Gamma Knife Radiosurgery for Brain Tumors: Postirradiation Volume Changes Compared with Preradiosurgical Growth Fractions

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Abstract

The postradiosurgical volume changes were compared with preradiosurgical growth fractions defined as the tumor doubling time and/or MIB-1 staining index in 14 patients who underwent gamma knife radiosurgery for treatment of various brain tumors. The mean preradiosurgical observation period using neuroimaging techniques was 750 days (range 80-2967 days), and the mean follow-up period after radiosurgery was 664 days (range 328-1100 days). There were four neurinomas, three meningiomas, two craniopharyngiomas, two gliomas, one hemangioblastoma, one pituitary tumor, and one intracranially infiltrative lacrimal gland tumor. The mean patient age at the time of radiosurgery was 52 years (range 8-81 yrs). There were eight males and six females. Following gamma knife radiosurgery, the mean tumor half time was estimated to be 789 days (range 124-2101 days), and the volume reduction against the preradiosurgical tumor volume ranged from 6.3% to 76.1%. This study demonstrates that gamma knife radiosurgery can control tumor growth despite the lack of a correlation with preradiosurgical tumor growth or staining indices for MIB-1. Analyses of this type are essential to show that an “unchanged tumor volume” as demonstrated by postirradiation follow-up neuroimaging can be regarded as showing successful radiosurgery.

Key words: brain tumor, radiosurgery, gamma knife, growth fraction, tumor doubling time, MIB-1

Introduction

Stereotactic radiosurgery has become increasingly important as an alternative to initial or repeat surgical resection of brain tumors, particularly for neurinomas and meningiomas. However, the relationship between treatment results and the preradiosurgical tumor growth or tumor proliferation activity has not been analyzed. Such analyses are essential to confirm that an “unchanged tumor volume” demonstrated by postirradiation follow-up neuroimaging is the outcome of radiosurgery.

We compared the postradiosurgical volume changes with preradiosurgical growth fractions defined as the tumor doubling time and/or MIB-1 staining index in 14 patients who underwent gamma knife radiosurgery for treatment of various brain tumors.

Materials and Methods

I. Patient population

Fourteen of 30 patients treated by gamma knife radiosurgery for various brain tumors since 1991 were selected for evaluation of the treatment results defined by postradiosurgical volume changes and the tumor doubling time before irradiation (Table 1). The preradiosurgical observation period using neuroimaging techniques was sufficiently long (mean 750 days, range 80-2967 days) and the qualities of all images obtained both pre- and post-radiosurgically were adequate for the determination of tumor volume. Preradiosurgical neuroimaging examina-
Tumors were not available or their quality was not adequate for the volume determination in the other 16 patients. The mean follow-up period after radiosurgery was 664 days, and ranged from 328 to 1100 days. The eight males and six females harbored four neurinomas, three meningiomas, two craniopharyngiomas, two gliomas, one hemangioblastoma, one pituitary tumor, and one intracranially infiltrative lacrimal gland tumor. These categories are based on pathology in nine cases and on neuroradiology only in five. The mean patient age at the time of radiosurgery was 52 years (range 8-81 yrs).

### II. Gamma knife radiosurgery

Gamma knife radiosurgery was performed at our facility in nine patients, at the Fujieda Heisei Memorial Hospital in four (Cases 1, 8, 10, and 11), and at the University of Tokyo in one (Case 2). The selected dose at the tumor periphery was 12-18 Gy for neurinoma, 15-18 Gy for meningioma, 10 Gy for craniopharyngioma, 10 or 12.5 Gy for glioma, 15.5 Gy for hemangioblastoma, 21 Gy for pituitary tumor, and 20 Gy for intracranially infiltrative lacrimal gland tumor.

### III. Determination of tumor volume and tumor doubling time

Tumor volume was determined by one of the authors (SH), who was blinded to clinical data and the day of the examination, using post-gadolinium magnetic resonance (MR) images or postcontrast computed tomography (CT) scans using a 5 mm slice thickness. In two of the 14 cases, tumor areas were measured on CT scans in cm² using an image analyzing program because MR imaging was not available. Tumor volume was calculated as the total area multiplied by the slice thickness (0.5 cm). In the 12 other cases, two diameters were determined on an axial MR imaging slice including the maximum diameter, and the other diameter on a coronal slice, using the same image-analyzing program. Tumor volume was calculated by multiplying the three diameters by 0.52 ($d^3 \times 0.52$).

Tumor doubling time was calculated as $T \times \log_2/ (\log V_1 - \log V_0)$, where $V_0$ is the initial tumor volume, $V_1$ is the latest tumor volume before radiosurgery, and $T$ is the interval (days) between two examinations. In one patient with acoustic neurinoma (Case 1), the initial CT scans demonstrated no enhanced tumors. It is possible that a small tumor, with all diameters within 1.0 cm, was present and undetected by CT. Therefore, we calculated the tumor doubling time using $0.52 \text{ cm}^2 \times 1.3 x 0.52$ as the initial volume, assuming that any tumor present would have a maximum diameter not exceeding 1.0 cm. Similarly, the postradiosurgical tumor half time was calculated, where $V_0$ is the most recent tumor volume and $V_1$ is the preradiosurgical tumor volume.

### IV. Calculation of MIB-1 staining index

The method used to determine the MIB-1 staining index, defined as the number of MIB-1-positive cells divided by the total number of tumor cells in a 1.037 mm² area on a slide (%), was presented in detail elsewhere.

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*Assumed volume undetected by neuroimaging.*
where. In 10 of the 14 patients, the MIB-1 staining index was determined using formalin-fixed, paraffin-embedded archival tissue sections previously obtained during surgery. All analyses were performed by two of the authors (MI and YU), both blinded to the clinical data, using a randomized technique to examine 122 samples including the 10 samples above. The samples included 61 meningiomas, 24 neurinomas, and 37 other tumor types.

In one patient (Case 2) with bilateral acoustic neurinomas, total removal had been carried out on one side in 1984 and gamma knife radiosurgery was performed on the other side in 1991. The MIB-1 staining index was calculated using a tissue section obtained during the previous surgery. In the nine other patients, the mean interval between surgery and radiosurgery was 997 days, ranging from 108 to 2978 days.

Results

Table 1 summarizes the clinical data and results.

I. Neurinoma (Cases 1–4)

Preradiosurgical tumor doubling times were less than 300 days (216, 249, and 296 days) in three of the four cases and 1733 days in the other case. MIB-1 staining indices were 2.00% in one case and less than 1.00% in the other three. Postradiosurgical tumor shrinkage was remarkable in three cases and tumor growth (cyst enlargement) was clearly controlled in Case 3 (Fig. 1). In three of the four cases, transient tumor enlargement was demonstrated within 100–200 postradiosurgical days. The tumor half time after irradiation was 1604 days in Case 3 with a cystic neurinoma and 650 days or less in the other three. Postradiosurgical tumor half times were not correlated with either the MIB-1 staining indices or preradiosurgical tumor doubling times. However, there was a tendency for the postradiosurgical tumor half times to correlate with the doses selected.

II. Meningioma (Cases 5–7)

Preradiosurgical tumor doubling times were 3793 days in one of the three cases and less than 1000 in the other two. The MIB-1 staining index was 0.58% in Case 5 with a recurrent meningioma. The mean tumor half time after irradiation was 1000 days, with a range of 796–1380 days. Postradiosurgical tumor half times did not correlate with preradiosurgical tumor doubling times. Postradiosurgical tumor shrinkage was remarkable in all cases (Fig. 2). However, the tumor in Case 5 continued to grow with almost same tumor doubling time as that demonstrated preradiosurgically until the 400th postradiosurgical day when it was observed to be shrinking.

III. Craniopharyngioma (Cases 8 and 9)

In the two craniopharyngioma cases, preradiosurgical tumor doubling times were 62 and 46,265 days and MIB-1 staining indices were 3.50% and 2.02%, respectively. The tumor half times after irradiation were 552 and 592 days. Postradiosurgical tumor...
shrinkage was remarkable in Case 9, who had a solid tumor, but Case 8 with a cystic craniopharyngioma showed enlargement of the tumor cyst, with nearly the same tumor doubling time as that preradiosurgically, on the 200th postradiosurgical day and necessitated another aspiration (Fig. 3). Following the aspiration, cyst enlargement has been controlled.

IV. Other tumors (Cases 10-14)

Case 10 with a regrowing hemangioblastoma had a tumor doubling time of 895 days and a MIB-1 staining index of 0.34%, but tumor growth was well controlled by the 800th postradiosurgical day at which point tumor shrinkage was remarkable (Fig. 3). The volume reduction rate and the tumor half time, which were determined using the most recent imaging examinations obtained on postradiosurgical day 1073, were 76.1% and 2101 days, respectively. Case 11 with a regrowing optic glioma had a tumor doubling time of 104 days and a MIB-1 staining index of 2.94%, and tumor growth was controlled as of the 332nd postradiosurgical day. Case 12 with a histologically unverified hypothalamic glioma showed remarkable tumor shrinkage by the 328th postradiosurgical day. Case 13 with a pituitary tumor showed a tumor doubling time of 1821 days, and tumor growth had been controlled as of the 483rd postradiosurgical day. Case 14 with a lacrimal gland tumor had a tumor doubling time of 1660 days and a MIB-1 staining index of 5.47%, and gradual tumor shrinkage was observable following radiosurgery (Fig. 4).

Discussion

Our present study, although the sample size is small, demonstrates that gamma knife radiosurgery can control tumor growth regardless of preradiosurgical tumor growth and MIB-1 staining indices. Following gamma knife radiosurgery, the mean tumor half time was estimated to be 789 days, with a range of 124-2101 days, and the volume reductions against the preradiosurgical tumor volumes ranged from 6.3% to 76.1%.

The effects of radiosurgery on benign brain tumors are considered to be a direct cytotoxic effect on the tumor cells and an intratumoral delayed vascular obliteration which leads to coagulation necrosis of the tumor. Gradual, and eventually permanent, tumor regression is regarded as the ideal treatment result in radiosurgery for brain tumors. Nevertheless, all reported series describing radiosurgery for benign brain tumors such as neurinomas, meningiomas, and pituitary tumors include 40-50% of cases in which the sizes of the treated tumors remained unchanged for many years.

Such "unchanged in size" tumors after radiosurgery were also regarded as showing successful treatment results based on the hypothesis that the vast majority of untreated brain tumors, even if benign, show gradual growth. However, recent analyses of the natural courses of neurinomas and meningiomas using neuroimaging techniques have disclosed that some of these tumors do not grow for many years, though spontaneous shrinkage is very rare.
Olivero et al. reported recently that 35 (58%) of 60 patients with meningiomas had no tumor growth, with a mean follow-up of 29 months (range 3–72 mos). Therefore, we think that, unless significant tumor growth has been observed before radiosurgery, “unchanged in size” after radiosurgery cannot be regarded as a successful treatment result, as shown in two of our cases (Cases 4 and 10).

Further studies involving larger series of patients should be designed to resolve the debate as to whether “unchanged in volume” following radiosurgery for benign brain tumors constitutes a good treatment result.

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