Stereotactic Radiosurgery of Pituitary Adenomas

E.D.F. Motti, M. Losa, S. Pieralli, A. Zecchinelli, B. Longobardi, E. Giugni, and L. Ventrella

The first gamma knife (GK) treatment of a pituitary adenoma in 1967 was meant as an alternative to the primitive surgical approaches that prevailed at the time, with consequent unsatisfactory results. Surprisingly, pituitary adenomas still account for only 7.8% of the 27,000 cases treated in GK centers worldwide. Transnasosphenoidal surgery has greatly improved and surgeons are reluctant to give up a relatively safe and effective operative technique. Radiosurgery is not currently vying to be the primary method of "surgery," but has a definite role following failed pituitary surgery and for tumors that extend into the cavernous sinus. Of 300 patients treated in our GK service, 30 had pituitary adenomas and most had undergone surgery. To date, we have not noted any side effects in the pituitary group. Published information is also reviewed and divided, where possible, into the pre–computed tomography (CT) era and the era of CT–magnetic resonance imaging (MRI). Growth hormone (GH)-secreting adenomas and prolactinomas tend to be larger and cannot be treated with the high doses successful against corticotropin (ACTH)-secreting tumors in Cushing's disease. Radiation fall-off is steep in GK radiosurgery, with the 20% isodose curve being only millimeters away from the point of maximal radiation. The effective dose has mostly been decided on the basis of maintaining safe levels at the sensitive perisellar neural structures. The safety of GK treatment (with no mortality and no permanent morbidity) is compared with other radiosurgical techniques. Good patient response owes much to the cumulative experience of GK pioneers and also to recent advances in images and computers that have enabled increasingly precise sterotaxic targeting and dose planning.

PITUITARY DISORDERS have been among the earliest targets[1] for the clinical application of irradiation techniques in all their forms. This is doubtless due to the convenient location of the pituitary inside a bony recess, so that it is readily identifiable on conventional x-ray plates. Conventional external radiotherapy, stereotactic implantation of radioisotopes, charged particle irradiation, Linac, and gamma knife (GK) stereotactic radiosurgery have all been employed.

Limitations with earlier neuroradiological techniques and computational capacity mostly restricted the goal of therapy to pituitary ablation by means of high-dose radiation. The current great advances in diagnosis and imaging have made the selective destruction of tumor, with preservation of the surrounding functional pituitary tissue, an attainable therapeutic goal. There are essentially two external radiosurgical methods—stereotactic particle-beam irradiation (available in two US and two Russian centers) and GK radiosurgery by fixed cobalt sources (available at about 60 sites around the world). Linear accelerators (Linac) adapted for stereotactic procedures have also been employed.

Radiosurgery can be defined[2] as the precise stereotactic delivery in a single session of a high radiation dose to a delimited target with sharp fall-off of radiation at the target margins. Currently, the definition also accommodates the practice of dose fractionation in four to five sessions as employed at charged-particle cyclotron centers.

The great diffusion of radiosurgery based on the GK is accounted for by its easy introduction into the clinical routine of a busy neurosurgical center. This compares with clinical charged-particle installations, which are rare because they require major financial and staffing investment for establishment and operation. Nevertheless, it is surprising that pituitary adenomas, given the long history of interest in the context of radiosurgery and the features that make them almost ideal targets, account for only 7.8% of the 27,000 accrued cases treated in GK centers worldwide (up to December 1994). The most likely explanation is that transnasosphenoidal microsurgery has come a long way in the years since the first GK treatment of a pituitary adenoma in 1967 (as an alternative to the prevailing primitive surgical approaches, which had unsatisfactory results). Surgeons are understandably reluctant to give up a relatively safe and effective operative technique. Radiosurgery is not currently vying to be the primary method of "surgery."

Imperfect methods of stereotactical imaging of the pituitary (such as plain axial computerized tomography [CT]) have further hampered development of the field; it is only recently that good-quality magnetic resonance imaging (MRI) reconstruction in the coronal plane has allowed a new degree of precision for the stereotactic radiosurgeon. Macroadenomas are not a casual radiosurgical target; even when well outlined by modern imaging techniques and located in extracerebral space, they are closely located to delicate structures (visual pathways, trigeminal and oculomotor nerves, hypothalamus, and normal pituitary) and thus place tight constraints on the physical range of the safe radiosurgical parameters. The field is replete with anedoctal episodes (mostly unpublished) of serious damage (mostly wrought by cruder Linac techniques) to perisellar structures. Unlike most radiosurgery, which aims to obliterate life-threatening growths, radiosurgical treatment of the pituitary, like microsurgery, also aims at functional control—reversal of a menacing endocrinopathy, rather than "removal" of tumor mass. All of these factors have contributed to obscure the advantages of radiosurgery in the treatment of pituitary tumours. The situation may be exacerbated because the technical limitations prevailing at the time of

From the Neurosurgery Clinic of the University, and Neuroradiology and Physics Department, San Raffaele Scientific Institute, Milan, Italy.

Address reprint requests to E.D.F. Motti, MD, Neurosurgery Clinic of the University, San Raffaele Scientific Institute Milano, Via Olgettina 60, I-20139 Milan, Italy.

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the early GK series and the uneven quality of Linac techniques employed in different centers have not produced results as successful as expected.

What emerges from the available published experience[3-6] is that corticotropin (ACTH)-secreting tumors are often very small and require high dosages at the periphery to achieve cure. Growth hormone (GH)-secreting tumors and prolactinomas are larger, and their larger size has possibly prevented use of the high dosages shown to be successful in Cushing's disease. However, they are currently being shown to be more radiosensitive than the ACTH-secreting growths.[3]

PRELIMINARY EXPERIENCE IN MILAN

In the 2-year period between December 1993 and November 1995, of 300 patients treated in our GK service, 30 were pituitary adenomas, most having already undergone either single or repeat surgery. Pituitary adenomas were not considered for radiosurgery if the optic chiasm was closer than 4 mm from the tumor margin. Although exceeding the worldwide prevailing ratio of pituitary to nonpituitary cases, our radiosurgical experience is still limited both in the number of pituitary patients treated and in follow-up time: 12 GH-secreting (only two were not recurrences), seven ACTH-secreting (only one was not a recurrence), six nonsecreting (all recurrences following surgery), four thyrotropin (TSH)-secreting (all recurrences following surgery), and one prolactin (PRL)-secreting (residual at surgery).

We have not fully analyzed the data as yet. Our initial results, at early follow-up after radiosurgery, in two GH-, two ACTH-, and two nonsecreting adenoma patients, are presented in Table 1. Among the three patients who did not have surgical recurrences, one acromegalic had steadfastly refused surgery over a period of 15 years and the other two were assessed unfit for anaesthesia and transnasosphenoidal surgery for circulatory and respiratory reasons.

The treatment dose at the target margin (always administered in a single session) ranged between 12 Gy and 22 Gy; the maximal dose was mostly decided by working backwards from a ceiling of the safe values that could not be exceeded at the margin of the sensitive neural structures. In all cases, treatment was shaped to conform closely to the target volume; to obtain this, the number of isocenters ranged between one and 13 and a number of specific individual modifications (partial plugging of secondary collimators and appropriate positions [gamma angles]) were employed (Fig 1).

REPORTED RESULTS

We expect our long-term results to parallel the sparsely published reports in the world literature, which give the following success rates (divided where possible into the pre-CT era and CT-MRI current methods).

ACTH-Producing Tumors

Early Series

- Out of 51 patients (localized by pneumoencephalography), 70% to 80% were cured by GK (including diverse treatment strategies adopted in the course of the longer follow-up of 2 to 15 years).[7]
- Seven of 22 patients failed to respond following stereotactic helium ion-beam irradiation.[8]

Recent Series

- A short follow-up of limited cases treated in GK shows that five of seven patients achieved complete remission.
- The remaining two improved (100% did not require replacement therapy).[7]
- In another series of 12 patients with Cushing's disease with longer follow-up, three patients normalized and four improved.[9]
- Forty of 42 were successfully treated following stereotactic helium ion-beam irradiation.[10]

GH-Secreting Tumors

- Tumor size reduction or stabilization is reported to occur following GK.[9]

Table 1. Initial Results, at Early Follow-Up After Radiosurgery, in Two GH-, Two ACTH-, and Two Nonsecreting Adenoma Patients

GH Patients	Suppression Therapy	Substitution Therapy	Serum GH	Somatomedin	Size at MRI	Follow-Up
1 34-yr male	No (unchanged)	Irregular	**Reduced**	**Reduced**	=	1 yr
2 31-yr female	No (unchanged)	No (unchanged)	**Normalized**	**Normalized**	=	6 mo
ACTH Patients	**Substitution Therapy**	**Serum ACTH**	**Urinary Cortisol**	**Serum Cortisol**	**Size at MRI**	**Follow-Up**
3 49-yr female	Unchanged	Unchanged	Unchanged	Unchanged	=	6 mo
4 39-yr male	**Withdrawn**	**Normalized**	**Normalized**	**Normalized**	=	6 mo
Nonsecreting Patients	**Hypopituitarism**	**PRL**	**Visual Acuity**	**Visual Field Defects**	**Size at MRI**	**Follow-Up**
5 74-yr male	No (unchanged)	Normal (unchanged)	**Improved**	Unchanged	**Reduced**	6 mo
6 34-yr male	No (unchanged)	Normal (unchanged)	Unchanged	Unchanged	=	6 mo

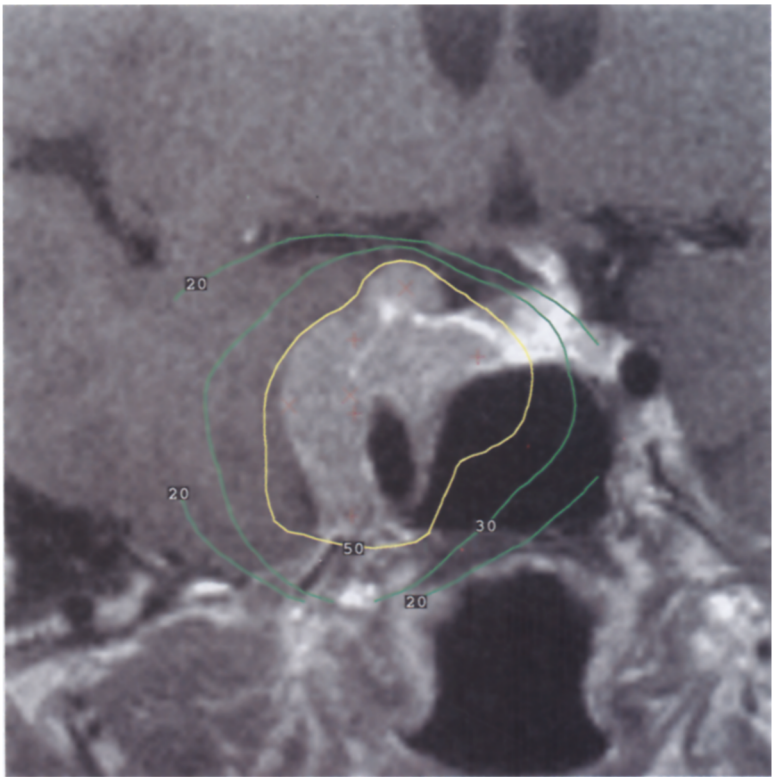

Fig 1. A 51-year-old woman had a large nonsecreting pituitary adenoma residual at operation with extension in the right cavernous sinus. MRI coronal reconstruction with overimposed treatment plan outline shown. Treatment has been prepared to deliver 15 Gy at the 50% isodose curve. The 20% isodose curve (6 Gy) is outside the optic chiasm.

Early Series

- GH levels normalized in 10 of 21 patients (localized by pneumoencephalography), decreased in four, and were unaffected in seven.[7]
- Mean GH levels decreased by nearly 70% within 1 year and continued to decrease over a 10-year period following stereotactic helium ion-beam irradiation, with most treatment failures resulting from inaccurate assessment of extrasellar tumor extension.[8]

Recent Series

- In a 9-month follow-up of four cases treated by GK, three of four patients had complete remission and the fourth showed improvement.[7]

PRL-Secreting Tumors

- Tumor size reduction is reported following GK but, more meaningfully, hyperprolactinemia levels decrease and so become amenable to nontoxic bromocriptine doses.[3,7]
- Nineteen of 20 patients had a marked fall in PRL levels (12 to normal levels) following stereotactic helium ion-beam irradiation.[8]

Nonsecreting Tumors

- After GK radiosurgery in 10 patients, five had a decrease in tumor size and five had no change, so that while tumor size did not decrease, neither did it enlarge.[9]

SIDE EFFECTS

In contrast to other radiosurgical series, which report a 20% incidence of complications,[11] we have to date seen no serious side effects in our overall series of 300 treated cases. Unwanted effects have included delayed resistant headache in skull-base tumors (two cases that resolved within 1 month) and a local increase in peritumoral brain edema (three cases responsive to corticoids). No side effects were noted in the pituitary-treated group.

In the initial series of heavy-particle pituitary radiosurgery, two of 283 patients had temporal lobe injury following stereotactic helium ion-beam irradiation.[8] Temporal lobe injury occurred in three of seven patients who had stereotactic helium ion-beam irradiation following conventional radiotherapy.[8] Mild or transient visual symptoms occurred in five patients. In recent series, GK and heavy-particle beam centers have not reported any deleterious effects on normal pituitary function or any neuroophthalmological morbidity.

CONCLUSIONS

If patients nowadays respond better overall to treatment than those of the past, this is due to the cumulative experience of the pioneers who provided the guidelines with regard to dose, conformation, safety precautions, and surgical strategies. Credit is also due to the great recent advances in imaging and computers, which have enabled precise targeting and much more reliable dose planning in three-dimensional displays.

The safety of GK treatment (with no mortality and no

permanent morbidity, along with the great improvements in localization following the introduction of high-resolution MRI) means that radiosurgery now has a role as an adjunct to failed pituitary surgery. Extension in the cavernous sinus is already an indication to radiosurgery, which has no suitable alternative. Once the relationships between dose and volume and radiosensitivity in each of the different endocrinopathies have been elucidated, imaging techniques may well take a further leap forward (as in previous 5-year intervals). Radiosurgery, with its great record for safety, may then be redefined as the elective primary therapy for relatively small intrasellar pituitary adenomas.

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