

Gamma knife surgery for treatment of residual nonfunctioning pituitary adenomas after surgical debulking

MARCO LOSA, M.D., MICOL VALLE, M.D., PIETRO MORTINI, M.D., ALBERTO FRANZIN, M.D., CAMILLO FERRARI DA PASSANO, M.D., MARCO CENZATO, M.D., STEFANIA BIANCHI, M.D., PIERO PICOZZI, M.D., AND MASSIMO GIOVANELLI, M.D.

Pituitary Unit, Department of Neurosurgery; and the Department of Ophthalmology, Istituto Scientifico San Raffaele, Università Vita-Salute, Milano, Italy

Object. Radiation therapy diminishes the risk of recurrence of incompletely removed nonfunctioning pituitary adenoma (NPA). The authors evaluated the efficacy and safety of gamma knife surgery (GKS) in patients with residual NPA following surgical debulking of the tumor.

Methods. Fifty-four patients, 26 men and 28 women, ranging in age from 29 to 72 years underwent gamma knife treatment. Baseline and follow-up studies involved magnetic resonance imaging, hormone evaluation, and neuroophthalmological examination 6 and 12 months after GKS and at yearly intervals thereafter. The mean follow up after GKS was 41.1 ± 3.1 months. Two of 52 patients undergoing follow up had a recurrence 40 and 49 months after GKS. In both of these patients the treated lesion had reduced in size, but a new lesion appeared in the contralateral side of the sella turcica. The recurrence-free interval at 5 years was 88.2% (95% confidence interval 72.6–100%). Tumor volume decreased from a baseline value of 2.3 ± 0.2 to 1.7 ± 0.2 cm³ at the last follow up ($p < 0.001$). Twenty-two patients (42.3%) had a 20% or greater reduction in tumor volume. The administered radiation dose had been significantly higher in patients who experienced tumor reduction. Visual function and motility did not deteriorate in any patient. New cases of hypogonadism, hypothyroidism, and hypoadrenalism occurred in 12.5, 8.6, and 2.3%, respectively, of assessable patients at risk.

Conclusions. Gamma knife surgery was effective in controlling the growth of residual NPA after previously performed maximal surgical debulking. The major advantage of GKS compared with fractionated radiotherapy seems to be a lower risk of side effects, especially a lower risk of hypopituitarism.

KEY WORDS • radiotherapy • radiosurgery • pituitary tumor • pituitary surgery • hypopituitarism • gamma knife surgery

CLINICALLY, NPAs consist of a heterogeneous group of tumor subtypes and represent approximately one quarter of all pituitary adenomas.¹⁴ At presentation, almost all NPAs are large extrasellar macroadenomas; therefore, clinical symptoms in patients with an NPA, such as visual disturbances, headache, and impaired pituitary function, are usually caused by compression of surrounding structures. The initial management of NPA involves surgical debulking of the tumor via either the transsphenoidal or the transcranial approach. The aims of surgery are to relieve mass effects on adjacent structures, to obtain a definite pathological diagnosis, and to remove as much of the tumor as possible.¹⁹ Nonetheless, many tumors are not completely resectable without undue morbidity, because of a location next to critical nervous structures or an invasion into the cavernous sinuses. Data from several surgical series demonstrate the presence of adenomatous tissue, as visualized on postoperative computerized tomography scanning or MR imaging, in more than 50% of patients with NPAs.^{6,18,}

^{21,34} One notable exception is the result from a small, recent series of 45 patients, showing postoperative residual disease in only 15% of cases.¹⁶

The persistence of residual adenomatous tissue after surgery is clearly associated with a higher risk of tumor recurrence. This point is well documented both in old surgical series in which the clinical recurrence of NPAs occurred in a substantial percentage of patients^{5,7,8,33} and in more recent studies in which the results were analyzed according to the more sensitive criterion of sequential neuroimaging examinations.¹⁸ There is also no question that radiotherapy significantly diminishes the risk of tumor recurrence.² Gittos and coworkers¹¹ compared the long-term outcome in patients with an NPA who had undergone follow up at two different centers, one offering routine radiotherapy after surgery and the other withholding such treatment in most cases. The actuarial progression-free survival rate was 93% at both 5 and 15 years posttreatment in the radiotherapy-treated group and 68 and 33%, respectively, in the group that had not received radiation.¹¹ Note, however, that fractionated radiotherapy may cause complications such as hypopituitarism,^{17,23,27,29,36} radiation-induced optic neuropathy,^{1,2,3} neurocognitive impairment,²⁵ and development of secondary brain tumors.^{3,4,32} In an attempt to reduce complications

Abbreviations used in this paper: FSH = follicle-stimulating hormone; GH = growth hormone; GKS = gamma knife surgery; LH = luteinizing hormone; MR = magnetic resonance; NPA = nonfunctioning pituitary adenoma; SEM = standard error of the mean.

Radiosurgery for nonfunctioning pituitary adenomas

caused by radiation injury to nearby normal tissue and to improve efficacy, new methods of delivering stereotactic radiation to the tumor have been developed in the last few decades.

Gamma knife surgery is the precise stereotactic delivery of a high dose of radiation to a delimited target during a single session, with a sharp decrease in radiation at the margins of the lesion. It allows for the application of a therapeutic dose of radiation to the tumor, while sparing surrounding normal tissues.¹⁰ Gamma knife surgery is a relatively new technique; thus, there are few published data about its use in the treatment of NPAs.

Our investigation was conducted to evaluate the efficacy and safety of gamma knife treatment in patients with an NPA who had previously undergone surgical treatment at our center and who had residual disease following surgery.

Clinical Material and Methods

Between January 1994 and June 2002, 54 patients (26 men and 28 women) with a diagnosis of NPA who had previously undergone surgical treatment at our center, underwent GKS for residual pituitary tumor. No patient had clinical or biochemical evidence of hormone hypersecretion. Thirty-five patients (64.8%) had undergone surgery once; 17 patients (31.5%), twice; and the remaining two patients (3.7%), three times. No patient had previously received external fractionated radiotherapy and none was undergoing treatment with dopaminergic drugs or somatostatin analogs at the time of GKS. The mean maximal tumor diameter at the time of surgery was 32.2 ± 0.9 mm (range 18–46 mm). Invasion of one or both cavernous sinuses, as demonstrated on preoperative MR imaging studies, was noted in 42 patients (77.8%). Histological analysis revealed the presence of a pituitary adenoma in all patients. Immunocytochemical studies were performed in all patients except two by using standard methods on paraffin-embedded tissue sections. Results were nondiagnostic in three other patients, because the tumor tissue was necrotic or hemorrhagic. Twenty tumors (40.8%) containing more than 5% of cells positive for LH or FSH were classified as gonadotropinomas, whereas 28 tumors (57.1%) were null cell adenomas. The remaining tumor was an occult adrenocorticotrophic hormone–secreting adenoma.

Evaluation of pituitary function included measurement of urinary free cortisol excretion and basal serum free triiodothyronine, free thyroxine, thyroid-stimulating hormone, LH, FSH, prolactin, and cortisol levels. Moreover, testosterone in men and 17 β -estradiol levels in premenopausal women were also measured. Neuroophthalmological examination consisted of a computerized visual field examination. Endocrine and visual functions were evaluated before GKS in all patients. Follow-up studies included MR imaging, evaluation of pituitary function, and neuroophthalmological examination at 6, 12, 24, 36, and 48 months after GKS and at 2-year intervals thereafter. All studies were performed at the Istituto Scientifico San Raffaele when possible; otherwise, the referring physicians performed testing at a local facility, and results, including hard copies of MR images, were sent to us for review. Recurrence of NPA during follow up was defined as evidence on repeated MR imaging of pathological tissue not previously

revealed or growth of residual adenomatous tissue in comparison with its appearance on the earlier MR image. A significant reduction in residual tumor was considered to have occurred when the estimated tumor volume decreased 20%, at least compared with its volume before GKS.

Tumor size was estimated by measuring the maximal anteroposterior, vertical, and horizontal diameters of the lesion on MR images. Tumor volume was calculated using the following formula: $0.5 \times \text{anteroposterior dimension} \times \text{vertical dimension} \times \text{horizontal dimension}$.²⁰ Given the irregular shape of some tumors, volume measurement should be considered to be only a rough estimate of the actual tumor volume.

Hypogonadotropic hypogonadism was diagnosed in premenopausal women with amenorrhea and in men with subnormal testosterone levels. Low or normal gonadotropin levels were also required in both sexes. Postmenopausal women with inappropriately low or normal gonadotropin levels were also considered to have gonadotropin deficiency. Secondary hypothyroidism was diagnosed in patients with a low free thyroxine level and a normal or suppressed thyroid-stimulating hormone concentration; five patients, already on thyroxine replacement therapy because of previous thyroidectomy (two patients) or multinodular goiter (three patients), were not included in the analysis of thyroid function. Secondary hypoadrenalism was diagnosed in patients with low 24-hour free urinary cortisol levels, low morning cortisol levels, and/or clinical symptoms of hypoadrenalism responding to replacement therapy with glucocorticoid agents.

Patient Characteristics

The mean age of patients at the time of GKS was 51.1 ± 1.7 years and ranged from 29 to 76 years. Forty-five patients (83.3%) were treated with GKS because the first postoperative MR image had revealed the presence of residual tumor, whereas the other nine patients (16.7%) chose to undergo GKS after a follow-up MR image had demonstrated enlargement of a previously visualized residual tumor. Neuroophthalmological examination results obtained before GKS were normal in 38 patients (70.4%) and abnormal in the other 16 (29.6%). Even in this latter group, visual function had improved after surgery in 14 patients and had remained unchanged in the other two patients. Note that two patients (3.7%) had abnormal oculomotor function before surgery: one recovered completely at the time of GKS, whereas the other patient suffered an irreversible palsy of the left sixth cranial nerve. Gonadal, thyroid, and adrenal functions before GKS were normal in 26 (48.1%), 38 (77.6%), and 46 (85.2%) patients, respectively. Mean prolactin levels were 10.5 ± 1.2 $\mu\text{g/L}$, ranging from 2.6 to 38 $\mu\text{g/L}$.

Radiosurgical Treatment

Patients underwent placement of the Leksell stereotactic headframe (model G; Elekta Instruments, Stockholm, Sweden) after a local anesthetic agent had been applied. High-resolution Gd-enhanced MR imaging (1.5 tesla, Magnetom Vision; Siemens, Erlangen, Germany) was performed to obtain precise information on the shape, volume, and three-dimensional coordinates of the residual tumor. The MR imaging sequences used were T_1 -weighted, T_1 -weighted with

TABLE 1
Gamma knife surgery parameters for 54 patients with NPA

Characteristic	Value	
	Mean \pm SEM	Range
target volume (cm ³)	2.3 \pm 0.2	0.6–7.8
prescription isodose (%)	50.1 \pm 0.1	50–52
prescription dose (Gy)	16.6 \pm 0.4	12–21
max dose (Gy)	33.2 \pm 0.7	24–42
dose to optic chiasm (Gy)*	6.1 \pm 0.3	1.6–11.0
no. of isocenters	9.6 \pm 0.6	3–23

* Data were available in only 47 patients.

contrast enhancement, and T₂-weighted in axial and coronal planes at 2-mm intervals. Treatment was then planned with the Kula system until 1995 and the Leksell GammaPlan system (Elekta Instruments) thereafter. Radiosurgery was performed using a 201-source ⁶⁰Co gamma knife (model B until December 2001 and model C thereafter). The entire tumor was covered within the 50% isodose line. Several isocenters (range 3–19, median 8.5) were distributed throughout the target volume to conform the dose to the tumor margins. To this aim, small collimator sizes (4 and 8 mm) were used, and frequent source blocking was applied to obtain a sharper dose decrease toward the optic nerves and chiasm. All patients were discharged the day after radiosurgery.

Statistical Analysis

Continuous data were examined for homogeneity of variance and are expressed as the means \pm SEM. Correlation coefficients were calculated with the aid of regression analysis. The Student t-test for paired and unpaired data, as appropriate, was used to compare continuous variables among groups. Categorical variables were compared with the aid of the Pearson chi-square test or the Fisher exact test when subgroups contained fewer than five patients. The Kaplan–Meier method was used to analyze the primary end point of recurrent tumor growth during follow up. Recurrence-free survival was measured from the date of GKS to the date of relapse. Patients with no evidence of tumor regrowth were excluded from analysis at the date of the last MR imaging follow up.

A probability value of less than 0.05 was considered to indicate statistical significance, and all reported values are two-sided. All calculations were performed using a commercially available statistical software package (Stat-View, version 5.0; Abacus Concepts, SAS Institute, Inc., Cary, NC).

Results

Control of Tumor Growth

The principal characteristics of GKS are summarized in Table 1. The mean follow up was 41.1 \pm 3.1 months (range 8–90 months). Fifty patients were followed up for at least 12 months; 39, for at least 24 months; and 20 patients, in excess of 48 months. No patient died during follow up. Two patients declined to undergo further follow up for personal

Recurrence-free survival (%)

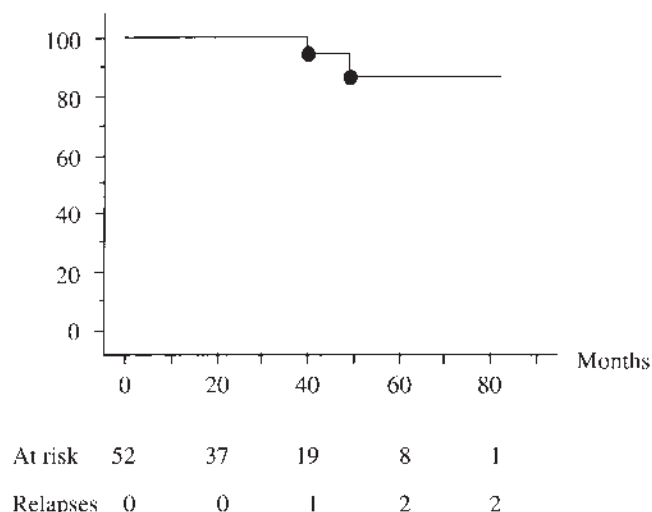


FIG. 1. Graph demonstrating results of a Kaplan–Meier analysis of time to recurrence of NPA in 52 patients who had undergone GKS for residual tumor and at least one MR imaging study post-GKS. A relapse occurred in two patients at 40 and 49 months after GKS. The recurrence-free survival at 5 years was 88.2% (95% confidence interval 72.6–100%).

reasons: their data are included in the analysis of early safety, but not in that regarding control of tumor growth, visual function, and pituitary function. At the last contact by phone, 48 and 59 months after GKS, these two patients are well and deny worsening of visual function or symptoms of hypopituitarism. Another two patients, each with stable residual disease, were lost to follow up after the first MR imaging study. During follow up, two of 52 patients who had undergone at least one MR imaging study after GKS met our predefined criteria for tumor recurrence. Relapse was detected in them 40 and 49 months after GKS. Figure 1 features the disease-free survival curve in the entire group of 52 patients. The recurrence-free interval at 5 years was 88.2% (95% confidence interval 72.6–100%).

Both patients who had experienced a recurrence showed growth of adenomatous tissue located in the contralateral side of the treated lesion (Fig. 2), but this had not been visible on the MR imaging study obtained before GKS. Interestingly, both patients had a clear-cut reduction (> 50%) in the residual tumor that had previously been treated using GKS. Therefore, the control rate of treated lesions was 100%. One of these two patients underwent another gamma knife treatment for recurrent tumor (Fig. 2), whereas the other patient underwent resection of the tumor portion in contact with the optic nerve and is now scheduled to undergo another gamma knife treatment of the residual tissue within the cavernous sinus.

Reduction of the tumor volume was sequentially assessed on MR images obtained in all patients. In this analysis we included the two patients who had shown recurrence of the tumor contralateral to the treated lesion. Tumor volume decreased from a baseline value of 2.3 \pm 0.2 to 1.7 \pm 0.2 cm³ at the last follow up ($p < 0.001$). Individual responses are shown in Fig. 3. During follow up, 22 patients (42.3%) had a significant reduction in tumor volume, which

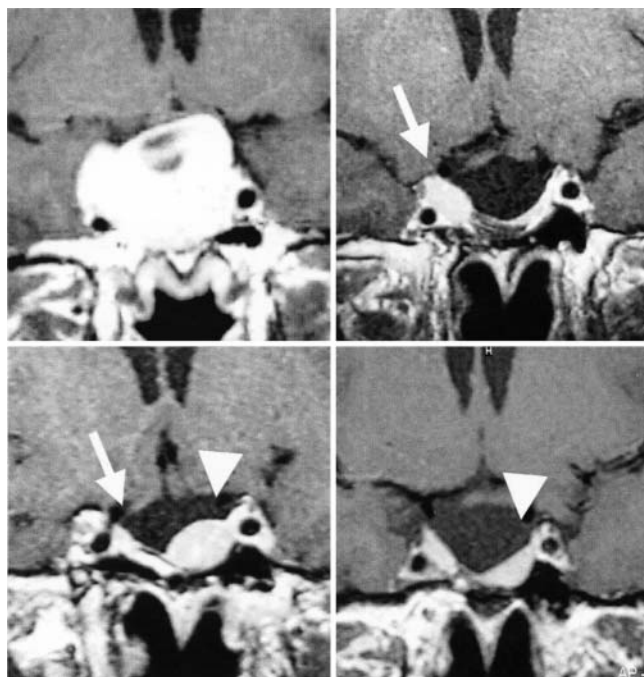


FIG. 2. Several T₁-weighted Gd-enhanced MR images obtained in a 29-year-old man with an NPA. *Upper Left*: Tumor appearance before transsphenoidal surgery. *Upper Right*: First postoperative control image obtained 4 months after surgery. The majority of the tumor has been removed, but there is residual adenomatous tissue located in the right cavernous sinus (arrow). There is no evidence of tumor in the sella turcica or in the contralateral cavernous sinus. Gamma knife treatment was then performed, targeting the tumor in the right cavernous sinus. *Lower Left*: Follow-up image obtained 40 months after GKS. Residual tumor located in the right cavernous sinus (arrow) has markedly decreased in size, but regrowth of adenomatous tissue can be discerned in the left side of the sella turcica (arrowhead). Another GKS was performed, targeting the lesion on the left side of the sella turcica. *Lower Right*: A control MR image obtained 1 year after the second GKS. Recurrent adenomatous tissue in the left side of the sella turcica has diminished in size (arrowhead).

was defined as a decrease of at least 20% compared with pretreatment volume. Table 2 features the main clinical characteristics of patients with tumor shrinkage compared with those harboring stable residual tumor. The radiation dose applied to the periphery of the tumor had been significantly higher in patients who experienced tumor reduction compared with that in patients with stable tumor volume (17.4 ± 0.5 Gy compared with 15.9 ± 0.5 Gy, $p = 0.04$).

Side Effects of GKS

No serious side effects occurred immediately after GKS. Two patients complained of moderate headache for approximately 2 and 4 months after GKS. Visual function did not deteriorate in any patient. One (6.2%) of 16 patients with abnormal results on examination before GKS experienced slight improvement of a visual field defect. No new deficit of oculomotor nerves occurred during follow up. Pituitary function was analyzed separately for each axis. New cases of hypogonadism occurred in three (12.5%) of 24 patients at risk; one man and one premenopausal woman received

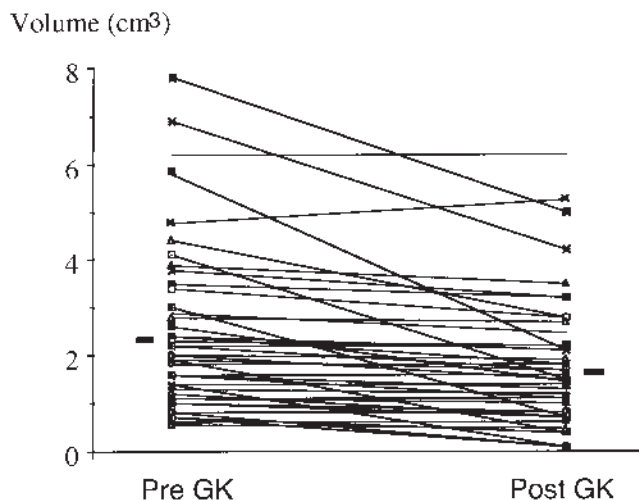


FIG. 3. Individual volumes of residual NPA before and at last follow up after gamma knife treatment in 51 patients with residual or recurring NPA. The two bars indicate the mean values. The difference is significant ($p < 0.001$, paired Student t-test).

replacement therapy, whereas the remaining woman was postmenopausal and did not receive replacement therapy. New cases of hypothyroidism occurred in three (8.6%) of 35 patients at risk; in each of these cases, replacement therapy with L-thyroxine was started. A new case of hypoadrenalism occurred in only one of 43 patients at risk (2.3%). In total, five patients experienced loss of pituitary function: one whose pituitary function had been normal before GKS developed panhypopituitarism, whereas each of the other four patients lost one pituitary axis. No case of diabetes insipidus occurred after GKS.

Discussion

The usefulness of radiotherapy for incompletely removed

TABLE 2
*Clinical characteristics in 52 patients with NPA, grouped according to whether a significant reduction in residual tumor occurred following GKS**

Characteristic	Patients W/ Tumor Shrinkage	Patients W/O Tumor Shrinkage	p Value
no. of patients	22	30	
age (yrs)	50.7 ± 2.8	51.7 ± 2.3	0.80
sex (M/F)	11/11	14/16	0.84
basal prolactin level ($\mu\text{g/L}$)	9.8 ± 1.3	11.3 ± 1.9	0.46
duration of follow up (mos)	41.2 ± 4.6	38.9 ± 4.7	0.55
reason for GKS:	19/3	24/6	0.81
prevention/regrowth			
gonadotropinoma (Y/N)†	10/10	8/18	0.31
no. of isocenters	9.0 ± 0.8	10.1 ± 0.8	0.37
prescription dose (Gy)	17.4 ± 0.5	15.9 ± 0.5	0.04
target volume (cm^3)	2.5 ± 0.4	2.1 ± 0.3	0.37

* Values are given as the means \pm SEM. Abbreviations: N = no; Y = yes.
† Immunocytochemical results were not available in six patients (two with tumor shrinkage and four without tumor shrinkage).

NPA is now widely accepted.^{2,19} Fractionated radiotherapy administered postoperatively in patients with residual tumor detected on neuroimaging studies reduces the likelihood of tumor regrowth.² Nonetheless, considering the benign and slow-growing nature of most NPAs, a low complication rate is a vital requisite for any therapy aimed to control adenoma growth. In this respect, fractionated radiotherapy has well-known side effects, such as the frequent occurrence of hypopituitarism and a low risk of developing second cancers and radionecrosis of nervous tissue.^{1,2} The methodology of GKS has been developed to reduce the exposure of surrounding normal tissues to radiation and therefore to reduce the risk of side effects. Probably because of the limited availability of GKS equipment, there are few data on the effectiveness and safety of GKS in patients with NPA. We studied a homogeneous series of patients treated with GKS for residual NPA. To assure the homogeneity of surgical treatment, we included only patients previously treated at our center by two of us (P.M. and M.G.). Indeed, the amount of residual NPA after surgery seems to be an important prognostic factor of tumor control after fractionated radiotherapy.¹² Maximal debulking of the tumor would seem even more important in the case of GKS to create more space between residual adenoma and critical neural structures, such as the optic pathway and hypothalamus, thereby enabling safer and more effective dose planning. Therefore, it is important to standardize surgical results to permit a correct interpretation of GKS results. The tumor control rate in our series—88.2% at 5 years—is comparable to that achieved in series featuring fractionated radiotherapy,^{5,8,11,12,22,23,31,34} despite differences in the definition of tumor recurrence, especially in the oldest series using clinical rather than neuroradiological criteria. Preliminary results of GKS are in keeping with our experience; that is, unchanged or decreased tumor volume has been reported in 22 of 23 patients with NPA treated using GKS.¹³ In another study there was only one recurrence in 27 patients still undergoing follow up.²⁴ Very recently, the enlargement of treated residual tumor together with a worsening of visual function has been reported in one of 42 patients with NPA.²⁸ Two other cases of GKS failure have been described in a series of 45 patients.³⁵ The patient's condition in both cases was controlled by performing a second gamma knife treatment.³⁵ In a recent paper by Petrovich and coworkers,²⁶ no recurrence of NPA in a group of 56 patients was reported.

The two relapses that occurred in our series deserve comment. In both cases, the target lesion that was treated by GKS decreased in size during follow up, whereas regrowth of adenomatous tissue occurred in the contralateral side that had not been covered by radiation, because no pathological tissue was visualized at the time of GKS (Fig. 2). These two patients represent well the strength and weakness of GKS of NPA. In fact, the highly focused and potent radiation delivered during GKS not only arrested tumor growth, but also induced a marked size reduction in residual tumor. Nonetheless, the selective and precise radiation field afforded by GKS did not cover a few tumor cells, which were not visible on MR imaging at the time of GKS and were located outside the treatment targets, thus leading to recurrence 40 and 49 months after GKS. It is unclear whether other relapses of NPA described in the literature^{13,24,35} either represent primary failure of GKS to control the treated lesion, as in the case reported by Sheehan and coworkers,²⁸ or in-

dicade, as in our cases, growth of tissue located outside the original treatment plan. Besides the already accepted contraindications to GKS, that is, a tumor volume greater than 12 to 15 cm³ or no clearance between the optic pathway and the lesion, it is our current policy to recommend fractionated radiotherapy rather than GKS for residual NPA characterized by heavy and diffuse infiltration into surrounding structures, especially the skull base, to allow for a complete coverage of the tumor bed.

A significant reduction in tumor size ($\leq 20\%$ of pretreatment value) occurred in 42.3% of our patients. Izawa and coworkers¹³ reported tumor shrinkage in 26.1% of 23 patients with NPA. A similar value (22.2%) was also observed by Mokry and coworkers.²⁴ Note, however, that no exact definition of tumor shrinkage was given in either of these reports, making comparisons difficult among the different studies. In the series reported by Sheehan and coworkers,²⁸ 18 (42.9%) of 42 patients had a decrease of at least 2 mm in one of the three maximal tumor diameters. Wowra and Stummer³⁵ sequentially measured tumor volumes by using GammaPlan software. In a subgroup of 30 patients available for quantitative analysis, there was a significant reduction in tumor volume from 1.7 cm³ at baseline to 0.6 cm³ at the last follow up.³⁵ We found no significant association between several patients' characteristics and occurrence of tumor shrinkage, except for the radiation dose applied at the periphery of the lesion.

A low complication rate is a vital consideration for any new therapy aimed at controlling the development of usually slow-growing benign tumors such as NPA. No serious side effect occurred in our series or in others.^{24,35} On the other hand, one patient each in the series of Izawa, et al.,¹³ and Sheehan, et al.,²⁸ experienced deterioration of visual fields without evidence of tumor growth, probably because of radiation-induced optic neuropathy. To minimize the risk of serious injury, a dose of less than 8 Gy to the optic chiasm is advisable, even though a dose of 10 Gy is unlikely to cause optic neuropathy.¹⁵ We and other investigators of similar reported series^{13,24,28,35} did not detect any new deficit of oculomotor function, thus confirming the well-known radioresistance of oculomotor nerves. Hypopituitarism following fractionated radiotherapy is the most common long-term complication,² developing in 50 to 60% of patients treated using surgery and radiotherapy.^{17,31} The contributing role of fractionated radiotherapy to development of hypopituitarism has been estimated at 20 to 40%.^{23,27,31,36} Although pituitary insufficiency can be corrected by life-long hormone replacement therapy, there is concern about the long-term sequelae of hypopituitarism. Indeed, patients with hypopituitarism have an almost doubled risk of death compared with that in healthy volunteers.^{2,30} Gamma knife treatment of residual NPA induced new cases of pituitary insufficiency in only 12.5, 8.6, and 2.3% of assessable patients at risk for hypogonadism, hypothyroidism, and hypoadrenalism, respectively, after a mean follow up of more than 3 years. We excluded GH deficit from our analysis because we did not perform a GH stimulation test in all patients either before or during follow up. Other study data revealed contrasting results in patients with NPA. Mokry, et al.,²⁴ detected deterioration of pituitary function, requiring new replacement therapy in two patients, but it is unclear how many patients had normal pituitary function before GKS. In another two series authors reported no develop-

ment of new pituitary insufficiency after GKS.^{13,28} The only study that featured actuarial analysis demonstrated that the risk of GKS-induced pituitary damage was 14% at 6 years.³⁵ At odds with these results, Feigl and coworkers⁹ found a relatively high probability of hypopituitarism in a series of 92 patients with pituitary adenoma, 61 of which were NPAs, treated using GKS. After a mean follow up of 4.6 years, the percentages of patients with new pituitary insufficiency requiring replacement therapy were 21.7, 23.9, 8.7, and 13% for gonadal, thyroid, adrenal, and GH function, respectively. This study, the only one revealing data on GH deficit, demonstrated a higher probability of new pituitary insufficiency in patients receiving a higher radiation dose to the pituitary stalk. Fractionated radiotherapy has been reported to cause neurocognitive impairment in patients with pituitary adenoma,²⁵ but no data are yet available on the behavioral effects of gamma knife treatment. Nonetheless, the highly focused radiation delivered during GKS should expose the normal nervous tissue to a lower radiation than that after fractionated radiotherapy.

Because GKS is a relatively new treatment modality, the main limitation of the present study as well as other similar series reported as yet,^{9,13,24,26,28,35} is the short duration of follow up. Progression of tumor growth after fractionated radiotherapy seems to continue at a steady rate as long as 20 years after treatment.⁴ A mean follow up of approximately 4 to 5 years is therefore sufficient to outline the results of GKS in the short term and midterm, but real control of tumor growth in the long term necessitates continuing follow up of these patients. The same caveat holds true for some side effects of radiotherapy; in particular, the probability of new pituitary insufficiency and development of secondary brain tumors seem to increase with time after fractionated radiotherapy.

Conclusions

We found GKS to be effective in controlling the growth of residual NPA after maximal surgical debulking. The major advantage of GKS, compared with fractionated radiotherapy seems to be a lower risk of side effects, especially if the minimal risk of hypopituitarism reported in our and other series will be confirmed in future studies with longer follow-up periods. Regardless, careful selection of patients with NPA is necessary to obtain the best results. At present, gamma knife treatment in patients with heavily infiltrating NPA should be indicated cautiously because of the risk of recurrence of the tumor outside the field of radiation.

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Address reprint requests to: Marco Losa, M.D., Department of Neurosurgery, Istituto Scientifico San Raffaele, Via Olgettina 60, 20132-Milano, Italy. email: losa.marco@hsr.it.