ASIA-PACIFIC JOURNAL OF ENDOCRINOLOGY REVIEW ARTICLE

Gamma Knife Radiosurgery: A New Therapeutic Tool of Relevance to the Endocrinologist

Hari Chandran, FRCS, Thomas Philip David Blackburn, FRCS and P Nicholas Plowman, MD, FRCR, FRCP

Affiliation: *The London Gamma Knife Centre at Barts, St Bartholomew's Hospital, London, UK*

ABSTRACT

The management of pituitary adenomas entails a multidisciplinary approach that involves neurosurgeons, endocrinologists, and radiation oncologists. Traditionally, the treatment included medical management, surgery (transsphenoidal microsurgical resection and transcranial approaches), and conventional fractionated radiotherapy. Stereotactic radiosurgery, through the various competing radiosurgical techniques, has been shown to be effective in the management of residual or recurrent pituitary adenomas. It is effective in controlling adenoma growth and achieving endocrine remission. Brain metastasis from thyroid malignancies is rare, and gamma knife radiosurgery, like surgical resection, has been shown to be potentially beneficial. We have reviewed the outcome of gamma knife radiosurgery in the treatment of recurrent and residual pituitary adenomas and brain metastasis from thyroid carcinoma. The conclusion was that gamma knife radiosurgery is a safe and effective treatment for recurrent or residual pituitary adenomas, although surgery remains the primary treatment modality, and brain metastases from thyroid carcinoma.

Keywords: gamma knife, pituitary adenomas, secretory, non-functioning, thyroid carcinoma, metastasis

Correspondence: Hari Chandran, 15, Jalan Awan Cina, Taman Yarl, 58200 Kuala Lumpur, Malaysia. Tel: 006012 2366991. Fax: 00603 79586360. e-mail: hari666@gmail.com

INTRODUCTION

Stereotactic radiosurgery has been used in the treatment of tumors of interest to the endocrinologist for more than 30 years [1]. It has emerged as a viable treatment option in the management of pituitary adenomas and the rare brain metastases from thyroid carcinoma.

Pituitary adenomas are tumors that arise primarily from the adenohypophysis. Neurohypophyseal tumors are extremely rare. They are common lesions and represent about 10–20% of intracranial tumors. Epidemiology studies have shown that nearly 20% of the general population have a pituitary adenoma [2]. They are commonest in the third and fourth decades, and males and females are equally affected. There is an increased incidence in multiple endocrine neoplasia (MEN) [3].

Pituitary adenomas are classified, based on their size, into microadenomas (<1 cm in diameter) and macroadenomas. About 50% of pituitary tumors are less than 5 mm at the time of diagnosis [3]. Pituitary adenomas are also classified broadly into functioning/secretory and non-functioning/non-secretory adenomas, based on their ability to cause clinical hormone hypersecretion syndromes. The former secrete excess amounts of pituitary hormones. Non-functioning adenomas are also called endocrine inactive tumors. They are either non-secretory or secrete products, such as gonadotropin, that do not cause any endocrinological symptoms. The clinical syndromes associated with functioning pituitary adenomas depend on the type of hormones secreted.

Prolactinomas are the most common secretory adenomas. They cause amenorrhoea–galactorrhoea syndrome in females, impotence in males, and often infertility in either sex. They also causes bone loss [3]. Cushing's disease is an adenocorticotropic hormone (ACTH)-secreting adenoma. This causes either Cushing's syndrome due to hypercortisolism or Nelson's syndrome in patients who have undergone bilateral adrenalectomy for the treatment of Cushing's syndrome. The growth hormone (GH)-secreting adenomas cause acromegaly in adults and, rarely, gigantism in prepubertal children before epiphyseal closure. The rarer functioning pituitary adenomas are the thyrotropin (TSH)-secreting adenoma, which causes thyrotoxicosis, and the gonadotropin (leutinizing hormone (LH) and follicle-stimulating hormone (FSH))-secreting adenomas, but these do not usually produce clinical syndromes [3].

Non-functioning pituitary adenomas account for about 30% of pituitary tumors [2, 4]. They do not usually present with clinical symptoms until they reach a sufficient size within or beyond the confines of the pituitary fossa to cause clinical manifestations due to mass effect. Compression of the optic apparatus can result in a spectrum of visual field defects, commonly bitemporal hemianopia and junctional scotoma. They commonly result in panhypopituitarism as a result of compression of the normal functioning pituitary gland.

The evaluation of a patient with a pituitary adenoma starts with a history and physical examination. Ophthalmology review with formal visual acuity and visual field testing and

endocrinological evaluation follows. Routine and special endocrinological tests are carried out depending on the underlying suspected pathology. For Cushing's and Nelson's syndrome, this would include the morning and mean serum cortisol levels [5], plasma ACTH levels, and 24-h urine free cortisol determination. Tests for GH-secreting adenomas include fasting serum GH level, GH levels in response to a glucose challenge, and the serum insulin-like growth factor (IGF)-1 levels. Serum prolactin levels are assayed for prolactinomas. These hormonal levels are also used as prognostic indicators and in defining remission following treatment.

Following the first failed surgical attempt in 1893 for a GH-secreting adenoma via a temporal craniotomy, surgery for pituitary adenomas has gone from the initial transsphenoidal success in 1907–1910 to the development of effective transcranial approaches and back to the transsphenoidal approach in the 1970s and thereafter [6]. Today, transsphenoidal microsurgical resection of adenomas, alone or in combination with medical therapy, remains the mainstay of treatment for patients with symptomatic tumors, i.e., ACTH- and GH-secreting adenomas and prolactin-secreting tumors after failed medical therapy with dopamine agonist drugs bromocriptine and carbagoline [7]. The transnasal endoscopic approach is fast gaining popularity among pituitary surgeons.

However, recurrent or persistent disease remains an important problem in a minority of patients. Long-term outcome of transsphenoidal surgery in a series of 4020 patients with pituitary adenomas treated over three decades reported by Laws *et al* showed the following [8, 9]: (i) in patients with non-functioning adenomas, the recurrence rate at 10 years was 16%; (ii) in patients with GH-secreting adenomas, the biochemical remission was achieved post-operatively in 88% of microadenomas and 65% of macro-adenomas; (iii) the recurrence rate was 13% at 10 years for patients who underwent surgery for prolactinomas and achieved normalization of prolactin postoperatively. Here, biochemical remission occurred in 87% of those with microadenomas and 56% of those with macroadenomas; (iv) in patients with Cushing's disease, the analysis revealed that there was a higher recurrence rate among children (42%) than among adults (12%), and postoperative remissions, defined as a normal 24-h urinary free cortisol level, was achieved in 91% of those with microadenomas and 65% of those with macroadenomas; (v) among those patients with acromegaly that was persistent or recurred after surgery, 68% went on to achieve remission after adjuvant radiosurgery.

Conventional radiotherapy has been used in the treatment of pituitary adenomas since the early twentieth century. There remains debate as to which cases should be given post-operative radiotherapy. Radiotherapy was used as adjuvant treatment of choice for recurrent or residual pituitary adenomas [8, 10]. This was particularly so in residual disease that was surgically inaccessible, e.g., disease in the cavernous sinus, with a high risk of recurrence (large non-functioning adenomas) and in macroadenomas presenting with compression of the optic apparatus [8]. Conventional radiotherapy, however, had several limitations [7, 11–13]. In the case of secreting adenomas, the time to endocrine normalization was slow, and there was a significant rate of post-radiotherapy hypopituitarism. The effects of conventional radiotherapy, which usually consisted of 45 Gy administered over 5 weeks, included late endocrine deficits: hypocortisolism, hypogonadism, or hypothyroidism in up to 50% of the patient after 10 years. With conventional fractionation, other complications are rare.

Radiosurgery is now commonly used in cases of tumor recurrences [2, 14–19] or persistent imageable disease. There are limited instances where it has been used as a primary modality of treatment with satisfactory outcomes. As opposed to conventional radiotherapy, which is given in a fractionated manner at standard doses of 1.8–2 Gy per daily fraction, five times/week for 5 weeks [7, 8], the advantage of stereotactic radiosurgery is that it delivers a highly focused dose of radiation to a tumor in a single session. With the aid of image guidance and blocking strategies, a steep radiation dose curve is achieved, thus sparing the surrounding tissue from the harmful effects of radiation and delivering the treatment dose with a high level of conformity and selectivity [7]. This is particularly important in pituitary adenomas as they are often located close to critical structures in the sellar, parasellar, and suprasellar regions [17, 20].

Of interest to endocrinologists is thyroid carcinoma. Although it may metastasize within the body to other organs, brain metastasis from thyroid carcinoma, whether of the papillary, follicular, medullary, or anaplastic type, is extremely rare and occurs in only about 1% of patients. With improvement in the management of the systemic disease, the potential for cerebral metastases from thyroid carcinoma may become higher. Chiu *et al* [21] reported surgical resection to be associated with a favorable outcome for patients with solitary metastases. McWilliams *et al* [22] have suggested that either resection or radiosurgery is potentially beneficial for brain metastases from thyroid carcinoma.

RADIOSURGICAL TECHNIQUES

Stereotactic radiosurgery with regards to intracranial pathology is a neurosurgical procedure whereby radiation is delivered using stereotactic principles. It requires a multi-disciplinary team approach and is used to treat a predetermined target with minimal radiation to the surrounding tissues without opening the skull. Lars Leksell first described stereotactic radiosurgery in 1951 as ''closed skull destruction of an intracranial target using ionizing radiation''. In 1968, he treated the first pituitary adenoma patient with a gamma knife. Since then, stereotactic radiosurgery has been used quite routinely on patients with recurrent or residual pituitary adenomas to control tumor growth and to achieve endocrine remission [19, 23–32]. At the same time, attention and detail have been given to enhancing the conformity of dose planning and delivery to preserve the surrounding neuronal, vascular, and hormonal structures [12, 17].

Stereotactic radiosurgery can be performed using a gamma knife, a Linac (linear accelerator)-based system, heavy

charged particle beam (proton radiosurgery), and the cyberknife, and all have been used in the treatment of pituitary adenomas and brain metastases with good results [7, 17].

Gamma knife radiosurgery involves multiple isocenters of different beam diameter to achieve a dose plan that conforms to the irregular three-dimensional volumes of most mass lesions. The number of isocenters (''shots'') may vary depending on the number, size, and shape of the lesions. The source of radiation is cobalt-60, a radioactive isotope of cobalt with a short half-life of 5.27 years, which decays by negative beta decay to the stable isotope nickel-60.The activated nickel atom emits two gamma rays with energies of 1.17 and 1.33 MeV.

A Linac produces X-rays from the impact of accelerated electrons striking a high Z target (usually tungsten). A Linac can therefore generate any number of high-energy X-rays, although usually 6 MeV photons. In the Linac-based systems, multiple radiation arcs are used to cross-fire photon beams at a target defined as stereotactic space. Numerous techniques have been developed to enhance the conformity of dose planning and delivery using Linac-based systems.

The gamma knife perfexion has 192 sources (model 4C: 201 sources) arrayed in the helmet to deliver a variety of treatment angles. On a Linac, the gantry moves in space to change the delivery angle. Both can move the patient in space to change the delivery point. Both systems use a stereotactic frame to restrict the patient's movement.

Although the gamma knife and Linac are frame-based systems, the cyberknife, which is a frameless robotic system, is proving to be useful for treatment of intracranial pathology. Several generations of the frameless cyberknife robotic systems have been developed since its initial inception in 1990.

The heavy charged particle beam radiosurgery system uses either the Bragg–Peak method, where the charged particles stop within the target volume, or the Plateau–Beam method in which the highly charged particles are cross-fired at the target [2].

PITUITARY ADENOMAS

Treatment of pituitary adenomas with gamma knife radiosurgery

Pretreatment workup and preparation

The preparation of a patient with a pituitary adenoma for gamma knife radiosurgery requires the joint efforts of the endocrinologists and neurosurgeons.

Patients with pituitary adenomas will undergo a detailed clinical and endocrinological evaluation. Imaging of the pituitary and sellar region is achieved with fine-sliced pre- and post-gadolinium-enhanced magnetic resonance imaging (MRI). Fine-sliced computed tomography (CT) scans are obtained in cases where MRI is contraindicated.

In patients with prolactin- or GH-secreting tumors, many advocate a temporary cessation of the hormonal suppressive medication in the preoperative period [33]. This was based on the reports by Landolt *et al* [33, 34], which showed significantly lower hormone normalization rates in acromegalic patients who were receiving octreotide at the time of radiosurgery. This suggested that antisecretory medications may act as radioprotective agents. Since then, several other groups have documented a counterproductive effect of antisecretory medication on the rate of hormonal normalization following radiosurgery [2, 33–35]. The optimal period for temporary cessation of antisecretory medication where possible remains unclear, but published studies have recommended that somatostatin analogs used in GH-secreting adenomas be discontinued 8 weeks before and resumed 6–8 weeks after radiosurgery [2, 33]. Dopamine agonists for prolactinomas are withheld 2 months prior to radiosurgery.

Stereotactic frame fitting

On the day of treatment, the Leksell frame is fitted under local anesthesia. The areas of pin placement to secure the frame are cleaned with antiseptics and infiltrated with a local anesthetic (2% lidocaine with 1:200000 adrenaline). The position of placement of the frame is determined by the location of the lesion. In the case of pituitary adenomas, the frame is placed, centered neutrally using the angle for the optic chiasm as the axis for the frame.

MRI

Following frame placement, unless otherwise contraindicated, the patient undergoes fine-sliced (usually 1.5 mm/slice) volume acquisition pre- and post-gadolinium-enhanced MRI sequences to define the tumor in the sellar region. Other image sequences such as fat suppression techniques are used in patients who have undergone previous surgery to differentiate the tumor from fat grafts [17].

Treatment planning and radiation dosimetry

Once the images have been acquired with the stereotactic frame in place, treatment planning is carried out. The dose plans are generated using Gamma Plan (Elekta Instruments, Version 9). Proximity to radiosensitive structures is taken into account, and a reverse planning process may be utilized. Here, the total dose administered is determined by that which will expose the optic chiasm to a maximum of 8 Gy in patients with no previous radiotherapy exposure and 4 Gy for the previously irradiated patient [5].

The dose prescription is determined based on several factors, namely tumor volume, histology, whether previously irradiated, distance from the optic chiasm, and establishing and maintaining normal endocrine function. Generally, a margin dose exceeding 20 Gy (25–30 Gy) for secreting adenomas and 14–16 Gy for non-functioning adenomas is desirable [36].

In obtaining a conformal plan, various shielding strategies are utilized. These range from beam blocking to plug patterns, to shift the prescription isodoses away from the optic apparatus [17]. With the gamma knife perfexion, Gamma Plan allows shielding to be accomplished by closing off any one or combination of eight sectors that comprise the 192 source collimator. Sectors can be closed in an automated

fashion, and dynamic shielding is applied in a four-tier grading scheme [17].

The importance of neuroanatomical considerations in treatment planning in radiosurgery cannot be overstated. There is a difference in the tolerance of the different cranial nerves to radiation [37]. The sensory nerves (optic and vestibularcochlear) tolerate the least radiation, whereas the nerves in the parasellar region (third, fourth, and sixth), facial nerves, and the lower cranial nerves are more resilient [38, 39]. The radiosensitivity of these cranial nerves and their proximity to the tumor often limits the dose given. Most authorities [38, 39] advocate a single dose of 8 Gy or less to the optic nerve or chiasm. The distance between the optic nerve and the chiasm and the lesion being treated should be between 3 and 5 mm (**Figures 1 and 2**).

Results of gamma knife radiosurgery for pituitary adenomas

The aim of gamma knife radiosurgery is to stop or control tumor growth in non-functioning and secretory adenomas and achieve endocrine remission in secreting adenomas. Following treatment with gamma knife radiosurgery for residual or recurrent disease, there is a more rapid fall in the hormone levels in secreting adenomas than with conventional fractionated radiotherapy [8, 40]. The place of gamma knife radiosurgery as a primary therapy has yet to be established [41]. It is likely that this role will be reserved for small discrete tumors away from the optic chiasm, particularly those with extensions into the cavernous sinus. A more definite role has already been defined with regard to recurrent disease, especially that invading the parasellar structures.

This work reviews the results of gamma knife radiosurgery for the hormone-secreting adenomas [26, 32, 35, 43] including acromegaly [19, 24, 25, 28, 29, 44, 45], Cushing's disease [23, 46, 47], Nelson's syndrome [31, 48], and prolactinoma [30], and non-functioning pituitary adenomas [18, 49–52].

Secretory pituitary adenomas

Cushing's disease

Cushing's disease is associated with significant morbidity and mortality. Even after transsphenoidal surgery, up to 30% [47] of patients may have persistent or recurrent disease. Neurosurgeons and endocrinologists have debated the criteria for defining the postoperative control of Cushing's disease, with many favoring the use of the 24-h urinary cortisol determination as the goal standard [54]. Others advocate the measurement of serum ACTH, basal serum cortisol, or the mean serum cortisol [5]. Jagannathan *et al* [17] have reported that the rate of hormone normalization after radiosurgery for Cushing's disease is difficult to predict, with remission occurring as early as 2 months and as late as 8 years after gamma knife radiosurgery. However, most patients who have remission will do so within the first 2 years after radiosurgery. Published endocrine remission rates following gamma knife radiosurgery vary from 10% to 100%, with higher remission rates when radiosurgery follows surgical debulking [17]. Endocrine remission rates range from 17% to 83% after a median follow-up of 2 years in series with at least 10 patients [17]. The main radiosurgical margin doses for these series ranged from 15 to 32 Gy [2].

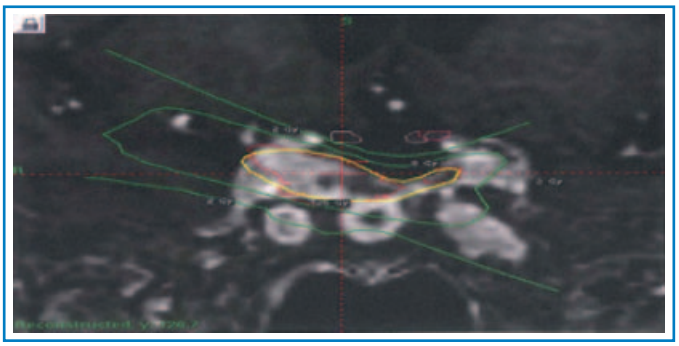

Figure 1. Coronal MRI gadolinium-enhanced T1-weighted image showing the dose plan for Cushing's disease after transsphenoidal surgery. The tumor margin received 25 Gy, maximum dose to the adjacent optic nerve was 6 Gy, and distance from chiasm was 2 mm

Nelson's syndrome

Endocrinological remission rates and growth control are critical for Nelson's syndrome as they tend to fall at the more aggressive end of the biological spectrum. There are relatively few studies detailing the results of gamma knife radiosurgery for Nelson's syndrome [31, 48]. Cure rates ranged from 0% to 36%, whereas tumor growth control rates varied from 82% to 100% [17].

Acromegaly

In the literature, the rates of endocrine remission after gamma knife radiosurgery vary widely. Comparative studies are difficult because the criteria for defining remission vary. The most widely accepted guidelines for remission in acromegaly consist of a GH level of less than 2 ng/mL in response to a glucose challenge and a normal serum IGF-1 when matched for age and gender [55]. A review of 22 studies from 1993 to 2003 detailed the results of gamma knife radiosurgery treatment for 413 patients with acromegaly [2]. The mean radiosurgery margin doses in these series ranged from 15 to 34 Gy [2]. Cure rate following radiosurgery varied from 0% to 100%. In those series with at least 10 patients and a median follow-up of at least 2 years, endocrinological remission rates ranged from 20% to 96% [2]. The most recent published series of gamma knife radiosurgery for GH-secreting adenomas was by Jagannathan *et al* [56] in 2008, which reported an overall remission rate 53% with a mean time to remission of 30 months in 135 patients with a mean follow-up of 57 months (**Table 1**).

Prolactinoma

With prolactin-secreting adenomas, endocrinological remission is defined as a normal serum prolactin level for gender. Nineteen studies report the results of 357 patients with prolactinomas. The mean radiosurgical dose margin varied from 13.3 to 33 Gy. Cure rates varied from 0% to 84% [2]. The largest series reported by Pan *et al* [57] reported a

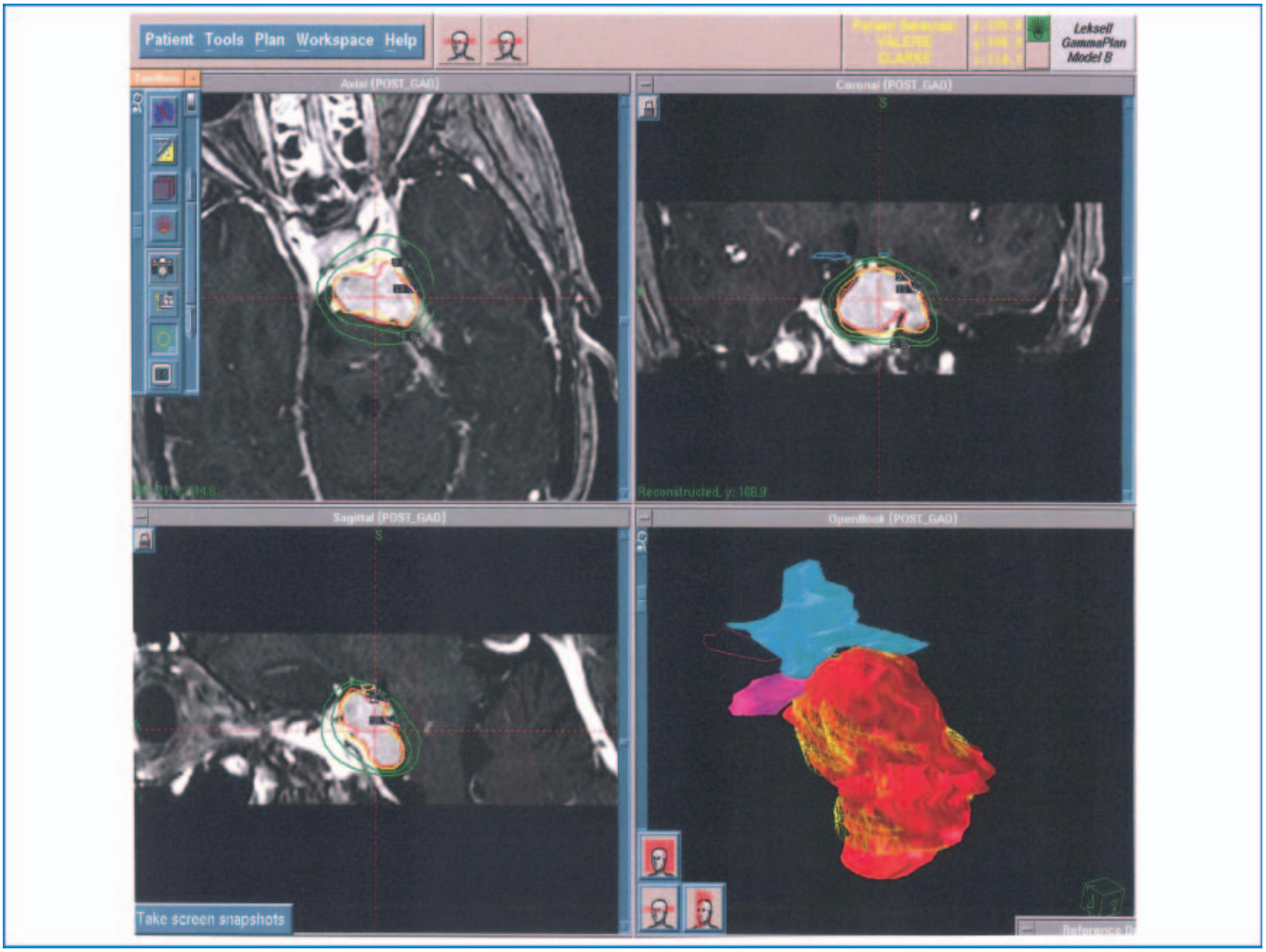

Figure 2. Dose plan for a pituitary adenoma with three-dimensional reconstruction of tumor and related chiasm

15% endocrinological remission rate achieved for 128 patients with a median follow-up of 33 months.

Non-functioning pituitary adenoma

Most series define tumor control as tumors that appear decreased or unchanged in size on follow-up imaging. Most studies reported a >90% control of tumor size. In a recently published series, Jagannathan *et al* [17] reported that, in 90 patients treated for non-functioning adenomas, tumor volume decreased (59 patients) or remained unchanged (24 patients) in 83 patients.

Most series involving gamma knife radiosurgery for non-functioning tumors (**Table 2**) have demonstrated excellent tumor growth control with a mean tumor control rate of 95% in patients with 4 or more years of follow-up [2].

Complications following gamma knife radiosurgery

Cranial neuropathies

The recommended upper limit of tolerance of the optic apparatus is 8 Gy (8–12 Gy) [36, 37]. Another important consideration for limiting damage to the optic apparatus during radiosurgery is a distance of at least 3 mm between the tumor and the optic chiasm. The other cranial nerves appear to be more resistant to injury from gamma knife radiosurgery [38, 39].

Pituitary insufficiency

The incident of hypopituitarism after radiosurgery is believed to be lower than with conventional radiotherapy. Hypopituitarism results from both hypothalamic and pituitary dysfunction. The incidence is not known, but a study from the Karolinska Institute, with a mean follow-up of 17 years, reported an eventual 72% incidence of hypopituitarism [58].

Other complications

Other complications of gamma knife radiosurgery are rare and include injury to adjacent vascular structures and injury to adjacent parenchyma with risk of inflammation/radionecrosis.

Follow-up assessments

Following gamma knife radiosurgery, patients should be reviewed with regular follow-up and surveillance imaging. Intervals of follow-up and imaging vary, but many centers advocate clinical evaluation and serial imaging every 6 months for the first 3 years and every year or two after that.

Table 1. Endocrine and Radiographic Outcomes of GKRS for GH-Secreting Pituitary Adenomas [56]

First author	Year	Pt no.	Follow-up (months)	Peripheral dose	IGF-1 normalization (%)	Tumor volume change (%)			New hormone deficit (%)	Visual complication (%)
						Decreased	Unchanged	Increased		
Jagannathan	2008	95	57	22	53	32	6	2	34	4

The patients are assessed clinically for the development of any psychological and neurological changes following radiotherapy, detailed visual field and acuity assessments, and endocrinological evaluations.

Depending on the underlying histology, hormonal assays are carried out to assess endocrinological control.

Unless contraindicated, a gadolinium-enhanced MRI is the favored follow-up imaging of choice.

BRAIN METASTASIS FROM THYROID CARCINOMA

Gamma knife radiosurgery for brain metastasis from thyroid carcinoma

Stereotactic frame fitting

In the case of metastatic lesions, the frame is lateralized in the anterior–posterior, right–left lateral, and superior–inferior axes depending on the location of the tumor, so as to center the lesion in the stereotactic space.

Results of metastatic brain tumors from thyroid carcinoma

The reported incidence of brain metastases from thyroid cancer is 1%. There are only rare reports [42, 53] of the management of cerebral metastases from thyroid cancer. Although surgical resection has been reported to be associated with favorable outcome for patients with solitary metastasis, McWilliams *et al* [22] have suggested that either resection or radiosurgery is potentially beneficial. Kim *et al* [42] reported a high control rate of 96% (25 out of 26 patients) and a prolonged progression-free period (mean 14.6 months) with an overall median survival of 33 months after gamma knife radiosurgery.

Follow-up assessment

For metastatic brain tumors, surveillance with 3-monthly follow-up and imaging is advocated with close attention to the primary and systemic disease and the patient's performance score.

CONCLUSION

The management of pituitary adenomas has progressed into a multidisciplinary approach involving endocrinologists, neurosurgeons, and radiation oncologists. Surgery, i.e., transsphenoidal microsurgical resection, remains the primary modality of treatment in surgically fit patients, particularly when the lesion is demonstrating a mass effect on the optic apparatus or causing hormonal overproduction.

Some 20–50% of patients demonstrate recurrence, and adjuvant treatment is recommended for these patients.

Table 2. Gamma Knife Radiosurgery for Patients with Non-Functioning Pituitary Adenomas [2]

First author (year)	Radiosurgery unit	No. of patients	Mean or median follow-up (months)	Margin dose (Gy)	Growth control (%)
Martinez et al. (1998)	GK	14	36	16	100
Lim et al. (1998)	GK	22	26	25	92
Witt et al. (1998)	GK	24	32	19	94
Hayashi et al. (1999)	GK	18	16	20	92
Inoue et al. (1999)	GK	18	>24	20	94
Mokry et al. (1999)	GK	31	21	14	98
Izawa et al. (2000)	GK	23	28	22	94
Shin et al. (2000)	GK	3	19	16	100
Feigl et al. (2002)	GK	61	55	15	94
Sheehan et al. (2002)	GK	42	31	16	98
Wowra & Stummer (2002)	GK	30	58	16	93
Petrovich et al. (2003)	GK	56	41	15	100
Pollock et al. (2003)	GK	33	43	16	97

GK, gamma knife radiosurgery.

Traditionally, conventional fractionated radiotherapy was used to treat recurrent or residual pituitary adenomas, but this has a prolonged latency for the desired affect and is associated with significant side-effects.

Gamma knife radiosurgery has been demonstrated to be a safe and highly effective treatment for patients with recurrent or residual pituitary adenomas, achieving effective tumor growth control and hormonal normalization in a shorter latency period than fractionated radiotherapy. It may also serve as a primary treatment for patients with pituitary adenomas deemed unfit for surgical resection as a result of comorbidities, or for tumors in surgically inaccessible locations.

Although surgical resection remains the mainstay of treatment for isolated metastatic lesions, and whole-brain radiotherapy for multiple metastasis, gamma knife radiosurgery has been shown to be comparable in the management of metastatic tumors from thyroid carcinoma in both isolated and multiple metastasis.

Disclosure: The authors declare no conflict of interest.

Acknowledgments: The authors wish to thank Mr Ian Paddick, consultant physicist, and Dr Meriem Amarouche for their assistance in the preparation of this manuscript.

REFERENCES

1. Pollock BE. Radiosurgery for pituitary adenomas. *Prog Neurol Surg*. 2007; 20:164–171.
2. Laws ER, Sheehan JP, Sheehan JM, Jagnathan J, Jane JA, Jr., Oskouian R. Stereotactic radiosurgery for pituitary adenomas: a review of the literature. *J Neurooncol*. 2004;69(1–3):257–272.
3. Greenberg MS. Tumor. In: Greenberg MS(ed.) *Handbook of Neurosurgery*. 6 ed. Canada. Thieme; 2006:438–456.
4. Milker-Zabel S, Debus J, Thilmann C, Schlegel W, Wannenmacher M. Fractionated stereotactically guided radiotherapy and radiosurgery in the treatment of functional and nonfunctional adenomas of the pituitary gland. *Int J Radiat Oncol Biol Phys*. 2001;50(5):1279–1286.
5. Swords FM, Monson JP, Besser GM, *et al*. Gamma knife radiosurgery: a safe and effective salvage treatment for pituitary tumours not controlled despite conventional radiotherapy. *Eur J Endocrinol*. 2009;161(6):819–828.
6. Laws ER. Surgery for acromegaly: evolution of the techniques and outcomes. *Rev Endocr Metab Disord*. 2008;9(1):67–70.
7. Ghostine S, Ghostine MS, Johnson WD. Radiation therapy in the treatment of pituitary tumors. *Neurosurg Focus*. 2008;24(5):E8.
8. Edwards AA, Swords FM, Plowman PN. Focal radiation therapy for patients with persistent/recurrent pituitary adenoma, despite previous radiotherapy. *Pituitary*. 2009;12(1):30–34.
9. Laws ER, Jane JA, Jr. Neurosurgical approach to treating pituitary adenomas. *Growth Horm IGF Res*. 2005;15(Suppl A):S36–S41.
10. Plowman PN. Pituitary adenoma radiotherapy—when, who and how? *Clin Endocrinol (Oxf)*. 1999;51(3):265–271.
11. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. *Clin Endocrinol (Oxf)*. 2006;64(5):542–548.
12. Minniti G, Gilbert DC, Brada M. Modern techniques for pituitary radiotherapy. *Rev Endocr Metab Disord*. 2009;10(2):135–144.
13. Swords FM, Allan CA, Plowman PN, *et al*. Stereotactic radiosurgery XVI: a treatment for previously irradiated pituitary adenomas. *J Clin Endocrinol Metab*. 2003;88(11):5334–5340.
14. Akabane A, Yamada S, Jokura H. Gamma knife radiosurgery for pituitary adenomas. *Endocrine*. 2005;28(1):87–92.
15. Colin P, Jovenin N, Delemer B, *et al*. Treatment of pituitary adenomas by fractionated stereotactic radiotherapy: a prospective study of 110 patients. *Int J Radiat Oncol Biol Phys*. 2005;62(2):333–341.
16. Jackson IM, Noren G. Role of gamma knife therapy in the management of pituitary tumors. *Endocrinol Metab Clin North Am*. 1999;28(1):133–142.
17. Jagannathan J, Yen CP, Pouratian N, Laws ER, Sheehan JP. Stereotactic radiosurgery for pituitary adenomas: a comprehensive review of indications, techniques and long-term results using the Gamma knife. *J Neurooncol*. 2009;92(3):345–356.
18. Losa M, Valle M, Mortini P, *et al*. Gamma knife surgery for treatment of residual nonfunctioning pituitary adenomas after surgical debulking. *J Neurosurg*. 2004;100(3):438–444.
19. Losa M, Gioia L, Picozzi P, *et al*. The role of stereotactic radiotherapy in patients with growth hormone-secreting pituitary adenoma. *J Clin Endocrinol Metab*. 2008;93(7):2546–2552.
20. Fukuoka S, Ito T, Takanashi M, Hojo A, Nakamura H. Gamma knife radiosurgery for growth hormone-secreting pituitary adenomas invading the cavernous sinus. *Stereotact Funct Neurosurg*. 2001;76(3–4):213–217.
21. Chiu AC, Delpassand ES, Sherman SI. Prognosis and treatment of brain metastases in thyroid carcinoma. *J Clin Endocrinol Metab*. 1997;82(11): 3637–3642.
22. McWilliams RR, Giannini C, Hay ID, Atkinson JL, Stafford SL, Buckner JC. Management of brain metastases from thyroid carcinoma: a study of 16 pathologically confirmed cases over 25 years. *Cancer*. 2003;98(2):356–362.
23. Aghi MK. Management of recurrent and refractory Cushing disease. *Nature Clin Pract Endocrinol Metab*. 2008;4(10):560–568.
24. Attanasio R, Epaminonda P, Motti E, *et al*. Gamma-knife radiosurgery in acromegaly: a 4-year follow-up study. *J Clin Endocrinol Metab*. 2003;88(7): 3105–3112.
25. Castinetti F, Taieb D, Kuhn JM, *et al*. Outcome of gamma knife radiosurgery in 82 patients with acromegaly: correlation with initial hypersecretion. *J Clin Endocrinol Metab*. 2005;90(8):4483–4488.
26. Castinetti F, Nagai M, Morange I, *et al*. Long-term results of stereotactic radiosurgery in secretory pituitary adenomas. *J Clin Endocrinol Metab*. 2009; 94(9):3400–3407.
27. Gutt B, Wowra B, Alexandrov R, Uhl E, Schaaf L, Stalla GK, *et al*. Gamma-knife surgery is effective in normalising plasma insulin-like growth factor I in patients with acromegaly. *Exp Clin Endocrinol Diabetes*. 2005;113(4):219–224.
28. Iwai Y, Yamanaka K, Yoshimura M, Kawasaki I, Yamagami K, Yoshioka K. Gamma knife radiosurgery for growth hormone-producing adenomas. *J Clin Neurosci*. 2010;17(3):299–304.
29. Jezkova J, Marek J, Hana V, *et al*. Gamma knife radiosurgery for acromegaly—long-term experience. *Clin Endocrinol (Oxf)*. 2006;64(5):588–595.
30. Jezkova J, Hana V, Krsek M, *et al*. Use of the Leksell gamma knife in the treatment of prolactinoma patients. *Clin Endocrinol (Oxf)*. 2009;70(5):732–741.
31. Mauermann WJ, Sheehan JP, Chernavvsky DR, Laws ER, Steiner L, Vance ML. Gammak surgery for adrenocorticotropic hormone-producing pituitary adenomas after bilateral adrenalectomy. *J Neurosurg*. 2007; 106(6):988–993.
32. Tinnel BA, Henderson MA, Witt TC, *et al*. Endocrine response after gamma knife-based stereotactic radiosurgery for secretory pituitary adenoma. *Stereotact Funct Neurosurg*. 2008;86(5):292–296.
33. Landolt AM, Haller D, Lomax N, *et al*. Octreotide may act as a radioprotective agent in acromegaly. *J Clin Endocrinol Metab*. 2000;85(3): 1287–1289.
34. Landolt AM, Lomax N. Gamma knife radiosurgery for prolactinomas. *J Neurosurg*. 2000;93(Suppl 3):14–18.
35. Pollock BE, Nippoldt TB, Stafford SL, Foote RL, Abboud CF. Results of stereotactic radiosurgery in patients with hormone-producing pituitary adenomas: factors associated with endocrine normalization. *J Neurosurg*. 2002;97(3):525–530.
36. Leber KA, Bergloff J, Pendl G. Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. *J Neurosurg*. 1998;88(1):43–50.
37. Stafford SL, Pollock BE, Leavitt JA, *et al*. A study on the radiation tolerance of the optic nerves and chiasm after stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. 2003;55(5):1177–1181.
38. Tishler RB, Loeffler JS, Lunsford LD, *et al*. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. *Int J Radiat Oncol Biol Phys*. 1993; 27(2):215–221.

39. Girkin CA, Comey CH, Lunsford LD, Goodman ML, Kline LB. Radiation optic neuropathy after stereotactic radiosurgery. *Ophthalmology*. 1997; 104(10):1634–1643.
40. Kong DS, Lee JI, Lim DH, *et al*. The efficacy of fractionated radiotherapy and stereotactic radiosurgery for pituitary adenomas: long-term results of 125 consecutive patients treated in a single institution. *Cancer*. 2007; 110(4):854–860.
41. Zhang N, Pan L, Dai J, *et al*. Gamma knife radiosurgery as a primary surgical treatment for hypersecreting pituitary adenomas. *Stereotact Funct Neurosurg*. 2000;75(2–3):123–128.
42. Kim IY, Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD. Gamma knife radiosurgery for metastatic brain tumors from thyroid cancer. *J Neurooncol*. 2009;93(3):355–359.
43. Patil CG, Hayden M, Katznelson L, Chang SD. Non-surgical management of hormone-secreting pituitary tumors. *J Clin Neurosci*. 2009;16(8):985–993.
44. Pollock BE, Jacob JT, Brown PD, Nippoldt TB. Radiosurgery of growth hormone-producing pituitary adenomas: factors associated with biochemical remission. *J Neurosurg*. 2007;106(5):833–838.
45. Milker-Zabel S, Zabel A, Huber P, Schlegel W, Wannenmacher M, Debus J. Stereotactic conformal radiotherapy in patients with growth hormone-secreting pituitary adenoma. *Int J Radiat Oncol Biol Phys*. 2004;59(4):1088–1096.
46. Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML. Gamma knife surgery for Cushing's disease. *J Neurosurg*. 2007;106(6): 980–987.
47. Sheehan JM, Vance ML, Sheehan JP, Ellegala DB, Laws ER, Jr. Radiosurgery for Cushing's disease after failed transsphenoidal surgery. *J Neurosurg*. 2000;93(5):738–742.
48. Vik-Mo EO, Oksnes M, Pedersen PH, *et al*. Gamma knife stereotactic radiosurgery of Nelson syndrome. *Eur J Endocrinol*. 2009;160(2):143–148.
49. Hoybye C, Rahn T. Adjuvant gamma knife radiosurgery in non-functioning pituitary adenomas; low risk of long-term complications in selected patients. *Pituitary*. 2009;12(3):211–216.
50. Pollock BE, Cochran J, Natt N, *et al*. Gamma knife radiosurgery for patients with nonfunctioning pituitary adenomas: results from a 15-year experience. *Int J Radiat Oncol Biol Phys*. 2008;70(5):1325–1329.
51. Minniti G, Jaffrain-Rea ML, Osti M, Cantore G, Enrici RM. Radiotherapy for nonfunctioning pituitary adenomas: from conventional to modern stereotactic radiation techniques. *Neurosurg Rev*. 2007;30(3):167–175.
52. Yamada S, Vidal S, Sano T, Horvath E, Kovacs K. Effect of gamma knife radiosurgery on a pituitary gonadotroph adenoma: a histologic, immunohistochemical and electron microscopic study. *Pituitary*. 2003; 6(1):53–58.
53. Cha ST, Jarrahy R, Mathiesen RA, Suh R, Shahinian HK. Cerebellopontine angle metastasis from papillary carcinoma of the thyroid: case report and literature review. *Surg Neurol*. 2000;54(4):320–326.
54. Sheehan JP, Niranjan A, Sheehan JM, *et al*. Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium. *J Neurosurg*. 2005;102(4): 678–691.
55. Giustina A, Barkan A, Casanueva FF, *et al*. Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab*. 2000;85(2):526–529.
56. Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Jr., Steiner L, Vance ML. Gamma knife radiosurgery for acromegaly: outcomes after failed transsphenoidal surgery. *Neurosurgery*. 2008;62(6):1262–1269.
57. Pan L, Zhang N, Wang EM, Wang BJ, Dai JZ, Cai PW. Gamma knife radiosurgery as a primary treatment for prolactinomas. *J Neurosurg*. 2000; 93(Suppl 3):10–13.
58. Hoybye C, Grenback E, Rahn T, Degerblad M, Thoren M, Hulting AL. Adrenocorticotropic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery. *Neurosurgery*. 2001;49(2):284–291.