than 70 may benefit from surgical treatment for malignant astrocytic tumour followed by reduced doses of limited field radiotherapy [11].

We propose, based on the findings of this retrospective study that thorough surgical resection should be considered even in elderly patients with malignant astrocytic tumour if their performance status is good and preoperative evaluation by MR imaging is available.

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Gamma knife surgery for hemangioblastomas

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Object. The authors reviewed their 14-year experience using stereotactic radiosurgery for the treatment of hemangioblastomas and define the role and the proper strategy for radiosurgery of this condition.

Methods. This is a retrospective study of 38 hemangioblastomas in 13 patients. Seven patients had von Hippel–Lindau disease. All patients have undergone at least one follow-up visit. The median and mean tumor volumes were 0.23 cm^3 and 0.72 cm^3 respectively (range 0.004::4.84 cm^3). Twenty-eight tumors received 20 Gy to the margin, and the remainder received 18 Gy. The median clinical follow-up period was 36 months (range 3–159 months).

No patient died. The survival rate was 84.6% (11 of 13 patients). The actuarial 5- and 10-year survival rates were both 80.8%. The median radiological follow-up period was 35 months (range 7–147 months). Only one tumor increased in volume 24 months after treatment in association with an intratumoral hemorrhage. The tumor control rate was 97.4% (37 of 38 tumors). Actuarial 5- and 10-year control rates were both 96.2%. New lesions and/or those increasing in size outside the irradiated area were discovered in five patients (38.5%). Nine tumors revealed peritumoral contrast enhancement which was seen more frequently in larger tumors with a volume greater than 0.5 cm^3 ($p = 0.0034$).

Conclusions. Gamma knife surgery is a safe and effective method to control hemangioblastomas for as many as 10 years. Higher doses and smaller tumors probably contribute to good outcomes. Recurrence outside the original irradiated area is common. Peritumoral contrast enhancement may be seen in larger tumors. The authors recommend regular imaging follow up and early repeated treatment in the face of new or growing tumors.

KEY WORDS • **stereotactic radiosurgery** • **gamma knife surgery** • **hemangioblastoma** • **von Hippel–Lindau disease**

HEMANGIOBLASTOMAS are rare benign tumors of the central nervous system that usually occur in the posterior fossa or upper cervical spinal cord. Approximately 20% of patients with intracranial hemangioblastoma have VHL disease, and they typically suffer from multiple tumors. Resection is the treatment of choice for most hemangioblastomas; however, their vascularity, critical locations, and multiplicity sometimes make resection a less attractive alternative, particular in patients with VHL disease. Conventionally fractionated radiotherapy has been used for the treatment of residual or unresectable hemangioblastomas. Sung, et al.,[7] reported 10-year survival rates of 56.5 % and 27.3 % in patients who received 40 Gy or more and 36 Gy or less, respectively. They recommended a dose of 45 to 50 Gy over a period of 4.5 to 5 weeks.

Recently, stereotactic radiosurgery has been used for the treatment of hemangioblastomas.[1–5] Although the authors of these few articles documented encouraging outcomes after radiosurgery, the long-term results have not been previously investigated nor have long-term appropriate strategies for the use of radiosurgery been established. In this report, we have undertaken a retrospective review of our 14-year experience and attempted to define the role of GKS and the proper strategy in this disease.

Abbreviations used in this paper: GKS = gamma knife surgery; MR = magnetic resonance; VHL = von Hippel–Lindau.

Clinical Material and Methods

Thirteen patients with 46 hemangioblastomas underwent GKS in a series of 15 treatments at the University of Tokyo Hospital between June 1990 and March 2004. We evaluated all patients (38 tumors), each of whom has undergone at least one follow-up visit (Table 1). There were ten men and three women. There were seven patients with VHL disease. The mean patient age was 43.4 years (range 26–84 years). All patients had undergone between one and four open surgeries before GKS, and diagnoses in all cases had been con-

TABLE 1

Patient characteristics

Characteristic	Value
no. of patients/tumors	13/38
male/female ratio	10:3
mean age in yrs (range)	43.4 (26–84)
VHL disease	7
prior surgery	13
prior conventional radiotherapy	1
tumor location	
cerebellar hemisphere	26
cerebellar vermis	5
brainstem	3
fourth ventricle	2
cervical spine	1
temporal lobe	1
tumor size	
median diameter in mm (range)	7.7 (2.0–21.0)
median volume in cm^3 (range)	0.23 (0.004–4.84)
dose (Gy)	
median max dose (range)	40 (36–40)
median margin dose (range)	20 (18–20)

firmed histologically at the time of GKS. Only one patient had received conventional radiotherapy before GKS, at a dose of 30 Gy. Twenty-six of 38 tumors were located in the cerebellar hemispheres. The median and mean tumor volumes were 0.23 cm^3 and 0.72 cm^3, respectively (range 0.004–4.84 cm^3).

Gamma knife surgery was performed using the Leksell gamma knife models (Elekta Instrument AB, Stockholm, Sweden). Treatment planning was performed using KULA or Leksell GammaPlan (Elekta Instruments AB) and stereotactic computerized tomography or MR images. The treatment protocol calls for the irradiation of the enhanced mass with a margin dose of 20 Gy. In cystic tumors only the mural nodule is targeted. In this series, all tumor margins were covered by the 50% isodose. Twenty-eight tumors received 20 Gy to the margin, and the remainder received 18 Gy.

Clinical and neuroradiological follow up were, in principle, requested 3, 6, and 12 months after the procedure. Afterward, follow-up evaluations were performed every 6 months for 2 years and then annually. We defined tumor control as lack of enlargement of the solid component on MR and/or computerized tomography images, regardless of any change in size of the cystic component.

Actuarial patient survival and tumor control rates were calculated by the Kaplan–Meier method.

The Fisher exact test was used for nonparametric variables. The level of significance is $p < 0.05$.

Results

The median clinical follow-up period was 36 months (range 3–159 months). Only two patients were followed-up for more than 5 years, but 12-year follow-up data were obtained in both of them. Two patients died, 3 and 35 months after the treatment, respectively. The causes of death were primary lung cancer and pleural carcinomatosis from a renal cell carcinoma in a patient with VHL disease. No neurological death was observed. The patient survival

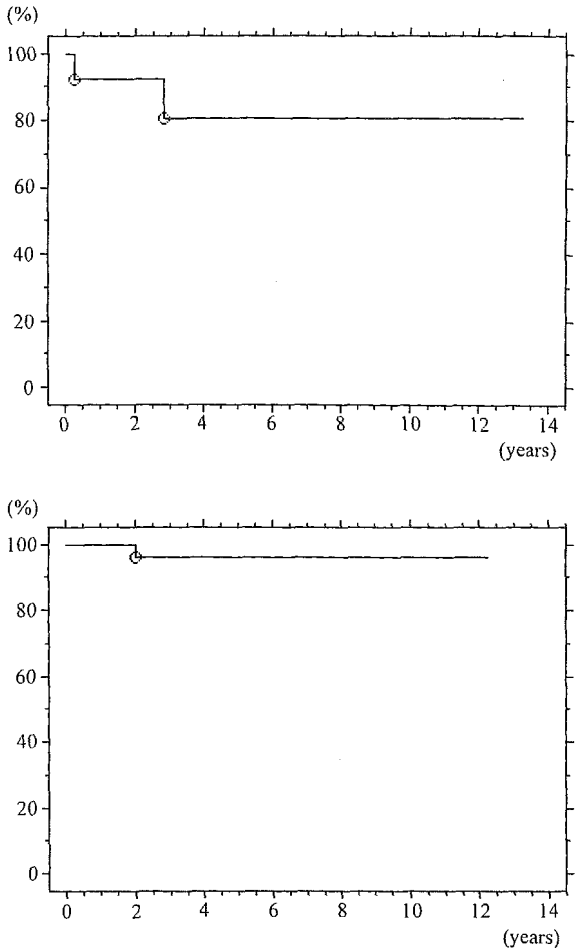

FIG. 1. Kaplan–Meier curves showing survival rate *(upper)* and tumor control rate *(lower)* after GKS for hemangioblastomas.

rate was 84.6% (11 of 13). Actuarial 5- and 10-year survival rates were both 80.8% (Fig. 1 *upper*).

The median radiological follow-up period in 38 tumors in 12 patients was 35 months (range 7–147 months). No neuroimaging studies were available in the patient who died of lung cancer 3 months after GKS. Only one tumor appeared to increase in size at 24 months after the treatment. In this case, intratumoral hemorrhage was revealed on MR images. It was not clear whether the tumor itself had grown. The other 37 tumors were controlled locally. One disappeared, nine regressed, and 27 remained unchanged. The tumor control rate was 97.4% (37 of 38 tumors) at the time of the most recent follow up. Actuarial 5- and 10-year tumor control rates were both 96.2% (Fig. 1 *lower*). Statistical evaluation of the effects of patient characteristics and treatment factors on survival and tumor control was impossible with such a small number of patients. New lesions and/or those increasing in size outside the irradiated area were discovered in five patients (38.5%) during the follow-up period.

Some adverse radiation effects were seen on the follow-up images. Brain edema was shown adjacent to eight tumors in three patients. With the exception of one case, all the tumors with radiation-induced edema also demonstrated peritumoral contrast enhancement. Another two lesions revealed abnormal peritumoral enhancement. These enhance-

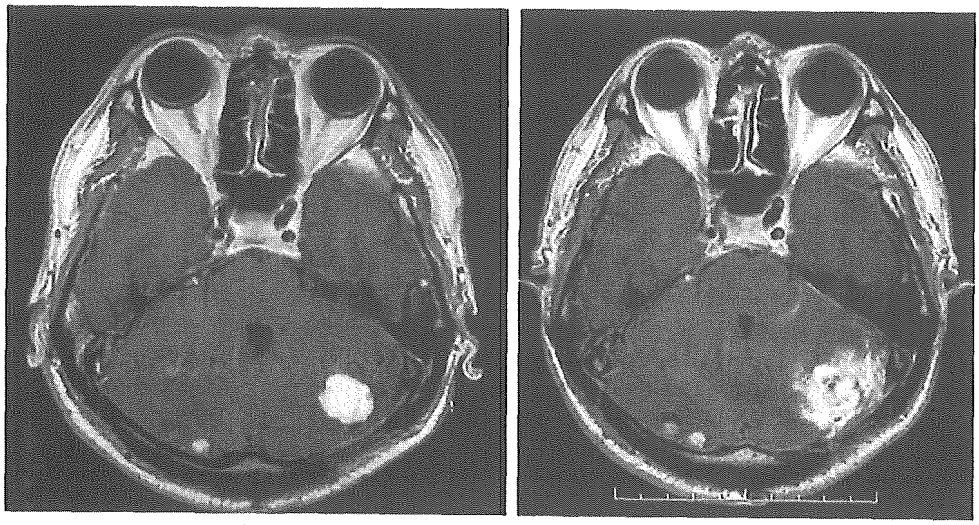

FIG. 2. Magnetic resonance images obtained in a man who underwent a second GKS for two hemangioblastomas in the left cerebellar hemisphere (another lesion is not shown) *(left)*. Two months later, abnormal peritumoral enhancement accompanied by brain edema was recognized, and 2 months later (4 months after GKS), the enhancement enlarged *(right)*.

ments arose between 2 and 6 months (median 3 months) after GKS and improved gradually with conservative management over 2 years (Fig. 2). This change was recognized more frequently in larger tumors (> 0.5 cm^3) than in smaller ones. The difference was statistically significant ($p = 0.0034$). Another possible unwanted change was an increase in the volume of the cystic component, which was noticed in five lesions between 2 and 36 months after GKS. One of these patients underwent an operation to resect the cystic mass. One other patient was transiently symptomatic.

Clinical neurological deterioration occurred in four patients, including the aforementioned patient with the transient increase in the cyst volume. Another patient, who was treated with GKS for four lesions in two sessions during a 13-year follow up as described previously, experienced transient hydrocephalus due to brain edema with enhancement and was treated conservatively. Symptoms in the other two patients were caused by new or growing tumors that had not been treated with GKS.

Discussion

The findings in our series indicate that GKS can be an effective method for achieving a local tumor control rate of 96.2% at 10 years. Authors of several reports have previously documented the effect of radiosurgery on hemangioblastomas, and the tumor control rate has been between 75% and 100%; however, in none of these studies were the long-term results such as 10-year tumor control rates described.[1–5] Hemangioblastomas are benign, slowly growing tumors so it can be difficult to judge whether the control of a tumor by GKS represents an improvement over the natural course of the untreated disease. In our cases, five patients developed new lesions and/or their lesions increased in size. Nonetheless, all GKS-treated tumors were controlled. Moreover, two patients, who were followed up for more than 12 years, both underwent a second GKS for new tumors, which arose after the initial treatment. These findings suggest that GKS can indeed control the tumors; however, long-term outcomes such as 15-, 20-, or 30-year survival and control rates will require continuing study.

We have summarized the outcomes of previously reported series and this present study in Table 2. Our outcomes are comparable to those reported by Niemelä, et al.,[3] and Chang, et al.[1] The control rates published by Patrice, et al.,[5] Pan, et al.,[4] and Jawahar, et al.,[2] seem to be worse. Patrice, et al., and Jawahar, et al., indicated that a higher radiosurgical dose and a smaller tumor volume significantly contributed to a higher tumor control rate. Chang, et al., also described the importance of higher dose. In conventional radiotherapy, patients who received 40 Gy or more lived longer than those who received 36 Gy or less.[7] The median margin dose in our study and the other two studies with higher control rates was 20 Gy or more, which was higher than in the other studies in which the control rates were lower. An additional factor in the high survival rate in the current series is the relatively low tumor volume.

In our series, peritumoral contrast enhancement was recognized on MR images in nine tumors. This change has not previously been mentioned in any detail. The enhancement was related to tumor volume. The mechanism of this enhancement is not known. Progressive thickening of the intimal layer begins as early as 3 months after GKS.[4,6] Hemangioblastomas have a rich capillary network; thus congestion due to intimal thickening could lead to an increased permeability of neighboring blood vessels.

Our results suggest that good tumor control may be achieved with small lesions and a high dose. On the whole, the development of new lesions or continued tumor growth requiring surgery and the development of complications were all related to larger tumors. The recommended strategy is to choose GKS for smaller tumors. After treatment, we recommend serial imaging follow up every 6 to 12 months to ensure that new or growing lesions may be detected when they are still small.

TABLE 2

*Summary of outcomes after stereotactic radiosurgery for hemangioblastomas**

Authors & Year	No. of Patients/ Tumors	Follow Up in Mos (range)	Technique	Tumor Size (range)		Margin Dose in Gy (range)	Control Rate %				Survival Rate %			
				Mean Diameter (mm)	Mean Volume in cm^3		Overall	2-Yr	5-Yr	10-Yr	Overall	2-Yr	5-Yr	10-Yr
Niemelä, et al., 1996	10/11	43 (13–122)	GKS	13.5 (6–43)		20 (5–35)	100.0	100.0	100.0		80.0	90.0	67.5	67.5
Patrice, et al., 1996	22/38	24.5 (6–77)	GKS or LINAC		0.97 (0.05–12)	15.5 (12–20)	86.2	86.0			81.9	88		
Chang, et al., 1998	13/29	43 (11–84)	LINAC		1.6 (0.07–65.4)	23.2 (18–40)	96.6				92.3			
Pan, et al.,1998	13/20	29 (24–36)	GKS	20 (7.5–55)		18.4 (12–24	69.2				92.3			
Jawahar, et al., 2000	27/29	48 (6–108)	GKS		3.2 (0.36–27)	16.1 (11.7–20)	75.9	84.5	75.2		77.8		75.1	
present study	13/38	36 (3–159)	GKS	7.7 (2.0–21.0)	0.23 (0.004–4.84)	20 (18–20)	97.4	96.2	96.2	96.2	84.6	92.3	80.8	80.8

* LINAC = linear accelerator.

Conclusions

Gamma knife surgery is a safe and effective method to control hemangioblastomas and achieve local tumor control of 96.2% at 10 years. Higher doses and smaller tumors probably contribute to better outcomes. Recurrence outside the original GKS-treated area is common and was seen in five patients (38.5% in this study). Peritumoral contrast enhancement is related to larger tumors and resolves with conservative management. Regular imaging follow up is important so that subsequent treatments, if needed, may be used on smaller lesions, which respond better.

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High-dose conformal radiotherapy for supratentorial malignant glioma: a historical comparison

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Summary

Background Although radiotherapy remains the main postoperative treatment for patients with malignant glioma, modifications to regimens have not improved the poor outlook of patients with this disease. We aimed to investigate whether high-dose conformal radiotherapy improves the survival of patients with supratentorial malignant glioma compared with conventional radiotherapy.

Methods 29 patients with anaplastic astrocytoma and 61 patients with glioblastoma who received high-dose conformal radiotherapy during 1990–2002 were compared with 34 patients with anaplastic astrocytoma and 60 patients with glioblastoma who received conventional 60 Gy radiotherapy during 1979–89. 77 of the 90 patients receiving high-dose radiotherapy were given 80 Gy; the remaining 13 patients, all with glioblastoma, received 90 Gy. Radiotherapy was planned on the basis of images taken before surgery, and doses were delivered in 2 Gy per fraction per day for 5 days a week. Hazard ratios for death were calculated with a Cox model, and were adjusted for age, Karnofsky performance scale, tumour size, and extent of resection.

Findings Patients who received high-dose radiotherapy had significantly longer overall survival compared with those who received conventional radiotherapy (adjusted hazard ratio 0·30 [95% CI 0·12–0·76], p=0·011 for anaplastic astrocytoma and 0·49 [0·28–0·87], p=0·014 for glioblastoma). Patients with anaplastic astrocytoma in the high-dose group have not yet reached median survival; median survival in the conventional radiotherapy group was 22·3 months (95% CI 20·6–24·0). 5-year survival was 51·3% (29·2–73·4) for the high-dose group and 14·7% (0·0–30·0) for the conventional group. Median survival in patients with glioblastoma was 16·2 months (12·8–19·6) for the high-dose group and 12·4 months (10·0–14·8) for the conventional group. 2-year survival was 38·4% (23·5–53·3) for the high-dose group and 11·4% (0·0–25·3) for the conventional group. Survival did not differ between those that received 80 Gy radiotherapy and those that received 90 Gy (hazard ratio 0·94 [95% CI 0·42–2·12]). The higher frequency of radiation-induced white matter abnormality in the high-dose group compared with the conventional radiotherapy group did not lead to increased disability.

Interpretation High-dose, standard-fractionated radiotherapy shows potential as the main postoperative treatment for patients with supratentorial malignant glioma.

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Introduction

Common treatment for newly diagnosed malignant glioma is resection to the maximum extent possible, followed by chemoradiotherapy.[1,2] Temozolomide has become a standard chemotherapeutic agent in Europe, Canada, and the USA,[3,4] whereas use of nimustine has been standard practice in Japan, despite the lack of definitive evidence.[5]

Malignant glioma cells are somewhat resistant to radiation and are highly invasive to surrounding healthy tissue.[6,7] Recurrence after initial radiotherapy is inevitable; the most common pattern of recurrence is regrowth at the primary location.[8,9] Undoubtedly, local tumour control is important for improving the survival of patients with malignant glioma.

Several reports[2,10,11] have suggested that survival of patients with malignant glioma depends on the total dose of the initial radiotherapy. An early report[10] showed that patients who received a median of 75 Gy (range 70–80) had significantly longer survival than did those who received a median of 50 Gy (50–55). A randomised control study[11] showed that 60 Gy lengthened survival by about 3 months compared with 45 Gy. However, a total dose of 60 Gy is regarded the limiting dose for the brain when delivered by the standard fractionation of 2 Gy per day.[12] Attempts to safely increase the total dose to beyond 70 Gy by use of hyperfractionation have not improved survival.[13–16]

Use of stereotactic radiosurgery before conventional radiotherapy did not improve the outcome of patients with glioblastoma,[17] and accelerated radiotherapy, in which 2-Gy fractions are given three times a day to a total dose of 30–60 Gy, or 1·5-Gy fractions are given twice a day to a total of 60 Gy, did not improve the outcome of patients with malignant glioma compared with those given conventionally fractionated radiotherapy.[18–20] These results, and the assumption that radiotherapy doses of higher than 60 Gy with standard fractionation would significantly increase morbidity, have prevented neuro-oncologists from using high-dose radiotherapy for patients with glioma in large-scale studies.[21]

Technological advances such as three-dimensional conformal radiotherapy have allowed minimum involvement of surrounding healthy tissue. Results of several

	Conventional radiotherapy		High-dose radiotherapy	
	Glioblastoma (n=60)	Anaplastic astrocytoma (n=34)	Glioblastoma (n=61)	Anaplastic astrocytoma (n=29)
Age				
Median (range), years	47 (15–77)	41 (15–71)	55 (15–76)	46 (15–73)
<50 years	32	25	25	19
≥50 years	28	9	36	10
Sex				
Women	24	13	21	7
Men	36	21	40	22
Karnofsky performance scale				
60–70	22	15	20	8
80–100	38	19	41	21
Tumour diameter				
Mean (SD), cm	4·3 (1·3)	4·4 (1·2)	4·6 (1·6)	4·5 (1·2)
<4 cm	36	19	29	14
≥4 cm	24	15	32	15
Tumour location				
Frontal	22	16	21	15
Temporal	16	10	24	7
Parietal	14	2	8	3
Occipital	5	1	7	3
Thalamus	3	5	1	1
Extent of resection				
<95%	39	17	35	14
≥95%	21	17	26	15
Chemotherapy				
Nimustine and vincristine	34	21	57	27
Nimustine	18	8	3	2
Carmustine	7	0	0	0
None	1	5	1	0
Repeat resection				
Yes	4	3	6	6
No	56	31	55	23
Salvage chemotherapy				
Interferon beta	1	5	3	0
Cisplatin and interferon beta	1	0	1	0
Intrathecal methotrexate	1	0	0	1
None	57	29	57	28

Data are number of patients unless otherwise indicated.

Table 1: **Patient and tumour characteristics**

small-scale studies[22–24] have suggested that high-dose radiotherapy (70–90 Gy) is tolerated well in patients with malignant glioma, and the frequency of cognitive impairment or necrosis was not notably raised in long-term survivors. Since 1990, we have been using radiotherapy with a total dose of 80–90 Gy, given with standard fractionation of 2 Gy per day, for all patients with supratentorial malignant glioma. We aimed to compare the outcomes of these patients with those who received the conventional 60 Gy radiotherapy given before 1990 at our institution.

Methods

Patients

We investigated 240 consecutive patients who had been newly diagnosed with glioblastoma or anaplastic astrocytoma according to WHO classification at University of Tokyo Hospital from 1979 to 2002, who met the inclusion criteria. Patients were included if they had histopathologically confirmed glioblastoma or anaplastic astrocytoma, were at least 15 years old, and had a Karnofsky performance scale of 60% or higher at the start of radiotherapy. Patients were excluded if they had secondary glioblastoma, chronic renal failure, restrictive pulmonary disease, or infratentorial or brainstem glioma (n=55), or chronic heart failure (n=1; died 2 months after surgery). All patients had maximum possible resection that avoided neurological worsening. Of 94 patients that received 60 Gy radiotherapy (conventional radiotherapy), 87 had craniotomy and seven had a biopsy; of the 90 patients that received high-dose radiotherapy, 87 underwent craniotomy and three had a biopsy before radiotherapy. The proportion of tumour volume resected was calculated from postoperative CT or MRI scan. With the exception of seven patients who refused chemotherapy, all patients received intravenous nimustine (Nidran®; Sankyo, Tokyo, Japan) or carmustine (BiCNU®; Bristol-Myers Squibb, New York, NY, USA) with or without vincristine (Oncovin®; Nippon Kayaku, Tokyo, Japan) during radiotherapy. All patients were assessed for the presence of radiation-induced toxic effects at follow-up examination by neurosurgeons. Written informed consent was obtained from all patients and from a member of their family before radiotherapy.

Radiotherapy

All treatments were planned on the basis of preoperative images, and done with a standard fractionation of 2 Gy per fraction per day for 5 days a week. Conventional radiotherapy started 7–21 days after surgery, and high-dose radiotherapy started 11–21 days after surgery. No patient died before the start of radiotherapy.

From 1979 to 1989, 60 patients with glioblastoma and 34 patients with anaplastic astrocytoma received conventional 60 Gy radiotherapy. Until 1984, patients received external-beam radiotherapy of 40 Gy to the whole brain followed by a local boost of 20 Gy (48 patients with glioblastoma and 18 patients with anaplastic astrocytoma). In 1984, a three-step cone-down technique was introduced, which was used in the remaining 12 patients with glioblastoma and 16 patients with anaplastic astrocytoma. Gross tumour volume was defined as the contrast-enhanced lesion depicted by contrast-enhancing CT scan or T1-weighted MRI (contrast-enhancing materials manufactured by Schering AG, Berlin, Germany, or Daiichi Pharmaceutical, Tokyo, Japan). Clinical target volume I was defined as the tumour, II as the tumour and surrounding oedema (high-intensity area on T2-weighted MRI) plus a 2-cm margin, and III as the whole brain. Planning target volume was defined as clinical target volume plus 0·5 cm for setup errors; thus, the margin with a setup error for planning target volume II was 2·5 cm. Planning target volume III was the whole brain plus 0·5 cm. The doses for planning target volumes I, II, and III were 60 Gy, 40 Gy, and 26 Gy, respectively.

From 1990 to 2002, 90 patients received high-dose radiotherapy with a total dose of 80 Gy or 90 Gy. Clinical target

volumes were modified and defined as tumour (I), tumour plus a 2-cm margin (II), and tumour and surrounding oedema plus a 2-cm margin (III). Planning target volume was defined as the clinical target volume plus 0·5 cm for setup errors. All 29 patients with anaplastic astrocytoma received 80 Gy radiotherapy: the doses of planning target volumes were 80 Gy, 60 Gy, and 40 Gy. Initially, patients with glioblastoma received a total of 90 Gy with planning target volumes of 90 Gy, 70 Gy, and 50 Gy (n=13). Because one patient showed grade-4 memory impairment, the total dose was reduced to 80 Gy for the subsequent 48 patients with glioblastoma, with planning target volumes similar to those for anaplastic astrocytoma. High-dose radiotherapy was done with the rotational conformal method, which uses a combination of coplanar gantry rotation and movement of a multileaf collimator.[25–27] The leaves were focused in two dimensions to avoid penumbra and moved independently from each other according to the gantry angles to create a dose distribution confined to the target volume. The area surrounding the target volume had a uniform gradient of dose fall-off.

Treatment lasted for 6 weeks in the 60-Gy group, 8 weeks in the 80-Gy group, and 9 weeks in the 90-Gy group. However, three patients in the 60-Gy group and two patients in the 80-Gy group had a 1-week interruption, and one patient in the 60-Gy group had an interruption of 2 weeks during treatment.

Follow-up

Follow-up CT or MRI scans were obtained at least every 4 months after radiotherapy; tumour progression and white-matter abnormalities were diagnosed on the basis of reports by neuroradiologists. Tumour progression was defined in accordance with MacDonald criteria.[28] Karnofsky performance scale was assessed for all patients. White-matter abnormality was defined as radiation necrosis, leucoencephalopathy, or brain atrophy. A contrast-enhanced lesion that appeared after radiotherapy on contrast-enhancing CT scan or T1-weighted MRI was diagnosed as radiation necrosis if a biopsy or resection sample showed a pathological diagnosis of radiation necrosis or if no uptake of fluorine-18 fluorodeoxyglucose or L-methyl-carbon-11 methionine could be seen on PET images.[29] PET has been done routinely on patients who developed contrast-enhanced lesions since 1990 at our institution.

Radiation-induced toxic effects were scored according to the common terminology criteria for adverse events (version 3.0).[30] Neurological symptoms that could not be explained by tumours were regarded as radiation-induced neurological deterioration.

Four independent neuropathologists reviewed the tumour histopathology of patients who survived for more than 20 months after radiotherapy to confirm the original diagnoses of glioblastoma or anaplastic astrocytoma. After tumour recurrence, patients were given further treatment at the discretion of treating doctors.

	Conventional (n=94)	High-dose (n=90)
Follow-up		
Median (range), months	7·7 (1·0–297·0)	15·5 (1·5–183·0)
Anaplastic astrocytoma		
Overall survival, months (median [95% CI])	22·3 (20·6–24·0)	Not reached
Progression-free survival, months (median [95% CI])	17·0 (12·8–21·2)	37·5 (NC)
5-year overall survival, % (95% CI)	14·7 (0·0–30·0)	51·3 (29·2–73·4)
2-year overall survival, % (95% CI)	44·1 (23·3–64·9)	78·1 (61·0–95·2)
Glioblastoma		
Overall survival, months (median [95% CI])	12·4 (10·0–14·8)	16·2 (12·8–19·6)
90-Gy group	NA	19·6 (13·3–25·9)
80-Gy group	NA	16·2 (12·6–19·8)
Progression-free survival, months (median [95% CI])	7·2 (4·0–10·4)	7·0 (5·0–9·8)
90-Gy group	NA	11·1 (3·0–19·2)
80-Gy group	NA	6·9 (5·5–8·3)
2-year survival, % (95% CI)	11·4 (0·0–25·3)	38·4 (23·5–53·3)
90-Gy group	NA	38·9 (8·5–69·3)
80-Gy group	NA	37·6 (20·4–54·8)

NC=not calculable. NA=not applicable.

Table 2: **Patient outcomes**

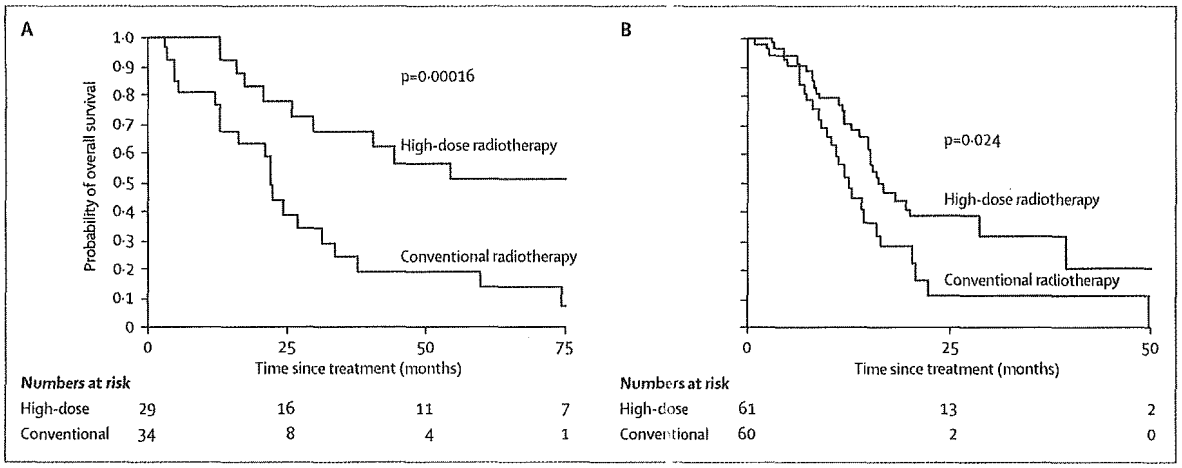

Figure 1: **Kaplan-Meier estimates of overall survival according to radiation dose in patients with anaplastic astrocytoma (A) and glioblastoma (B)**

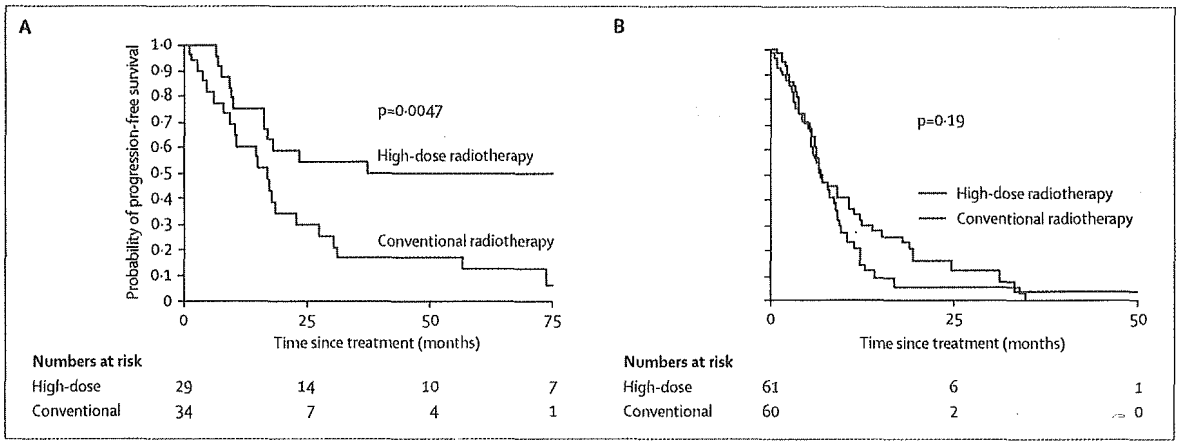

Figure 2: Kaplan-Meier estimates of progression-free survival according to radiation dose in patients with anaplastic astrocytoma (A) and glioblastoma (B)

Statistical analysis

Frequency distributions and summary statistics were calculated for all clinical and histological variables. χ^2 or Fisher's exact test were used for categorical variables, and the Kruskal-Wallis test for categorical continuous variables. Overall survival was calculated from the date of operation until the date of death or last follow-up, and progression-free survival until the date when recurrence was seen or until last follow-up. The Kaplan-Meier method was applied for survival analyses, and significance was calculated by the log-rank test. Cox's proportional hazard model was used to analyse prognostic variables and to ascertain the risk factors associated with time of onset of white-matter abnormality. Adjusted hazard ratios for death were calculated by adjustment for age, Karnofsky performance scale, tumour size, and extent of resection. Univariate and multivariate Cox regression analysis (with the entry cutoff level of p=0·05 and the stay cutoff of p=0·1) were used to assess the association of variables with survival or time to onset of white-matter abnormality. All data analyses were done with Dr SPSS II version 11.01 for Windows.

Role of the funding source

The funding sources had no role in study design; in collection, analysis, and interpretation of data; or in writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Table 1 shows the patient and tumour characteristics. The conventional group did not differ from the high-dose group in any of the characteristics listed. Median follow-up was 12·0 months overall (range 1·0–297·0; table 2).

Overall survival (figure 1), and 2-year and 5-year survival (table 2) were significantly improved in patients with anaplastic astrocytoma who received high-dose radiotherapy compared with those who received conventional radiotherapy. Median survival has not yet been reached in patients with anaplastic astrocytoma in the high-dose group. The adjusted hazard ratio for death in the high-dose group compared with the conventional group for patients with anaplastic astrocytoma was 0·30 (95% CI 0·12–0·76, p=0·011). These results were confirmed by sensitivity analysis that adjusted for the follow-up ranges.

In patients with glioblastoma, overall survival (figure 1), median survival, and 2-year survival (table 2) were significantly higher in the high-dose group than in the conventional group. The adjusted hazard ratio for death in the high-dose group versus the conventional group for patients with glioblastoma was 0·49 (95% CI 0·28–0·87, p=0·014).

However, the extra 10 Gy given to 13 of the 61 patients with glioblastoma who received high-dose radiotherapy did not result in a significant survival benefit compared with patients who received 80 Gy

	60 Gy		80 Gy		90 Gy
	Glioblastoma (n=60)	Anaplastic astrocytoma (n=34)	Glioblastoma (n=48)	Anaplastic astrocytoma (n=29)	Glioblastoma (n=13)
Any recurrence	39	22	37	12	10
Local recurrence only	32	16	26	5	4
Local recurrence and dissemination	7	6	11	6	0
Dissemination only	0	0	0	1	6

Data are number of patients.

Table 3: Recurrence by radiotherapy dose

	60 Gy (n=94)	80 Gy (n=77)	90 Gy (n=13)
Toxic effects			
Any	4	17	6
Cognitive dysfunction			
Grade 3	1	1	1
Grade 4	0	0	1
Memory impairment			
Grade 2	0	4	1
Grade 3	1	5	1
Grade 4	0	0	1
White-matter abnormality			
Radiation necrosis	0	7	2
Leucoencephalopathy	1	5	1
Brain atrophy	1	2	0
Time to onset (median [95% CI], months)	136·9 (NC)	32·5 (29·7–35·3)	24·8 (7·9–41·7)

Data are number of patients unless otherwise indicated. NC=not calculable. Some patients had more than one toxic effect.

Table 4: **Radiation-induced toxic effects**

(p=0·89, table 2). The unadjusted hazard ratio for death in patients with glioblastoma in the 90-Gy group relative to the 80-Gy group was 0·94 (95% CI 0·42–2·12, p=0·89) and the adjusted ratio was 0·70 (0·31–1·61, p=0·70).

Kaplan-Meier analyses based on the type of chemotherapy received showed that median survival for patients with anaplastic astrocytoma who received high-dose radiotherapy was not yet reached for those that received nimustine and vincristine, and was 40·6 months (95% CI not calculable because of small number of patients) for those who received nimustine alone (p=0·92). For the conventional radiotherapy group, median survival was 21·9 months (95% CI 14·2–29·6) for those on nimustine and vincristine, and 27·1 months (19·4–34·8) for those on nimustine alone (p=0·78). For patients with glioblastoma, median survival in the high-dose group was 15·8 months (13·4–18·2) for those on nimustine and vincristine, and median survival has not yet been reached in those receiving nimustine alone (p=0·29). In the conventional radiotherapy group, median survival was 15·9 months (8·3–23·5) and 12·1 months (7·5–16·7), respectively (p=0·24).

Progression-free survival was significantly lengthened by high-dose radiotherapy compared with conventional radiotherapy in patients with anaplastic astrocytoma, but not in those with glioblastoma (figure 2, table 2).

Most recurrences occurred at the primary site in both the conventional and 80-Gy groups (table 3). More local recurrences accompanied dissemination in the cerebrospinal fluid space in the 80-Gy group than in the 60-Gy group (p=0·14), and this trend was most notable in patients with anaplastic astrocytoma, although the numbers are small (table 3). Only one of 12 patients with anaplastic astrocytoma and none of 37 patients with glioblastoma who had recurrent disease after receiving 80-Gy radiotherapy had tumour dissemination in the cerebrospinal fluid space without local recurrence. By contrast, dissemination without recurrence was more frequent in patients with glioblastoma who received 90-Gy radiotherapy than in those who received 80 Gy (p<0·0001) or 60 Gy (table 3).

Table 4 shows the frequency and types of radiation-induced toxic effects recorded. The radiation-induced toxic effects that resulted from high-dose radiotherapy were generally tolerable. One patient who received 90-Gy radiotherapy developed grade-4 cognitive dysfunction and memory impairment, which led to reduction of the total dose to 80 Gy for patients with glioblastoma thereafter. None of these patients that received 80-Gy radiotherapy showed grade-4 toxic effects. White-matter abnormalities were significantly more frequent in the high-dose group than in the conventional group (p=0·0002, table 4). Nine patients in the high-dose group developed radiation necroses, compared with none in the 60-Gy group: five necroses were confirmed pathologically from surgical samples and four were diagnosed by PET. Four of these nine patients showed no neurological deterioration and maintained their active daily life after the diagnoses of radiation necrosis. One patient showed tumour recurrence 12 months after development of radiation necrosis. Kaplan-Meier analyses showed that, compared with the 60-Gy group, the median time to onset of white matter abnormality was significantly shorter for both the 80-Gy group (p=0·011) and the 90-Gy group (p=0·0043). Cox analyses showed that lower radiation dose was the only pretreatment clinical variable analysed that lengthened time to onset of white-matter abnormality (p=0·028).

	Hazard ratio (95% CI)	p
Univariate analyses		
Sex (women vs men)	1·51 (0·97–2·33)	0·067
Age (<50 years vs ≥50 years)	0·51 (0·32–0·80)	0·003
Histology (anaplastic astrocytoma vs glioblastoma)	0·43 (0·27–0·70)	0·001
Karnofsky performance scale (80–100 vs 60–70)	0·28 (0·18–0·44)	<0·0001
Tumour diameter (<4 cm vs ≥4 cm)	0·64 (0·42–0·98)	0·038
Tumour location		
Temporal vs frontal	1·14 (0·68–1·91)	0·61
Parietal vs frontal	1·22 (0·65–2·31)	0·52
Occipital vs frontal	0·96 (0·46–2·02)	0·92
Thalamus vs frontal	2·06 (0·85–5·00)	0·11
Extent of resection (≥95% vs <95%)	0·34 (0·21–0·55)	<0·0001
Chemotherapy (yes vs no)	0·81 (0·33–1·99)	0·64
Radiation dose (high dose vs 60 Gy)	0·49 (0·33–0·76)	0·001
Repeat resection (yes vs no)	0·39 (0·16–0·69)	0·003
Salvage chemotherapy (yes vs no)	0·72 (0·35–1·49)	0·38
Multivariate analyses		
Histology (anaplastic astrocytoma vs glioblastoma)	0·41 (0·25–0·67)	<0·0001
Karnofsky performance scale (80–100 vs 60–70)	0·39 (0·23–0·66)	<0·0001
Extent of resection (≥95% vs <95%)	0·41 (0·24–0·72)	0·002
Radiation dose (high dose vs 60 Gy)	0·42 (0·26–0·68)	<0·0001
Age (<50 years vs ≥50 years)	0·72 (0·43–1·23)	0·23
Tumour diameter (<4 cm vs ≥4 cm)	0·95 (0·56–1·62)	0·86
Repeat resection (yes vs no)	0·48 (0·22–1·02)	0·055

Table 5: **Univariate and multivariate analyses for favourable prognostic factors**

Univariate Cox analyses showed that seven of 11 clinical factors analysed were associated with favourable prognosis: age younger than 50 years, anaplastic astrocytoma histology, Karnofsky performance scale of at least 80%, tumour diameter of less than 4 cm, tumour removal of at least 95%, radiation dose of 80 Gy or higher, and repeat resection (table 5). Stepwise multivariate analyses showed that independent factors associated with favourable prognosis were histology of anaplastic astrocytoma, Karnofsky performance scale of at least 80%, tumour resection of at least 95%, and radiation dose of 80 Gy or more (table 5). Age of younger than 50 years was found to be an independent favourable prognostic factor only for the 60-Gy group (hazard ratio 0·32 [95% CI 0·14–0·73], p=0·007) when the 60-Gy and high-dose groups were analysed separately.

Discussion

Our results show that high-dose radiotherapy of 80–90 Gy delivered by a standard fractionation provides a significant survival benefit over standard 60-Gy radiotherapy for patients with supratentorial malignant glioma, without notable increases in radiation-induced disability. The efficacy of conventional radiotherapy of more than 70 Gy for malignant glioma has never been investigated in a multi-institutional randomised-controlled study, because of the general assumption that toxic effects to the brain induced by the radiation dose would outweigh the advantages.[21] The two groups compared in our study, both of which consisted of consecutive eligible patients, did not vary significantly from each other, with the exception of the radiotherapy approaches, since radiotherapeutic techniques have become more sophisticated over time. The survival benefit was most evident in patients with anaplastic astrocytoma. The survival results we recorded for high-dose radiotherapy are comparable with the best treatment outcomes reported to date for anaplastic astrocytoma.[31,32]

Furthermore, median survival and 2-year survival were higher for patients with glioblastoma who were given high-dose radiotherapy than for those given conventional radiotherapy. As expected,[33,34] we noted that radiation-induced white-matter abnormality was significantly more frequent, and the time to onset shorter, with high-dose radiotherapy than with conventional radiotherapy; however, radiation necroses were controllable by steroid administration or surgery. The frequency of impairment to cognition or memory was not significantly increased by the raised dose, and high-dose radiotherapy was generally tolerated well by patients with malignant glioma, which is in agreement with others' findings.[22–24] In support of our findings, Shrieve and colleagues[35] showed that a radiosurgical boost after conventional radiotherapy in 78 patients with glioblastoma resulted in median survival of 19·9 months (95% CI 18·2–23·0) in patients with glioblastoma, even though 39 (50%) patients needed reoperation and 20 (51%) patients who had a reresection had radiation necrosis without evidence of tumour. A concern remains that intensified radiotherapy treatment could lead to long-term effects on cognitive functions that seriously affect quality of life, although this concern is yet to be investigated through careful follow-up of long-term survivors. A randomised trial[4] in patients newly diagnosed with glioblastoma showed that use of temozolomide during and after conventional radiotherapy improved median survival from 12·1 months (11·2–13·0) in those given radiotherapy alone to 14·6 months (13·2–16·8) in those receiving radiotherapy with temozolomide. In our study, use of nimustine-based chemotherapy did not significantly affect prognosis. Potentially, concomitant chemotherapy with temozolomide could further improve the survival benefit obtained by the high-dose radiotherapy.

As to the mechanism of the favourable outcome with high-dose radiotherapy: more patients in the high-dose group than in the conventional group showed dissemination in the cerebrospinal-fluid space, with six of ten patients with glioblastoma who recurred after 90 Gy radiotherapy showing dissemination without local failure, suggesting that tumour regrowth at the primary site is suppressed more efficiently by high-dose radiotherapy than by 60-Gy radiotherapy. Furthermore, in support of our findings, Nakagawa and colleagues[25] showed that 90 Gy radiotherapy in patients with glioblastoma resulted in significantly fewer local failures at the time of recurrence compared with the low-dose radiotherapy group. The high rate of dissemination at recurrence in the high-dose group seems paradoxical, but it should be noted that time to recurrence was significantly longer for patients with anaplastic astrocytoma who received high-dose radiotherapy than for those who received conventional radiotherapy. However, because this finding was from a small number of patients, it could be an artifact. Although many of the patients in our study had extensive removal of the tumour (≥95%), the survival benefit from high-dose radiotherapy was also seen in patients that had less than 95% of the tumour removed when Kaplan-Meier analyses were done separately for subtotal and partial resection (data not shown). This finding suggests that extensive tumour reduction is not needed for patients to benefit from high-dose radiotherapy, whereas it is an independent predictor of good prognosis. Patients with glioblastoma who received high-dose radiotherapy had longer overall survival but similar progression-free survival as did those who received conventional radiotherapy, suggesting that recurrent lesions detected by radiological images after high-dose radiotherapy require longer to cause death than do those seen after 60 Gy radiotherapy.

By contrast with our findings, Chan and co-workers[22] reported that a dose-escalation from 70–80 Gy to 90 Gy did not change survival or patterns of local failure in 34 patients with malignant glioma. An important feature of our high-dose conformal radiotherapy technique that might have affected outcome was that treatments were planned with preoperative CT or MRI scans, and treatments therefore did not take account of the extent of tumour resection. Furthermore, the initial planning target volume included the surrounding oedema plus a 2-cm margin. Many radiotherapy trials for malignant glioma have restricted their planning target volumes to the contrast-enhanced lesion plus a margin, because most patients who receive treatment have local failure, and to lessen radiation-induced toxic effects.[20,22,23,36–38] However, glioma cells are known to migrate along myelinated fibre tracts of the white matter and penetrate to the so-called surrounding oedema depicted on CT or MRI scans,[39] and proton magnetic-resonance spectroscopy has shown that malignant glioma can extend beyond the areas of T2-weighted signal changes on MRI.[40] For these reasons and because high-dose radiotherapy is tolerated well by patients with malignant glioma, inclusion of the regions of surrounding oedema plus a margin in the planning target volume could be important to obtain good local control.

Although new therapeutic approaches are being developed, radiotherapy remains the main postoperative treatment for malignant glioma. Our findings suggest that high-dose conformal radiotherapy with standard fractionation results in a significant lengthening of survival of patients with malignant glioma compared with conventional 60 Gy radiotherapy, without significantly increasing radiation-induced disabilities. If confirmed in correctly powered phase III trials with appropriate integration of systemic antitumour agents, 80 Gy conformal radiotherapy should be regarded as a standard postoperative treatment for supratentorial malignant glioma.

Contributors

M Tanaka analysed data and wrote the initial draft. Y Ino, K Nakagawa, and M Tago contributed to data collection. T Todo analysed and interpreted data, and wrote the article.

Conflict of interest

We declare no conflicts of interest.

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Clinical Study

Pathological changes after radiotherapy for primary pituitary carcinoma: a case report

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Key words: MIB-1 LI, pituitary carcinoma, PRL-producing, radiotherapy, tunnel stain

Summary

Pituitary carcinomas are extremely rare. The definition, diagnosis, therapy, and prognosis are controversial. So far, to our knowledge, there has been no report regarding pathological changes after radiotherapy for primary pituitary carcinoma. We reported a single case of a presumed prolactin staining pituitary carcinoma. We defined carcinoma by premorbid intracranial dissemination of the tumor. There were no proven extracranial metastases. The tumor was silent on PET scanning. The patient received external beam radiotherapy alone as primary therapy. Post-irradiation histology revealed that necrotic tissue made up approximately more than half. Tumor had viable cells. Probably approximately three-fifth of tumor cells were without alteration and approximately two-fifth were with degeneration. We confirmed that necrosis but no apoptosis were coexistent in the cells post irradiation for pituitary carcinoma.

Introduction

Malignant pituitary tumors (carcinomas), currently defined as primary adenohypophyseal neoplasms with evidence of metastatic spread, are quite uncommon and exceptionally rare. Silent corticotroph carcinomas of the pituitary gland represent 0.05% of adenohypophyseal tumors surgically treated at Mayo Clinic during a 20-year period and about 5% of all reported pituitary carcinomas [1]. Defined as tumors having metastasized, primary carcinomas of the pituitary gland represent 0.2% of all surgically treated adenohypophysial neoplasms [2, 3].

As part of initial treatment for pituitary carcinoma, X-ray radiotherapy (RT) was often selected. But so far there has been no report concerning pathological changes after RT. A PRL-secreting pituitary carcinoma is reported with emphasis on pathological changes after RT.

Case report

Presentation and treatment

The patient was a 30-year-old woman. She had noticed irregular menstruation (amenorrhea) in September 2002. She rushed to the Hospital on 20 August 2003, with a severe headache, right eye pain, and a narrow visual field.

Preoperative blood examination

Serum levels were sodium (Na): 132 mEq/l (low, 132–148 mEq/l), PRL: 55.9 ng/ml (high, 0–30 ng/ml), Cortisol (CS): 3.4 μg/dl (low, 4.0–23.3 μg/dl), and free triiodothyronine (FT3): 1.87 pg/ml (low, 2.8–4.5 pg/ml), TSH: 0.01 μU/ml (low, 0.49–3.83 μU/ml), thyroxine (T4): 7.94 μg/dl (normal, 5.71–10.11 μg/ml), triiodothyronine (T3): 0.90 ng/ml (low, 0.92–1.54 ng/ml), free thyroxine (FT4): 1.55 ng/dl (normal, 0.8–1.72 ng/dl), FSH: 1.0 mIU/ml (low, 1–17 mIU/ml), LH: 0.2 mIU/ml (low, 1–22 mIU/ml), GH: 1.29 ng/ml (normal, 0.28–8.7 ng/ml), aldosterone (ALDS): 5.6 ng/dl (normal, 2–13 ng/dl), somatomedin C (SM-C): 288 ng/ml (normal, 121–436 ng/ml), antidiuretic hormone (ADH): 0.15 pg/ml (low, 0.3–4.2 pg/ml), ACTH: 5 pg/ml (low, 7.0–56.0 pg/ml), and glucagon (IRG): 81 pg/ml. Then adrenocortical steroid drug (hydrocortisone, Cortril®: 20 mg/day), thyroid hormone drug (levothyroxine sodium, T4, Thyradin S®: 50 μg/day), potassium chloride drug (Slow-K®: 600 mg/day), and anti-epilepsy drug (sodium valproate, Depakene R®: 400 mg/day) were administered through mouth.

Preoperative radiological examination

Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a large cystic tumor located from sella turcica to suprasella. First of all, craniopharyngioma was suspected, and the treatment method of surgical mass reduction followed by RT was planned. On September 1, tumor resection was tried by interhemispheric approach.

Intraoperative finding

The tumor appearance was pinkish and it looked like vascular tumor. The tumor was soft like rubber and easy to bleed. So it was hard to resect widely and was resected just only to the extent of biopsy, hence postoperative CT and MRI in August 22nd revealed no remarkable change. A state of mania, disorientation and a lowering of encoding efficiency had appeared since then. CT of

the brain in August 29 revealed the pituitary tumor was enlarged rapidly (although we might possibly see the bleeding within tumor). She had disorientation of time and place. Her visual field was normal and her eye movement was full.

Serum levels of such tumor markers as α-fetoprotein, carcinoembryonic antigen, carbohydrate antigen (CA) 15–3, CA125, squamous cell carcinoma, neuron specific enolase, and CYFRA (CK 19 fragment) were all within normal limits. Urine analysis revealed that 17-KS was 1.3 mg/day (low, 2.4–11.0 mg/day), and 17OHCS, U-CS, U-ALDS, and U-TAT were within normal limits.

Postoperative and preradiation radiological examination
MRI of the brain in 1 September 2003 revealed there was a well enhanced mass (30 × 27 × 29 mm) in supresellar region containing a necrotic structure (Figure 1). CT of the chest in September 3, 2003 revealed there was no obviously abnormal finding in the bilateral lung. F-18 fluoro-deoxy-glucose (FDG) positron emission tomography (PET) in 18 September 2003 revealed there was hardly uptake in her pituitary and this result indicated this disease was a typical pituitary adenoma rather than carcinoma. Additionally there was no highly uptake region in her whole body. We searched metastatic lesion and primary lesion to suspect this pituitary tumor was a metastatic tumor, but CT of the abdomen and pelvis, ultrasonography (US) of the mammary gland, US of the thyroid gland, and F-18 FDG PET indicated no evidence of systemic disease. Since the outcome of F-18 FDG PET was negative and hemoccult test was negative in addition to her own bad compliance, we didn't perform fiberscope of the upper and lower digestive tract. We carried forward the treatment regarding as solitary pituitary tumor.

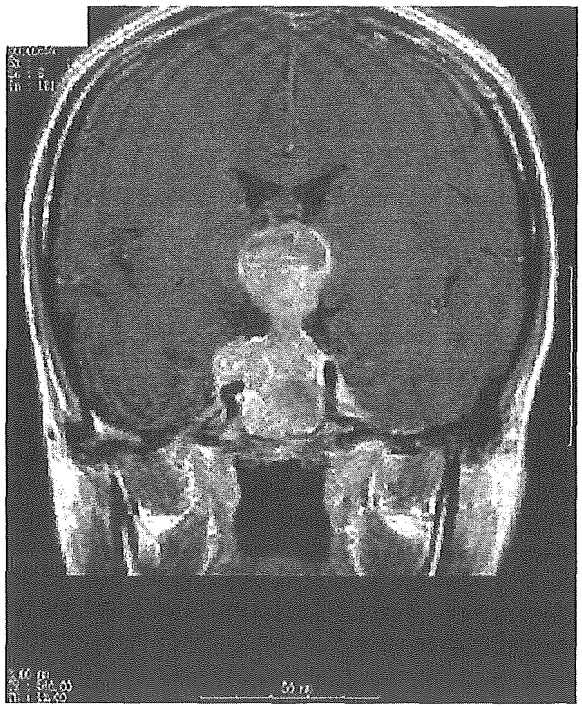

Figure 1. MRI of the brain (coronal, T1-weighted), with gadolinium enhancement before RT. There was a tumor from clivus to sella turcic and suprasellar region with internal necrosis or cystic component. There was a slight segmented tumor. Its diameter was 3.5 × 3 × 6.5 cm. The solid component was enhanced highly. In the right side, it also invade cavernous sinus and encased right distal internal carotid artery. There was an epidural hematoma just under frontal craniotomy region. The postoperative change along with dura was remarkable too. There was no hydrocephalus.

Pathological finding of surgical specimen
Tissue sections were stained with hematoxylin and eosin (H & E) (Figure 2). The diagnosis was the specimen which had tumor tissue with severe heterotype originated in pituitary anterior lobe gland and these histological features were consistent with pituitary carcinoma. Histologically, relatively small tumor cells with atypical nucleus whose body was clear were proliferous solidly . Cellularity was high. Bizarre nucleus and the image of nuclear fission were also outstanding. Additionally, bleeding was accompanied. Hemosiderin deposition was seen in places. In the region where the atypical was relatively weak, reticular structure, which was origin from pituitary, was also seen.

Immunohistochemically, tumor cell was epithelial membrane antigen (EMA): negative, keratin: infinitesimally partially positive, Vimentin: partially positive, LCA: negative, aynaptophysin: positive, chromogranin A: negative, glia fibrillary acidic protein (GFAP): negative (positive in cerebral tissue), MIB-1 (antigen Ki-67) labeling index (LI): 24.1% (proliferation indices were calculated as the percentage of labeled tumor nuclei per total tumor nuclei counted, in the area of greatest tumor labeling) (Figure 3), p53 expression: negative, p21 expression: negative, tunnel: negative, PRL: weakly positive in part, and mitoses (mitotic activity was evaluated at 400× magnification and expressed as number of mitoses per 10 high power fields): 3 × 10 HPF. The stain pattern of epithelial marker was slightly atypical but the findings indicated the tumor was carcinoma originated in neuroendocrine.

Radiation therapy
The patient then underwent dynamic conical conformal radiotherapy (total: 60 Gy, 2 Gy/fraction) using a c-arm-mounted for the sellar and parasellar area in order to control the tumor from 19 September 2003 to 11 November 2003 (Figure 4). At the beginning, we examined combined chemotherapy, but gave it up because of her bad compliance.

Tumor reaction during RT
In 23 September 2003, right palpebra drooping, right miosis, and right external ophthalmoplegia began to worsen. We thought due to direct compression by the tumor in right cavernous sinus, palsy of right oculomotor nerve and trochlear nerve developed. However as the treatment goes on, in mid-October the symptoms improved slowly.

CT in 3 October (at 20 Gy) revealed the tumor became larger slightly compared with CT in 17 September. CT in 17 October (at 38 Gy) and 31 October (at 58 Gy) revealed the cystic component expanded and the tumor had a tendency to become larger slightly.

Acute adverse reaction by RT to become an issue didn't occur.