

Gamma Knife in the Treatment of Pituitary Adenomas: Results of a Single Center

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ABSTRACT: Introduction: Gamma Knife (GK) radiosurgery for pituitary adenomas can offer a means of tumor and biologic control with acceptable risk and low complication rates. **Methods:** Retrospective review of all the patients treated at our center with GK for pituitary adenomas from Nov 2003 to June 2011. **Results:** We treated a total of 86 patients. Ten were lost to follow-up. Mean follow was 32.8 months. There were 21 (24.4%) growth hormone secreting adenomas (GH), 8 (9.3%) prolactinomas (PRL), 8 (9.3%) adrenocorticotrophic hormone secreting (ACTH) adenomas, 2 (2.3%) follicle stimulating hormone/luteinizing hormone secreting (FSH/LH) adenomas, and 47 (54.7%) null cell pituitary adenomas that were treated. Average maximum tumor diameter and volume was 2.21cm and 5.41cm³, respectively. The average dose to the 50% isodose line was 14.2 Gy and 23.6 Gy for secreting and non-secreting adenomas respectively. Mean maximal optic nerve dose was 8.87 Gy. Local control rate was 75 of 76 (98.7%), for those with follow-up. Thirty-three (43.4%) patients experienced arrest of tumor growth, while 42 (55.2%) patients experienced tumor regression. Of the 39 patients with secreting pituitary tumors, 6 were lost to follow-up. Improved endocrine status occurred in 16 (50.0%), while 14 (43.8%) demonstrated stability of hormone status on continued pre-operative medical management. Permanent complications included: panhypopituitarism (4), hypothyroidism (4), hypocortisolemia (1), diabetes insipidus (1), apoplexy (1), visual field defect (2), and diplopia (1). **Conclusions:** Gamma Knife radiosurgery is a safe and effective means of achieving tumor growth control and endocrine remission/ stability in pituitary adenomas.

RÉSUMÉ: Le scalpel gamma dans le traitement des adénomes pituitaires : résultats chez des patients traités dans un même centre. Contexte : La radiochirurgie par scalpel gamma (SG) pour traiter des adénomes pituitaires peut offrir un contrôle de la tumeur et un contrôle biologique comportant un niveau de risque acceptable et un faible taux de complications. **Méthode :** Nous avons effectué une revue rétrospective des dossiers de tous les patients traités dans notre centre au moyen du SG pour des adénomes pituitaires de novembre 2003 à juin 2011. **Résultats :** Nous avons traité un total de 86 patients. Dix ont été perdus au suivi. Le suivi moyen était de 32,8 mois. Parmi les adénomes, 21 étaient des adénomes qui sécrétaient de l'hormone de croissance (24,4%), 8 étaient des prolactinomes (9,3%), 8 sécrétaient de l'hormone adrénocorticotrope (9,3%), 2 sécrétaient de la gonadotrophine A/gonadotrophine B (2,3%) et 47 étaient des adénomes pituitaires non-fonctionnels. Le diamètre maximal moyen et le volume moyen étaient 2,21 cm et 5,41 cm³ respectivement. La dose moyenne à la ligne isodose 50% était 14,2 Gy et 23,6 Gy pour les adénomes sécrétoires et non sécrétoires respectivement. La dose maximale moyenne délivrée au nerf optique était 8,87Gy. Le taux de contrôle local de la tumeur était de 75 sur 76 (98,7%) chez les patients pour qui le suivi était disponible. Chez 33 patients (43,4%) la tumeur a cessé de croître et chez 42 patients (55,2%) la tumeur a régressé. Parmi les 39 patients qui avaient une tumeur sécrétante, 6 ont été perdus au suivi. L'état endocrinien s'est amélioré chez 16 (50%) et il est demeuré stable chez 14 patients dont le traitement médical préchirurgical a été maintenu. Les complications permanentes ont été les suivantes : le panhypopituitarisme (4), l'hypothyroïdie (4), l'hypocortisolémie (1), le diabète insipide (1), l'apoplexie (1), un défaut du champ visuel (2) et de la diplopie (1). **Conclusions :** La radiochirurgie par scalpel gamma est un moyen sûr et efficace de contrôler la croissance de la tumeur et de parvenir à une rémission endocrinienne/à la stabilisation des adénomes pituitaires.

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The treatment of pituitary adenomas is complex and multimodal. Treatment is indicated for hormone hypersecretion, disturbance of visual function, tumor growth and other neurologic sequelae secondary to mass effect. Classically, for those patients with pituitary adenomas, treatment has consisted of surgical resection and/or medical management of those secretory tumors.

Surgical approaches consist of transsphenoidal and formal craniotomy, amongst others, in order to debulk and remove as much tumor as possible, with the goal of tumor cure and improvement in neurological function and endocrine status.

Radiation therapy has been used in the past as an adjunct to treatment of recurrent and aggressive pituitary tumors, with mixed results. With the introduction of stereotactic radiosurgery,

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the ability to focus radiation dosing with sub-millimeter accuracy has allowed us to target pituitary adenomas for treatment with excellent results for tumor growth control and stabilization of endocrine function^{1,2}.

Transsphenoidal approaches, whether microsurgical or endoscopic transnasal, are currently the gold standard surgical treatment modality for pituitary adenomas. Stereotactic radiosurgery (SRS) has generally been reserved for those patients with recurrence or residual tumor, and those patients medically unfit to undergo the physiologic stress of an operation. The indications for SRS are expanding as experience with the technique increases.

Complication rates described with Gamma Knife (GK) for pituitary adenomas are quite variable, with the most common being pituitary axis disorders, ranging from 0-72%². Radiation induced optic neuropathy, parasellar cranial neuropathy and cavernous carotid injury have been described but are relatively rare.

We describe our institutional experience with GK SRS in the treatment of pituitary adenomas from November 2003 to June 2011, with the goal to define our local growth control rates, endocrine remission rates, and complications.

METHODS

Between November 2003 and June 2011, 86 patients with pituitary adenomas underwent GK radiosurgery at the Health Sciences Center in Winnipeg, Manitoba. We retrospectively reviewed the records of these patients and recorded data on: age, sex, tumour diameter and volume, GK treatment parameters, complications, time until tumour response, local control rates, and clinical/endocrine outcomes. Follow-up on this patient population was accrued up to Dec 2011, with this data

retrospectively accumulated from telephone contact, neuro-imaging and neurosurgical clinic chart review. Local research ethics board approval was obtained prior to starting this study.

RESULTS

Patient Demographics and Pituitary Adenoma Characteristics

There were a total of 86 patients identified as being treated for pituitary adenomas with GK during the review. These eighty-six patients received a single GK treatment at our institution, with none having had previous SRS. Procedures for tumor debulking were performed in 56 of the 86 patients (65.1%), prior to GK, with ten patients (11.6%) having two prior transsphenoidal operations. These surgical approaches included transsphenoidal resection in 50 patients (58%), and craniotomy in six patients (7.0%) for those tumors with significant parasellar/suprasellar extension. Average time from operation to GK treatment was 59.8 months. The average age at treatment was 55 years (range: 5 – 81). Forty-six patients (53%) were male and 40 patients (47%) female. Average follow-up time was 32.8 months (range: 2 – 79 months), with ten patients lost to follow-up. The median follow-up time was 35 months. Patient demographics for the 76 patients with follow-up are displayed in Table 1. Data pertaining to those patients lost to follow up can be seen in Table 2.

Of the ten patients lost to follow-up, all were referred to our facility by out of province physicians. They were subsequently lost to post-treatment follow up after returning to their respective provinces. Telephone contact was attempted on multiple occasions using the available contact information on file, but was unsuccessful.

Patients typically had multiple clinical presentations. Clinical manifestations on initial diagnosis were: visual field

Table 1: Demographic data of patients with follow-up

Demographic Category	Total Patient Population With Follow-Up (n = 76)
Age	19 – 81 (average: 55.8)
Sex	
Male	43
Female	33
Average Tumour Total Volume (cm ³)	5.41
Average Tumour Diameter (cm)	2.21
Average % Coverage	94.4
Average 50% Isodose Line Dose (Gy) for Secreting tumors	24.7
Average 50% Isodose Line Dose (Gy) for Non-secreting tumors	14.2
Average Time to Decrease in Tumour Size (months)	12.7
Total Number With Tumor Growth Control	75
Total Number of Permanent Complications	14

n = number; cm = centimetre; Gy = gray

Table 2: Characteristics of patients lost to follow-up

Sex	Presentation	Location	Function	Diameter of Tumour (cm)
F	Acromegaly	Sella, Suprasellar	GH	1.8
F	Cushing's Disease	Sella, Suprasellar, Lt Cav Sinus	ACTH	2.3
F	Amenorrhea	Sella	PRL	1.95
F	H/A, blurred vision	Sella, Suprasellar, Cavernous Sinus	Null	3.51
F	Cushing's Disease	Sella	ACTH	1.5
M	Dizzy, Deteriorating Lt vision	Sella, Suprasellar, Optic Chiasm	Null	2.4
F	H/A, fatigue	Sella, Supra, Cavernous Sinus	Null	3.52
M	Visual Blurring	Sella, Suprasellar	Null	1.8
M	Cushing's Disease	Sella	ACTH	2.1
F	Cushing's Disease	Sella, Rt Cav Sinus	ACTH	1.4

F = female, M = male, Lt = left, Rt = right, Cav = cavernous, GH = Growth Hormone, ACTH = Adrenocorticotropic Hormone, PRL = Prolactin, Null = Non-functioning

defect (20), acromegaly (18), headache (17), diplopia (7), Cushing's disease (7), blurred vision (5), amenorrhea (5), low libido (3), apoplexy (2), Addison's disease (1), diabetes insipidus (1), and relative afferent papillary defect (1). Nine patients had their pituitary adenoma discovered incidentally secondary to cranial imaging for unrelated complaints.

All were selected for treatment due to tumor progression or recurrence on follow up imaging. Refractory endocrinopathy was a factor in deciding to treat those patients with secreting adenomas, but all had demonstrated some interval change in size on pre-treatment imaging according to radiology interpretation, though some were quite small.

Eighty-one patients (94.2%) had adenomas within the sella turcica (with the remaining five having tumor burden extra-sellar as a result of previous surgical debulking), while tumor extension into the suprasellar cistern occurred in 53 (61.6%), into the cavernous sinus in 53 (61.6%), into the sphenoid sinus in 9 (10.4%), into the clivus in 5 (5.8%), and the middle fossa region in 2 (2.3%). The optic apparatus was compressed in 21(24.4%) patients. The average maximum diameter of the pituitary adenoma was 2.21 cm (range: 0.22 – 4.08 cm), and the average tumor volume was 5.41 cm³ (range: 0.33 – 14.3 cm³).

Forty-seven (45.3%) of the 86 patients treated had non-secreting pituitary adenomas. Of the remaining tumors there were 21 (24.4%) growth hormone (GH) secreting, 8 (9.3%) prolactin (PRL) secreting, 8 (9.3%) adrenocorticotropic hormone (ACTH) secreting, and 2 (2.3%) LH/FSH secreting adenomas. All patients with secreting tumors were on hormone modulating medications prior to treatment with GK, with the exception of the LH/FSH secreting adenomas. Hormone modulating medications were withheld temporarily prior to treatment with the GK.

Treatment Characteristics

Gamma Knife treatment planning was performed using magnetic resonance imaging (MRI) and computed tomography (CT) in 33 of 86 (38.4%), and only MRI in 53 (61.6%). Gamma

Knife treatment parameters consisted of an average maximum tumor dose of 36.8 Gy (range from 25 to 60 Gy). The average number of collimator shots was 15.6 per treatment. The prescription dose to the 50% isodose line was 18.5 Gy (range from 12 to 35 Gy). The average 50% isodose line dose for non-secreting adenomas was 14.2 Gy (range of 12 to 18 Gy). The average maximum dose for non-secreting adenomas was 28.6 Gy (range of 24 to 32 Gy). The average 50% isodose line dosage for secreting adenomas was 23.6 Gy (range from 13 to 35 Gy), with the average maximum dose for secreting adenomas being 46.8 Gy (range from 26 to 70 Gy). The average total volume covered (TVC) was 4.7 cm³ (range: 0.33 – 12.1 cm³), with average percent coverage of 94.4% (range: 82 – 100%). Eighty-four patients (97.7%) had a recorded a maximal dose to the optic nerve (ON) apparatus that was on average 8.9 Gy (range: 3.2 – 12.2 Gy). Twenty-eight patients (32.5%) had an ON dose recorded greater than or equal to 10 Gy. Thirteen (15.1%) patients had ON doses recorded a greater than or equal to 11 Gy. Ten (11.6%) patients had ON doses recorded at greater than or equal to 12 Gy.

Patients received post-treatment follow-up phone interviews within two weeks of GK treatment. Follow-up clinic visits were conducted six to eight weeks post treatment. Imaging was conducted at three and nine months post-GK, and then yearly with MRI to assess tumor control, all with follow-up clinic visits with the treating neurosurgeon.

Overall Tumor Growth Control

Tumor control, which was defined as the absence of lesion growth, or decrease in size, on follow-up imaging occurred in 75/76 (98.6%) of the patients with follow up; 42 (55.3%) demonstrated regression and 33 (43.4%) stability in tumor size. The average time until change in adenoma size post-GK was 12.6 months.

Only one patient (1.3%) demonstrated mild tumor growth despite GK treatment documented at approximately 3 mm in maximal diameter. This patient had a 2.3 cm non-functioning

Table 3: Secreting adenoma type, growth control, and endocrine outcome

Tumor Type	Regression	Stability	LTFU	Hormonal Improvement	Hormonal Stability	Hormonal Progression
GH	6 (30%)	14 (70%)	1	9 (40%)	10 (50%)	1 (10%)
PRL	3 (42.9%)	4 (57.1%)	1	5 (71.4%)	1 (14.3%)	1 (14.3%)
ACTH	2 (50.0%)	2 (50.0%)	4	4 (100%)	0 (0%)	0 (0%)
LH/FSH	2 (100%)	0	0	0 (0%)	2 (100%)	0 (0%)

GH = Growth Hormone, PRL = Prolactin, ACTH = Adrenocorticotrophic Hormone, LH = Luteinizing Hormone, FSH = Follicle Stimulating Hormone, LTFU = Lost to Follow-Up

pituitary adenoma and received 13 Gy to the 50% isodose line. She described a post treatment headache as a transient complication. Her total follow-up at the time of this study being six months. Hormonal status has remained normal. Close imaging follow up has been recommended.

Non-secreting Adenomas

Of the 47 patients with non-functioning adenomas treated during our review period, four were lost to follow-up. The remaining patients demonstrated a 42 of 43 (97.7%) tumor control rate, with 22 (51.2%) showing regression, and 20 (46.5%) showing tumor stability rates. Only one patient (2.3%) in the non-functioning adenoma group had tumor growth despite treatment (as described previously).

Secreting Adenomas

We defined improved endocrine functioning as either being off hormonal modulating medication, or having reduced pre-GK medication doses. In addition, we defined endocrine stability as no change in pre-GK medication dosing after treatment. Results for individual tumor types are as follows:

GH Adenomas

There were 21 patients, with one lost to follow-up. Overall, 100% tumor control was achieved in those with follow up, with 6 of the 20 (30%) patients displaying tumor stability, while the remaining 14 (70%) demonstrated tumor regression. Average time to tumor regression for the GH adenomas was five months.

Nine (45%) demonstrated improved hormonal functioning with 6 of 20 (30%) having their pre-treatment medications discontinued. Three had reductions in medication. However, two of the patients with reduction of their pre-treatment medications developed panhypopituitarism secondary to GK and one became hypothyroid; all requiring pituitary hormone replacement therapy. Of the remaining 11 of the 20 GH patients with follow-up, 10 (50%) had endocrine stability or stable doses of their pre-treatment medication continued, and one (10%) had ongoing increasing GH and insulin growth factor-1 (IGF-1) levels despite treatment. One patient with endocrine stability became hypothyroid as a result of GK requiring thyroid supplementation.

PRL Adenomas

Of the eight patients with PRL secreting adenomas, one was lost to follow up. Tumor control for the remaining seven patients was achieved in 100%, with three (42%) displaying tumor stability, and four (57%) having tumor regression. Average time until tumor regression in the PRL adenomas was 16.3 months.

Of those patients with PRL adenomas and follow-up, five (71.4%) demonstrated improved hormone status, with three (42.9%) coming off medication and having normalization of PRL levels, and two (28.6%) patients achieving a decrease in their medication dosage. However, one patient achieving “medication free” status developed hypothyroidism post-GK requiring supplementation. One patient (14.2%) had endocrine stability, and one (14.2%) had endocrine progression despite treatment.

ACTH Adenomas

We had eight patients with ACTH secreting adenomas; four were lost to follow-up. Of those with follow up there was 100% tumor control, with two (50%) having tumor stability, and two (50%) displaying tumor regression. Average time until tumor regression in the ACTH adenomas was 10.5 months. Endocrine status of these adenomas improved in 100% of those with follow-up. Two (50%) achieved reduction in medication dosage, while two (50%) were free of their pre-operative medication as of their last visit.

LH/FSH Adenomas

Only two patients in our experience had LH/FSH secreting adenomas and neither was on hormonal modulating medications pre GK. Both patients had tumor control as of last follow-up, with one (50%) displaying regression, noted at five months post-GK, and the other having tumor stability. As well, both patients achieved stable LH/FSH levels post treatment and were classified as endocrinologically stable. Neither achieved hormonal normalization.

A summary of the tumor control and endocrine function outcome is summarized in Table 3.

Complications

We divided our complications into transient minor complications, and serious permanent complications. Overall 31 of the 76 patients (34.2%) had transient complications, and 14 (18.4%) had serious permanent complications.

The transient complications for all tumor types included: pin site swelling (17), pin site infection (1), pin site dysesthesias (5), visual blurring (4), short term memory loss (2), and ataxia (1). All of these had resolved as of last follow-up. Transient complications in the secreting adenomas included: pin site swelling (6), pin site dysesthesias (2), and ataxia (1).

Serious permanent complications for all tumor types included: panhypopituitarism (4), hypothyroidism (4), hypocortisolemia (1), diabetes insipidus (1), apoplexy (1), visual field defect secondary to radiation induced optic neuropathy (2), and diplopia (1). All patients with new pituitary axis abnormalities post-GK required hormonal replacement, which they were on as of last follow-up, making our post-GK pituitary dysfunction rate 13.2%. The patient with apoplexy post-GK had a 3.3 cm³ adenoma treated with 15 Gy to the 50% isodose line. He developed headache and visual blurring five days post gamma knife, with radiographic evidence of hemorrhage consistent with apoplexy. He was taken to the operating theater for transsphenoidal resection due to mass effect on the optic apparatus and visual deterioration. As of last follow-up the patient still has a minor visual field deficit.

Radiation induced optic neuropathy was observed in two patients, leading to permanent visual field defects. One patient had a 4.06 cm GH pituitary adenoma with encroachment on the chiasm. He had previous transsphenoidal and transcranial resection due to optic apparatus distortion, with a mild pre-operative right eye temporal visual field defect. Gamma Knife SRS was elected as a treatment option considering the patient had failed both transsphenoidal and transcranial debulking, in addition to external beam radiation in the past. Gamma Knife treatment consisted of 20 Gy to the 50% isodose line, and a maximal recorded ON dose of 8 Gy. The patient developed a bitemporal field cut. On MRI the chiasm looked atrophic at six months post-GK. His symptoms started nine months post-GK. The second patient had a 3.47 cm non-secreting pituitary adenoma with suprasellar and right cavernous sinus extension and encroachment on the optic nerves, leading to right eye ophthalmoplegia. He had failed both transsphenoidal resection and external beam radiation. GK treatment consisted of a dose of 15 Gy to the 50% isodose line, with a maximal recorded ON dose of 9 Gy. During a follow-up visual field analysis 24 months post-GK, a left eye temporal field loss was noticed. This was not noticed by the patient. No specific abnormality of the optic apparatus could be identified on MRI.

Finally, diplopia developed post-GK in one patient who was treated for 3.79 cm non-secreting pituitary adenoma with suprasellar and right cavernous sinus extension. A 13 Gy dose to the 50% isodose line was administered. Diplopia was noted at the 3 month follow up on superior gaze. In addition mild right ptosis was noted, indicating a partial third nerve etiology. This deficit has been persistent since.

For the secreting pituitary adenomas, the serious permanent complications included: hypocortisolemia (1), panhypopituitarism

(3), hypothyroidism (2), radiation induced optic neuropathy (1), and diabetes insipidus (1).

DISCUSSION

Gamma Knife treatment has been described in the literature to result in tumor growth control rates ranging up to 92-100% for adenomas of all types^{2,3}. Endocrine stabilization or improvement for those tumors with secreting status varies depending on tumor subtype, with average remission rates for GH, PRL, and ACTH adenomas having been described as 0 - 67%¹⁻⁵, 0 - 84%^{1,2,6,7}, and 10 - 100%^{1,2} respectively. Long-term growth control has been described in up to 83% at 80 months⁸. Extended follow-up at a mean of 54 months for functioning pituitary adenomas post-GK in the literature demonstrates the chance of endocrinologic remission at 87% for ACTH, 67% for GH, and 18% for PRL adenomas⁹.

Overall our experience of a tumor growth control rate of 98.6% for all adenoma types is comparable to that found in the literature^{1,2}. Our results for growth control of non-secreting adenomas are within the literature experience^{1,2,10} at 97.7%. We attribute this to lessons learned from the literature including recommendations to maintain a dose between 12 - 18 Gy at the 50% isodose line for non-secreting tumors¹⁰. Our growth control rates of 100% for secreting adenomas are within the literature range described¹⁻⁹. We had four ACTH, one GH and one PRL patients lost to follow-up, however, and the overall tumor control rates may be less than we report here.

We had a relatively large proportion of GH adenomas in our patient population. This may be related to the local good tumor control rates for PRL adenomas and ACTH adenomas with standard transsphenoidal techniques and medical management. Our control of the GH adenomas is slightly better than that described¹⁻⁵, despite losing one patient to follow-up. Cessation of hormone modulating medications pre-GK¹⁰, and adherence to literature standards in dosing secreting adenomas¹¹ has allowed us to achieve this.

Our endocrine improvement and stability rates (see Table 3) for those patients with secreting adenomas are also within literature limits described above. For GH adenomas, our endocrine improvement rate of 45% and stability rate of 50% is slightly higher than that described in the literature¹⁻⁵. This is despite the majority displaying cavernous sinus extension, which has been described as a negative predictor of remission⁴. We again believe this stems from diligence with pre-operative medication cessation and dose prescription. Similarly our ACTH adenomas and PRL adenomas displayed endocrine improvement/stability rates of 71.4%/28.6%, and 50%/50% respectively. However, as previously mentioned six patients with functioning adenomas were lost to follow-up. Furthermore, two patients displaying hormonal regression developed panhypopituitarism while one developed hypothyroidism post-GK. As well, two patients with hormonal stability of their secreting adenomas developed hypothyroidism post-GK. Thus, despite positive endocrine outcomes in terms of tumour function, some traded one pituitary axis problem for another as a result of dysfunction secondary to radiosurgery.

The total number of patients with previous documented surgical intervention for their pituitary adenomas is small at 65%, relative to other series, and represents the ongoing success

with surgical treatment of pituitary adenomas. As well, the large proportion of patients without previous surgery demonstrates an institutional shift in our multi-modality treatment approach to pituitary adenomas, utilizing GK in some earlier in the disease process before surgery is necessary. Comparing those patients with previous surgery to those treated with GK as their first procedure, 55 (98%) patients versus 20 (100%) patients had tumor control respectively. For those patients with previous surgical resection and tumor control post-GK, 26 (46%) displayed decrease in size, while 29 (52%) demonstrated stability in size. In those patients without previous surgical attempts, 16 (80%) demonstrated tumor regression, while four (20%) demonstrated stability in size. Twenty-five patients with previous attempt at surgical resection had secreting tumors. The endocrine outcome for this group included: Improved hormonal status in 11 (44%), stable endocrine status in 13 (52%), and progression in 1 (4%). The nine patients with secreting tumors and without previous surgery displayed improved hormonal status in six (67%), stability in two (22%), and progression in one (11%). Given the overall tumor regression rate and improved hormonal status for secreting adenomas in the “no-surgery” group compared to the “previous-surgery” group, one could argue that GK radiosurgery as a primary treatment modality in pituitary tumors is a reasonable option to consider and requires future investigation. However, we acknowledge the disparity in numbers between the groups, and the small overall numbers in general. In addition, the comparatively improved hormonal and tumor regression rates we have experienced are likely related to the complex treatment refractory nature of the tumors in the “previous-surgery” group, hence why these patients have undergone multiple medical and surgical failures prior to GK.

Our complications were higher than described in the literature. We had 31 patients with transient minor complications. On further breakdown, the majority (74.2%) were stereotactic frame related and most literature sources do not describe these. If we exclude these, only seven patients had transient complications, all which completely resolved.

The permanent complication rate of 18.4% was predominantly secondary to pituitary axis dysfunction. Overall our pituitary axis dysfunction in 10 of 76 (13.2%) patients, is well within the limits described^{1,2}. The majority of the serious permanent complications, 8 of 14 (57.1%), occurred in the secreting adenomas. Of these, the majority of the pituitary axis dysfunction, 7 of the 10 (70.0%) described, post-GK occurred in the secreting adenoma population. Despite this, the objective in treatment planning should be to minimize this outcome in SRS, and so continue to keep the stalk and distal infundibular dose less than 15 Gy, where possible, in order to reduce this post SRS complication¹²⁻¹⁵. We had one unfortunate patient with pituitary apoplexy within five days of treatment. It is unclear that GK was the cause, as the relationship of apoplexy to GK is not clear and since radiation effects are rarely so acute.

The two patients with radiation induced optic neuropathy were of concern. Both of these patients had ON dosing under 10 Gy, and were within the 12 Gy limit recommended by Stafford et al¹⁶ and even the 10 Gy dose as recommended by earlier literature^{17,18}. This is just slightly above the literature rate of radiation induced ON at 2.6% compared to less than 2%¹⁶. We found that both of these patients had significant suprasellar

extension with optic apparatus deformation prior to the surgical debulking performed at pre-GK intervals of 10 and 205 months respectively. No MRI evidence of optic nerve compression secondary to tumour growth post-GK was found. We believe this previous compression of the optic apparatus predisposed these patients to radiation induced optic neuropathy in the setting of ON dosing less than 10 Gy. Finally, the one patient with new onset diplopia was likely related to cavernous sinus radiation dosing that led to a 6th nerve radiation neuropathy despite maintaining low cavernous sinus dosing as recommended¹⁹.

Permanent complications for the secreting adenomas were higher, with 8 of the 14 permanent complications occurring in the secreting group. Of interest is the high proportion of pituitary dysfunction, 7 of the 10 cases described occurred in the secreting adenoma group. This is likely related to larger infundibular doses seen secondary to the higher marginal dose required for tumor and endocrine control.

We recognize this study has several limitations. First, ten patients were lost to follow-up. Second, a large portion of the ACTH secreting adenomas were lost to follow-up, making the tumor growth and endocrine outcomes in that category of patients difficult to interpret. Third, the retrospective nature of the study left some follow up data difficult to obtain. Finally, the small patient population makes these results difficult to generalize to all pituitary adenomas treated with GK SRS.

Overall we believe good results can be achieved by the following: First, follow literature recommended 50% isodose line dosing for non-secreting and secreting tumors at 12-18 Gy and 18-30 Gy respectively¹¹. Second, attempts at maintaining infundibular and stalk dosing as low as possible to prevent post-GK hypopituitarism^{12,13} should be made, though adequate tumor dosing remains the primary goal. Third, instruct patients to stop taking their hormone modulating medications prior to GK in order to maximize endocrine remission in functioning adenomas^{10,11}. Fourth, strive to keep ON dosing under 10 Gy to reduce the risk of radiation induced ON as described in the literature¹⁶⁻¹⁸, though tolerances up to 12 Gy have been described. Finally, limit the parasellar radiation dosing (less than 19 Gy if possible) to reduce the risk of other radiation induced cranial neuropathies^{20,21}.

CONCLUSION

Gamma Knife stereotactic radiosurgery offers a relatively safe and effective means of achieving both tumor growth control and endocrine remission and stability in pituitary adenomas. With the advent of SRS and the implementation of this tool in the treatment of pituitary adenomas, those patients with residual or recurrent disease, and those medically unfit for surgery have a less invasive radiosurgical option to achieve tumor growth control and, potentially, improvement in hormonal status.

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