Gamma Knife Stereotactic Radiosurgery for Atypical and Malignant Meningiomas

Yoshimasa Mori, Takahiko Tsugawa, Chisa Hashizume, Tatsuya Kobayashi, and Yuta Shibamoto

Abstract *Background*: Non-benign meningioma has a known trend to recur repeatedly. The results of Gamma Knife stereotactic radiosurgery (GKS) for recurrent or residual atypical and malignant meningiomas are reported.

Methods: Thirty patients (13 men, 17 women) with World Health Organization (WHO) grade II (24 cases) or grade III (6 cases) intracranial meningiomas underwent GKS. Their age varied from 30 to 86 years (mean 64 years). Before GKS, the tumor was surgically resected in all patients, and 11 of them also underwent conventional external beam radiation therapy, LINAC-based stereotactic radiotherapy (SRT), or intensity-modulated radiation therapy.

Findings: Of the 30 patients, 23 were followed after the initial GKS for a median period of 28 months (range 2–135 months). Local tumor control after treatment was 74 % at 1 year, 52 % at 2 years, and 34 % at 3 years. A total of 15 patients underwent repeat GKS (one to nine times) because of local or distant intracranial tumor progression, seven were subjected to surgical re-resection of the neoplasm, and four had additional SRT. At the time of the last follow-up, 21 patients were alive, and 2 had died. One of the latter expired because of brain tumor progression at 91 months after the initial GKS, and the other patient died from lung cancer.

Conclusions: Although atypical and malignant meningiomas have a trend to recur repeatedly, aggressive tumor management with repeat GKS at the time of progression can provide long survival in these patients.

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Introduction

Meninigomas arise from the dura mater covering the brain. The majority of these tumors are benign, slow-growing, and well-circumscribed. Histologically, 4–7 % of meningiomas are considered atypical, and 1–2 % are anaplastic [9]. Non-benign neoplasms tend to recur within a relatively short time even after radical surgical resection. The 5-year survival rate for these histologically aggressive tumors is 50–70 % [7, 13].

Many recent reports demonstrated that benign meningiomas can be well controlled with stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) if their size after the initial surgical resection is not too large [7]. In the present series, Gamma Knife radiosurgery (GKS) was applied as salvage treatment in cases of recurrent or residual atypical or malignant meningiomas if the localized lesion after initial surgical resection had suitable volume. The objective of this study was to evaluate the efficacy of such treatment for control of the tumor growth and prolongation of the patient's survival.

Materials and Methods

Patient Characteristics

Between May 2004 and April 2011, a total of 30 patients (13 men, 17 women) with an intracranial atypical (24 cases) or malignant (6 cases) meningioma were treated with GKS. Their age at the time of first radiosurgical procedure varied from 30 to 86 years (mean 64 years). There were 6 convexital, 13 parasagittal, 3 tentorial, and 8 skull base tumors. All of the patients underwent surgical resection of the neoplasm before GKS. Additionally, external beam radiation therapy

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(EBRT) was done in eight cases, LINAC-based SRT in two, and intensity-modulated radiation therapy in one. Initial GKS was performed on 36 intracranial tumors (one to three per patient; median was one). Their volume varied from 0.4 to 35.3 cm^3 (median 8.6 cm^3).

GKS Procedure

The Leksell model G stereotactic coordinate frame (Elekta Instruments AB, Stockholm, Sweden) was fixed on the patient's head under local anesthesia supplemented by intramuscular and/or intravenous sedation. Stereotactic magnetic resonance imaging (MRI) was performed to define the tumor location and shape. Images were transferred via an ethernet connection to the Gamma Knife computer workstation (Leksell GammaPlan version 5.34 or, later, 10.1.1; Elekta Instruments AB), where treatment planning took place. Contrast-enhanced MRI was used for identifying irregular borders of the neoplasm. A neurosurgeon and a radiation oncologist identified the target and selected the dose. Choice of the prescription irradiation dose depended on the tumor volume and its spatial relation with adjacent anatomical structures, particularly the cranial nerves. The marginal irradiation dose varied from 11.0 to 20.15 Gy (mean 16.7 Gy). In all cases, stereotactic radiosurgery was performed using the Gamma Knife model C (Elekta Instruments AB) or, later, Perfexion (Elekta Instruments AB).

Follow-Up

The patients underwent regular follow-up at 2- to 6-month intervals. At each examination, the tumor response was evaluated by detailed comparison with the initial MRI scans. The response was categorized as complete (CR), defined as tumor disappearance; partial (PR), defined as >50 % reduction of the tumor volume; stable disease (SD); or tumor progression (PG), defined as >25 % increase in its volume or the appearance of new lesions. If development of the new tumors or progression of the treated neoplasm were revealed during follow-up, the patient typically was offered additional treatment with either repeat GKS or other modality.

Results

In all, 23 of the 30 patients (19 with atypical and 4 with anaplastic meningiomas) were followed after initial GKS for a median period of 28 months (range 2–135 months). A total of 15 patients underwent one to nine additional GKS procedures after the initial radiosurgery because of the development of new tumors or progression of the treated meningioma. Therefore, in total 68 GKS procedures were done in 30 patients (from 1 to 10 in each case). Additionally, during follow-up after initial radiosurgery, surgical re-resection of the tumor was performed in seven patients and SRT in four. No adverse effects—defined as deterioration of the patient's neurological status without tumor progression—were observed during the follow-up either after the initial or repeat GKS.

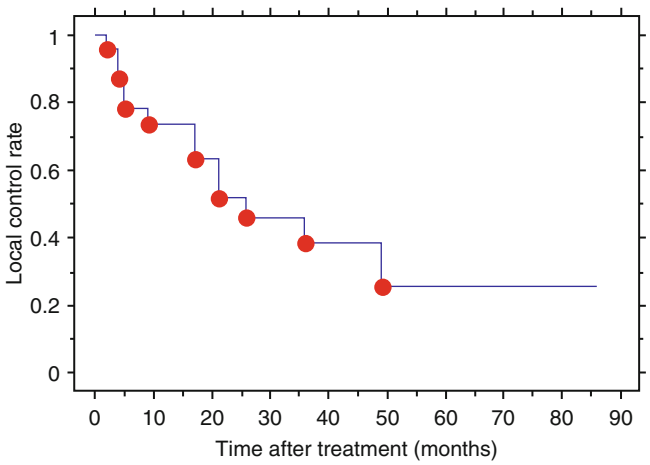

Fig. 1 Kaplan-Meier curve demonstrates the local tumor control rate after the first Gamma Knife radiosurgery of non-benign meningioma

Local Tumor Control

Local tumor control was evaluated in the 23 patients who were followed after first GKS. At the time of the initial treatment they had 26 tumors (mean volume 9.8 cm^3) that were irradiated with a mean marginal dose of 16.5 Gy (range 11.0–20.15 Gy). All of the patients were subjected to regular MRI examinations during the posttreatment follow-up.

The treated neoplasms were controlled (CR + PR + SD) in 10 patients until the last follow-up examination at 9–86 months after initial GKS. In the other 13 patients the treated tumors recurred within 2–49 months after treatment. Local tumor control after initial GKS for atypical and malignant meningiomas was 74 % at 1 year, 52 % at 2 years, and 34 % at 3 years (Fig. 1).

Patient Survival

Of the 23 followed patients, 21 remained alive, and 2 had died. One patient expired because of progression of the intracranial tumor 91 months after initial GKS. The second patient died from lung cancer 17 months after initial GKS.

Thus, cause-specific survival up to 91 months after initial GKS for atypical and malignant meningiomas in the series was 100 %.

Illustrative Case

A 67-year-old man underwent surgical resection of the parieto-occipital parasagittal tumor, which caused bone destruction and protruded under the skin. Histological investigation revealed an atypical meningioma. At 2 months after the operation the residual neoplasm, which had a volume of 18.6 cm^3, was treated with GKS with a marginal dose of 12.5 Gy (Fig. 2). Three years later, marginal progression of the anterosuperior part of the treated tumor was revealed. The enlarging lesion had a volume of 14.1 cm^3 and was selectively treated with a second GKS with a marginal dose of 14 Gy. However, 1.5 year later two newly developed tumors located at the occipital and parietal convexity in the vicinity of the craniotomy flap were disclosed during follow-up MRI investigation. The volumes of these lesions were 2.1 and 2.9 cm^3, respectively, and both underwent a third GKS with a marginal dose of 18 Gy. Six months later the marginal treatment failures in the two portions of the main parasagittal tumor were disclosed. The volumes of the progressing lesions were 23 and 4.5 cm^3, and they were selectively treated with a fourth GKS with marginal doses of 13 and 18 Gy, respectively. During the subsequent 10 months there was no evidence of further tumor progression. With the help of four GKS procedures, the growth of the lesion seems controlled at 6 years after the initial surgical resection, and the neurological condition of the patient remains stable.

Discussion

Compared to their benign (WHO grade I) counterparts, atypical (WHO grade II) and malignant (WHO grade III) meningiomas have higher local recurrence rates and lower patient survival. Previously, the typical initial management of such tumors included surgical removal followed by EBRT. Although this procedure should definitely be considered if gross total resection of the lesion is attained, it should be noted that residual or recurrent high-grade meningiomas are not particularly sensitive to conventional irradiation [2]. Therefore, early SRS in such cases was proposed [4, 5]. Because SRS and SRT can deliver higher irradiation doses to the tumor while sparing adjacent normal tissues, it can be expected that such treatment would be more effective for managing localized neoplasms of a suitable size. It is widely recognized that benign meningiomas, both residual and recurrent after initial surgical resection, can be effectively treated with SRS or SRT. In fact, 5-year local control rates of >90 % can be attained with both techniques [8, 11, 14]. However, only a few reports have mentioned treatment outcomes after such treatment in cases of WHO grade II and III meningiomas [4–6, 10–12, 14]. Moreover, some of the series included an overwhelming number of benign tumors, which does not permit detailed analysis of results [1, 3].

Previously published studies of GKS for atypical and malignant meningiomas are summarized in Table 1. Low local tumor control rates and poor long-term survival were usually recorded, especially for WHO grade III tumors. Stafford et al. [14] showed a striking difference in 5-year local control rates in atypical and anaplastic meningiomas (68 % vs. 0 %). In contrast, in the present series the 5-year local control rates for these two meningioma types did not differ (52 and 50 %, respectively, at 2 years after the initial GKS), although it should be noted that only 4 of our 23 patients that were followed after treatment had malignant tumors. The prescribed marginal radiation dose during GKS for non-benign meningiomas typically varied from 14 to 20 Gy, which is similar to doses for many other types of brain tumor. Of note: Kano et al. [6] reported the results of LINAC-based SRS for high-grade meningiomas and found significantly better outcomes for patients treated with a 20 Gy marginal irradiation dose than for those who received <20 Gy. Their 5-year progression-free survival rates were 63.1 % and 29.4 %, respectively. In the present series, dose selection depended on the tumor volume and location. For small tumors we usually used a marginal dose of 18–20 Gy; for neoplasms with a volume of ~10 cm^3, it was 16 Gy; and for larger lesions it was ~14 Gy. Seemingly, such dose selection permitted us to avoid adverse clinical effects, which were not observed during the follow-up in any patient either after the initial or repeated GKS.

It is evident that SRS fails to inhibit growth of high-grade meningiomas for a prolonged period of time. In the present series, the local tumor control rate after initial GKS was 74 % at 1 year, 52 % at 2 years, and 34 % at 3 years. The high risk of recurrence necessitates close clinical and neuroradiological follow-up. If detailed analysis of MRI scans reveals the appearance of new neoplasms or progression of the treated tumor, repeat GKS can be effective. As was clearly shown in our illustrative case, in patients with marginal treatment failure, further irradiation can be selectively applied only to the enlarging portion of the lesion. It may then lead to cessation of further growth for a prolonged period of time. Other treatment options (re-resection, SRT) should be considered as well. Such aggressive treatment strategy for non-benign meningiomas recurring after initial and repeat GKS permitted for us to obtain rather beneficial results. Although the presented series is not large and the follow-up period is

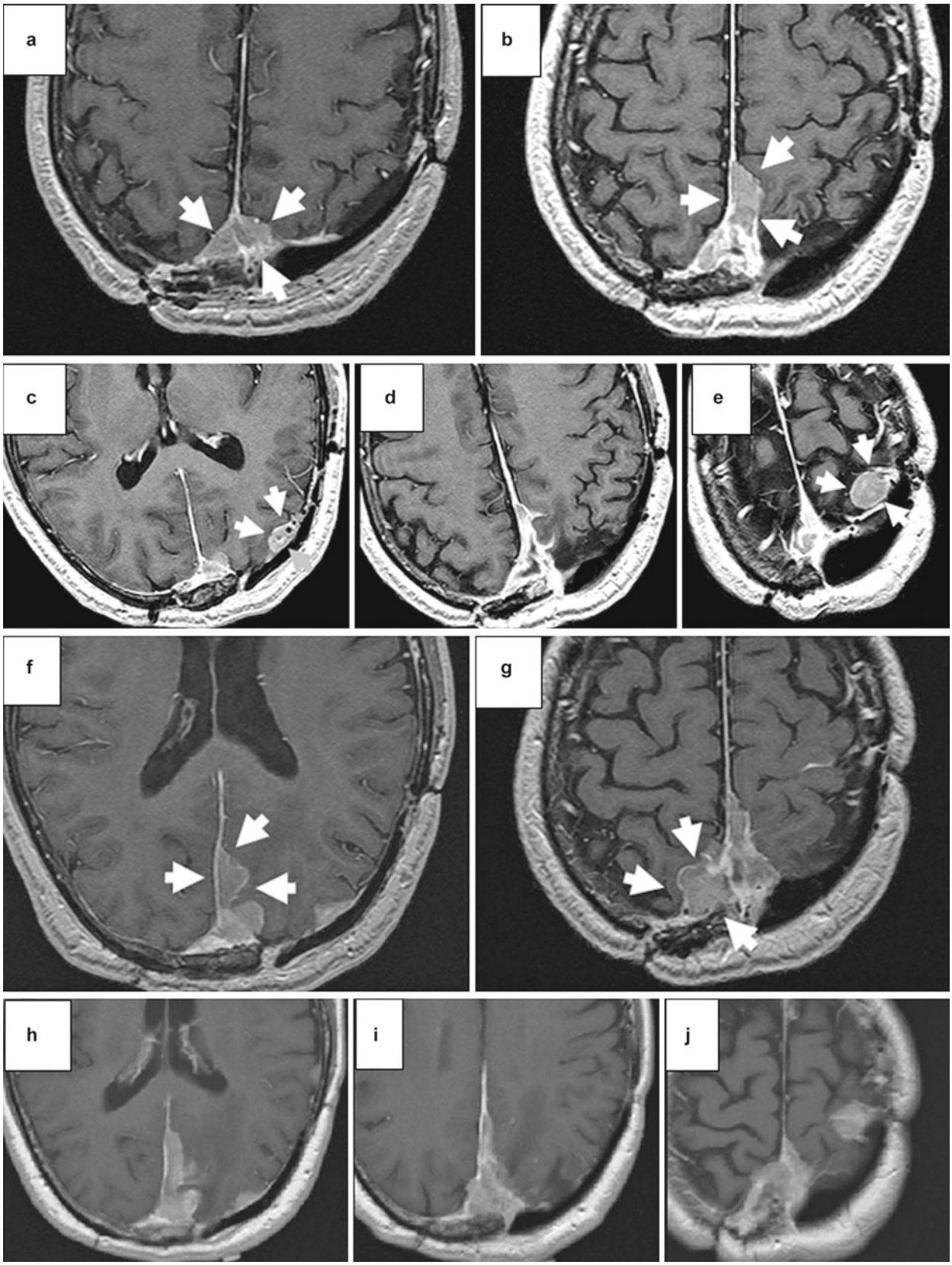

Fig. 2 Axial postcontrast magnetic resonance imaging (MRI) of an atypical meningioma in a 67-year-old man. (**a**) The first GKS was performed for residual tumor after the initial surgical resection (*arrows*). (**b**) The second GKS was performed 3 years later to treat regrowth of the anterosuperior portion of the tumor (*arrows*). (**c**–**e**) The third GKS was performed 1.5 years after the second GKS to address two newly developed distant tumors (*arrows*) in the occipital (**c**) and parietal (**e**) convexity adjacent to craniotomy flap. The main parasagittal lesion showed shrinkage (**d**). (**f**, **g**) The fourth GKS was performed 6 months after the third GKS to address two newly progressing portions of the tumor (*arrows*). (**h**–**j**) Ten months after the fourth GKS and 6 years after the initial surgical resection there is no evidence of further tumor progression

Table 1 Reported series of Gamma Knife stereotactic radiosurgery for non-benign meningiomas

Author, year of publication	Histological subtype	No. of patients (lesions)	Marginal dose (Gy)	Tumor control rate	Survival
Ojemann et al., 2000 [12]	Malignant	19[a] (23)	Mean 16; median 15.5	ND	PFS: 48 % at 2 years, 34 % at 5 years
Stafford et al., 2001 [14]	Atypical	13	Median 16; range 12–36[b]	68 % at 5 years	CSS: 76 % at 5 years
	Malignant	9		0 % at 5 years	CSS: 0 % at 5 years
Harris et al., 2003 [4]	Atypical	18	Mean 14.9	ND	PFS: 83 % at 5 years
	Malignant	12	Mean 15.7		PFS: 72 % at 5 years
Huffmann et al., 2005 [5]	Atypical	15 (21)	Range 14–18	93 % at 6 months	100 % within median follow-up of 35 months (range 21–67 months)
Present series	Atypical	19 (22)	Mean 16.5	74 % at 1 year	CSS: 100 % at 5 years
	Malignant	4 (4)		52 % at 2 years	
				34 % at 3 years	

ND no data, *PFS* progression-free survival, *CSS* cause-specific survival
[a]All patients had recurrent tumors after external beam radiation therapy
[b]Including benign meningiomas

limited, the 5-year cause-specific survival rate of 100 % among our patients seems impressive.

Conclusion

Based on results of the present study, it can be concluded that atypical and malignant meningiomas, both recurrent and residual after initial surgical resection, can be effectively treated with GKS if the volume of the neoplasm is not too large. Regular neuroradiological follow-up with timely identification of the development of new tumors or progression of the treated neoplasm followed by repeat management with GKS or other modalities (microsurgery, SRT) are important for prolongation of the patient's survival.

Conflict of Interest The authors declare that they have no conflict of interest.

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