CLINICAL STUDY

Gamma knife radiosurgery: a safe and effective salvage treatment for pituitary tumours not controlled despite conventional radiotherapy

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Abstract

Objective: We report the use of 'gamma knife' (GK) radiosurgery in 25 patients with pituitary adenomas not cured despite conventional therapy, including external beam radiotherapy.

Patients and methods: All patients had previously received conventional radiotherapy for a mean of 11.8 years prior to receiving GK; 23 out of 25 had also undergone pituitary surgery on at least one occasion. Seventeen had hyperfunctioning adenomas that still required medical therapy without an adequate biochemical control – ten somatotroph adenomas, six corticotroph adenomas and one prolactinoma, while eight patients had non-functioning pituitary adenomas (NFPAs).

Results: Following GK, mean GH fell by 49% at 1 year in patients with somatotroph tumours. Serum IGF1 fell by 32% at 1 year and by 38% at 2 years. To date, 80% of the patients with acromegaly have achieved normalisation of IGF1, and 30% have also achieved a mean GH level of <1.8 ng/ml correlating with normalised mortality. A total of 75% NFPAs showed disease stabilisation or shrinkage post GK. The patient with a prolactinoma showed a dramatic response: 75% reduction in prolactin at 2 years, with a marked shrinkage on magnetic resonance imaging. The results in corticotroph adenomas were variable. Prior to GK, 72% of the patients were panhypopituitary, and 42% of the remainder have developed new anterior pituitary hormone deficiencies to date. No other adverse events have been detected at a mean follow-up of 36.4 months.

Conclusions: These data indicate that GK is a safe and effective adjunctive treatment for patients with NFPAs and acromegaly not satisfactorily controlled with surgery and radiotherapy.

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Introduction

Neurosurgical treatments for pituitary tumours have rapidly advanced with the advent of magnetic resonance imaging (MRI), stereotactic CT mapping and advances in transsphenoidal surgery techniques. However, up to 60% of the patients with functioning pituitary tumours continue to show biochemical disease activity after surgery (1, 2), and non-functioning pituitary adenomas (NFPAs) continue to display high rates of recurrence even following radical surgery (3). Conventional radiotherapy (CRT) for pituitary tumours has therefore long had an established role, and results in a predictable decline in hormonal activity and tumour stabilisation in the majority of cases (3, 4). However, despite surgery and radiotherapy, ~10% of the pituitary tumours will still not be 'cured' in terms of either rendering hormone levels safe or preventing

tumour recurrence, and the efficacy of CRT may take many years to fully occur (3, 4).

Long-term medical treatments or further surgery is thus frequently used following non-curative radiotherapy for hyperfunctioning pituitary tumours. Somatostatin analogues can be particularly effective at controlling both size and biochemical activity of somatotroph adenomas. However, they are expensive, require parenteral administration and are incompletely effective in ~40% of the patients. The GH receptor antagonist pegvisomant appears to be highly effective in controlling serum insulin-like growth factor 1 (IGF1) (5), but it is also expensive, needs to be given parenterally, is not universally available and does not control residual tumour growth.

Dopamine agonists are highly effective at controlling both the size and hypersecretion of prolactinomas, but can be associated with adverse events, e.g. psychiatric disturbance and fibrotic reactions.

Currently used medical treatments can partly control cortisol excess, but they are ineffective at controlling corticotroph hypersecretion and size.

Unfortunately, no medical treatments are reliably effective for NFPAs. Repeat application of high-dose CRT has been attempted. Historically, this was associated with unacceptably high adverse events, particularly optic neuropathy, and although with increased availability of highly conformal fractionated radiotherapy, this is advocated by selected units and remains under evaluation (6, 7). Repeated surgery thus remains the only widely available option for such patients demonstrating further growth despite surgery and radiotherapy.

Hence, there exist a cohort of patients in whom a clinical need for another definitive treatment remains.

There is now extensive experience of 'radiosurgery', a single-dose multiple-port-focussed radiotherapy for pituitary tumours, as an alternative to CRT, and there are multiple reports of repeat applications of such a radiosurgery. Proponents of radiosurgery generally assume a lower incidence of significant side effects, and in some cases there is an accelerated fall in hormone levels when compared to CRT (8–11), although these data are inconsistent.

Our unit in London has extensive experience in pituitary radiotherapy, and has previously reported the use of both CRT and linear accelerator-based stereotactic radiosurgery to pituitary tumours (12–16). Here, we report the use of 'gamma knife' (GK) radiosurgery to 25 cases of pituitary adenomas not adequately controlled despite conventional treatments including radiotherapy.

Patients and methods

Patients

We present data on 25 consecutive patients with ongoing pituitary disease despite previous conventional treatments. All patients with NFPAs had evidence of tumour regrowth on serial scanning. All patients with functioning pituitary tumours had an ongoing hormone excess not controlled by or intolerant of medical therapy. All patients had undergone CRT, and 23 out of 25 had also undergone pituitary surgery on at least one occasion: eight on two occasions, and one on three occasions. The clinical details of patients are summarised in Tables 1 and 2.

Tumours were only considered for GK if they were anatomically defined on MRI scanning, and were more than 3 mm from the optic chiasm in order to minimise chiasmal radiation exposure as discussed below. No upper size limit was defined.

Acromegaly

We present data on ten patients with somatotroph adenomas. All had previously undergone CRT though none had achieved disease remission. The full data for disease activity at the time of diagnosis and at CRT administration are not available. Published reports estimate a 50% fall in GH within the first 2 years of CRT (14), and this cohort had received a modal dose of 45 Gy at a mean interval of 13.3 years (range 1.5–43 years) before GK delivery. Patients were thus generally deemed to be within the plateau phase of CRT before GK was considered. In the four patients in whom full data

Table 1 Clinical details of patients with somatotroph adenomas.

Patient	Age	Gender	Surgery	CRT (Gy)	GK dose (Gy)	Diagnosis GK (y)	CRT GK (y)	Follow-up (m)	Pituitary function	Treatment
1	52	M	TSS X2	45	15	16	16	36	Panhypopituitary	Peg
2	73	F	None	Yttrium	10	43	43	36	Panhypopituitary	Nil
3	66	M	TSS X1	45	15	18	17	33	Partial loss post GK	Nil
4	58	M	TSS X1	45	17.5	16	15	66	Panhypopituitary	SA
5	50	M	None	45	15	14	14	9	Partial hypopituitary	Nil
6	57	M	TSS X1	45	10	16	7	55	Partial loss post GK	SA ^a
7	34	F	TSS X1, TFS X1	45	10	4	3	78	Panhypopituitary	Nil
8	53	M	TSS X1	45	16	11	10	12	Panhypopituitary	SA ^b
9	37	M	TFS X1	40	10	7	6	54	Normal	Peg+SA
10	30	F	TSS	45	10	1.5	1.5	6	Normal	Peg

TSS, transsphenoidal surgery; TFS, transfrontal surgery; CRT, conventional radiotherapy; GK, gamma knife radiosurgery; y, years; m, months; Peg, pegvisomant; SA, somatostatin analogue. The column headed pituitary function indicates the level of anterior pituitary function at the time of GK: panhypopituitary patients were therefore requiring full hormone replacement therapy prior to receiving gamma knife. Where this is indicated as normal, the patients continue to have normal pituitary function on dynamic testing at their latest follow-up. One had partial pituitary deficiency at the time of gamma knife which remains unchanged, and in two patients, partial loss of anterior pituitary function has been detected since gamma knife treatment as indicated. Where indicated, patients were taking medical treatments throughout the treatment and follow-up periods. All the assessments were made on the same medical therapy.

^aA patient on somatostatin analogue therapy at the time of GK, in whom treatment was stopped for all pre- and post-GK assessments.

^bA patient on somatostatin analogue therapy at the time of GK, and for his assessments to 12 months, but in whom excellent control was achieved and medical treatment was subsequently stopped.

Table 2 Clinical details of all patients with non-somatotroph adenomas.

Patient	Diagnosis	Age	Gender	Surgery	CRT (Gy)	GK dose (Gy)	Diagnosis GK (y)	CRT GK (y)	Follow-up (m)	Pituitary function
11	Cushing's	30	F	TSS X 1 Adrenalectomy ^a	45	15	3	2	36	Normal
12	Cushing's	68	F	TFS X 1	45	10	22	22	12	Panhypopituitary
13	Cushing's	44	M	TSS, TFS X1 Adrenalectomy ^b , TSS ^b	45	10	7	7	24	Panhypopituitary
14	Cushing's	40	F	TSS X 1, TFS X 1 TFS X 2, TSS X 1 ^c	45	12.5	4	2	36	Panhypopituitary
15	Nelson's	65	F	TSS X 2, Adrenalectomy	45	20	4	4	36	Panhypopituitary
15	Nelson's	66	F	TSS X 2, Adrenalectomy ^d	45	20	5.5	5.5	18	Panhypopituitary
16	Nelson's	43	F	TSS X 1 Adrenalectomy	45	10	2	2	60	Panhypopituitary
17	NFPA	64	F	TSS X 1 TSS X 1 ^e	45	12.5	4	2	42	Panhypopituitary
18	NFPA	64	F	TSS X 1	45	14	5	5	51	Panhypopituitary
19	NFPA	72	M	TSS X 1	45	8	27	26	48	Panhypopituitary
20	NFPA	60	M	TSS X 2	45	12.5	20	20	48	Panhypopituitary
21	NFPA	55	M	TSS X 1	45	20	18	18	30	Partial hypopit + further loss post GK
22	NFPA	59	M	TSS X 3	45	10	21	21	30	Panhypopituitary
23	NFPA	33	M	TSS X 2	45	14	12	12	12	Panhypopituitary
24	NFPA	56	M	TSS X2 TSS X1, TFS X2 ^f	45	9	17	17	96	Panhypopituitary
25	Prolactinoma	75	F	TSS X 1	45	11	8	8	42	Panhypopituitary

NFPA, non-functioning pituitary adenoma.

^aThis patient underwent adrenalectomy 9 months following GK as her disease became cyclical and difficult to manage. Her pituitary imaging remains stable to date.^bThis patient showed no improvement post GK, underwent adrenalectomy at 10 and 14 months and repeat TSS at 20 months for ongoing pituitary tumour growth.^cThis patient showed initial control for 12 months, then had a dramatic and ultimately fatal relapse, requiring further pituitary surgery on three occasions.^dThis patient received GK on two occasions to two sites of disease recurrence. Unfortunately, she recurred 1 year following her second treatment, and has subsequently received chemotherapy.^eThis patient showed tumour stabilisation for 5 years followed by tumour regrowth requiring surgery.^fThis patient was stable for 5 years, but then developed a semi-cystic recurrence requiring three further surgical procedures.

are available, mean GH had fallen by 62% over a mean of 17 years following CRT and prior to receiving GK: from 38 to 13 mIU/L.

Two patients had not undergone previous standard surgery: one had received an Yttrium implant at diagnosis 43 years ago, and the other had multiple medical problems and so received primary CRT rather than surgery.

Patients were considered for GK only if they were not satisfactorily controlled on medical therapy. Satisfactory control was deemed to be a mean GH below 1.8 ng/ml and a normal age- and gender-related serum IGF1 and well-controlled symptoms. This patient group was considered to have an ongoing residual disease rather than a recurrent disease, as none had previously achieved remission without unacceptably high doses of medical treatments.

Where possible, patients were taken off the treatment both for the administration of GK and for all the assessments as indicated in Table 1 and Fig. 1. However, 60% were on medical treatments at the time of

GK: three were on long-acting somatostatin analogues, two were on pegvisomant, and one was on both treatments.

Cushing's disease and Nelson's syndrome

We present data on six patients treated for corticotroph adenomas, which are summarised in Table 2. These patients had a severe, ongoing disease. Four patients required ongoing treatment with anti-adrenal agents despite having undergone pituitary surgery, two on more than one occasion, as well as CRT. The remaining two had also undergone pituitary surgery and CRT, but had subsequently also required bilateral adrenalectomy, and then developed aggressive Nelson's syndrome. One of these received GK on two occasions to two distinct areas of disease recurrence as indicated in Table 2. The mean interval between conventional and stereotactic radiotherapy was 6.3 years (range 2–22 years).

Other pituitary tumours

We have also treated eight patients with NFPAs, all of whom had previously undergone surgery (four on more than one occasion) and CRT (interval mean 15.1 years, range 2–26 years). This patient group had a recurrent disease: with progressive increase in the size of visible tumour on serial imaging. One patient with a prolactinoma was also treated. She had undergone surgery and CRT 11 and 8 years prior to GK, as she had developed severe mania on dopamine agonist therapy. The indication for GK in this patient was the development of a diplopia secondary to a new cavernous sinus recurrence associated with a rise in serum prolactin (PRL) from 722 to 3740 mU/l (upper limit of normal 380 mU/l). The details of these patients are summarised in Table 2.

Previous radiotherapy

CRT had been administered at various different centres in the UK and elsewhere. The median dose was 45 Gy that was given in 25 fractions (range 40–45 Gy, with one radioactive Yttrium implant). The mean interval between CRT and GK radiotherapy was 11.8 years (range 1.5–43 years).

Follow-up assessments

A baseline evaluation included formal ophthalmological assessment of visual perimetry and visual acuity, contrast-enhanced MRI of the pituitary and basal endocrine function. In those patients not already documented to be panhypopituitary, dynamic endocrine testing using insulin-induced hypoglycaemia was used to seek deficiencies of the remaining anterior pituitary

Figure 1 (a) Graph illustrating the decline in mean value of a five-point day curve of serum GH following gamma knife radiotherapy in the seven patients not receiving pegvisomant therapy. (b) Serum IGF1 levels for each patient before and following gamma knife radiotherapy. Circles indicate values pre-GK, with triangles indicating the latest IGF1 value. Open symbols represent assessments made off all the medical treatments, filled symbols reflect assessments taken on medical therapy – as indicated in Table 1 and described in methods. *Indicates the patient on somatostatin analogue therapy at the time of GK, and for his assessments, but in whom excellent control was achieved and medical treatment was subsequently stopped.

hormones unless basal cortisol level was above 550 nmol/l at 0900 h, in which case it was deemed unnecessary. A dose of 0.15 U soluble insulin/kg was administered intravenously to achieve hypoglycaemia of <2.2 mmol/l to seek deficiencies of ACTH or GH. Where hypoglycaemia was inadequate by 45 min, a repeat dose of 0.15 U/kg insulin was administered. A rise in serum cortisol to above 550 nmol/l was defined as normal, and a GH peak above 9 mIU/l (~ 3.3 ng/ml) was taken to exclude severe GH deficiency (17).

All patients were also assessed clinically by a consultant endocrinologist and oncologist, and were discussed at a pituitary neurosurgical multidisciplinary meeting. Formal psychological testing was not available.

Following GK, patients were reviewed similarly every 3 months for the first year, and annually, including dynamic testing where indicated, thereafter. All patients were assessed clinically for the development of any psychological or neurological changes following radiotherapy, and detailed visual field and acuity assessments were conducted annually to seek evidence of damage to the optic apparatus.

Six out of ten patients with somatotroph adenomas were on treatment at the time GK was administered, although biochemical assessments were made off the medical therapy in one of these (patient 6, Table 1). In the five patients who remained on treatment, all assessments have been made on the same treatments before and after GK (Table 1 and filled symbols in Fig. 1).

Patients were assessed using a GH 'day curve' as described previously by taking the mean of five serum GH levels taken throughout the day and a serum IGF1 level (18). This laboratory measures GH in mIU/l. All analyses were performed by these units, which were then converted to ng/ml for this report, using a conversion factor of 5 mIU/l = 1.8 ng/ml.

Patients with corticotroph adenomas and Cushing's syndrome were similarly assessed by estimating the mean serum cortisol levels obtained from five samples taken through a day from 0900 to 1900 h (19), and those with Nelson's syndrome with a plasma ACTH level taken 120 min after a hydrocortisone dose (13). The patient with a prolactinoma was assessed using single PRL levels only.

All hormonal measurements were performed in the Department of Clinical Biochemistry, St Bartholomew's Hospital. Serum IGF1, GH and ACTH were measured using a semi-automated analytical platform (Immolute 2500 analyser, Siemens, Worcester, UK). Serum cortisol, PRL and TSH were assayed using a modular fully automated analytical platform (E170 analyser, Roche Diagnostics).

Contrast-enhanced MRI scanning was performed annually on all patients, with serial images reviewed by the same neuroradiologist (J E).

GK dose planning and administration

All patients underwent MRI scanning to localise their residual disease prior to GK planning. The targets were mapped by three-dimensional coordinates using both plain radiographs and CT scanning to aid stereotactic localisation to the bony landmarks. GK software was used to calculate the exact target volume (range 0.61–10.4 cc, modal volume 1.1 cc) and conformation, and to determine the optimal number of isocentres required (mode = six isocentres, range 4–16). Proximity to radiosensitive structures was also taken into account using a reverse planning process. Tumours lying within 3 mm of the optic chiasm were deemed unsuitable for GK, and for all others, the total dose administered was determined by that which will expose the optic chiasm to a maximum of 8 Gy in patients with no previous radiotherapy exposure, which was reduced pragmatically to 50%, or 4 Gy for the previously irradiated patients in this series. The modal marginal dose delivered in this series was 10 Gy, which was delivered to the tumour volumes that were between 84 and 97% (mean dose $\pm$ S.E.M. 13.2 ± 2.9 , range 10–20 Gy, modal coverage 93% target volume), although patients receiving GK as an alternative to CRT in this centre received a modal dose of 20 Gy (data not shown). 'Xknife' software was also used during this time period to determine whether linac-based or GK radiosurgery would be safer in delivering the largest dose to the tumour with the minimum dose to the chiasm (15, 20). Due to this conservative planning process, 14 patients were considered unsuitable for GK.

Four milligrams of dexamethasone were administered orally 2 h before, and six hourly for 36 h following administration of GK, as in the linear accelerator-based series, with all patients admitted overnight for the observation and detection of early complications (15).

Statistical methods

Microsoft Excel was used for all statistical calculations. Mean values and ranges are given for the fall in biochemical activity post GK and for follow-up times. Modal and mean values are given for GK doses.

Results

Acromegaly

GH data The biochemical data for the patients with somatotroph adenomas are summarised in Figs 1 and 2. The full data for disease activity at the time of diagnosis and at CRT administration are not available. Published reports estimate a 50% fall in GH within the first 2 years of CRT (14), and this cohort had a mean interval of 13 years between CRT and GK delivery. Patients were thus generally deemed to be within the plateau phase of CRT before GK was considered. In the four patients in whom

Figure 2 Histogram illustrating the mean serum GH value (left) and mean IGF1 (right) before and at 12 and 24 months post gamma knife, expressed as a percentage of mean GH that was presented for patients.

full data are available, mean GH had fallen by 62% over a mean of 17 years following CRT and prior to receiving GK: from 38 to 13 mIU/l. Mean serum GH fell by a further 49% within 12 months of GK (Figs 1a and 2).

However, selected patients were treated before this plateau phase had been reached. For example, patient 10 listed in Table 1 had received surgery and radiotherapy just 18 months prior to GK. She showed no response to somatostatin analogues or cabergoline, and only partially responded to pegvisomant: with an IGF1 still twice the upper limit of normal. However, within 6 months of GK her IGF1 had normalised on the same dose of pegvisomant, and it is anticipated that this treatment can be reduced and stopped as the effects of radiotherapy and radiosurgery continue.

To date, 43% (three out of seven patients) have achieved satisfactory control – mean GH levels <1.8 ng/ml, two of whom are now off all treatments. The third remains on low-dose somatostatin analogue therapy to control the symptoms of headache. Three patients remain on the GH receptor antagonist pegvisomant, on which it is not possible to interpret GH levels: IGF1 is used as the sole biochemical marker of their disease (Fig. 1b, excluded Fig. 1a).

The radiosurgical dose used did not correlate with the fall in disease activity in this series: patients treated with 10 Gy demonstrated a 61% fall in mean GH and in IGF1 compared to a 51% fall in GH and 37% fall in IGF1 in those treated with 15–17.5 Gy, with no significant difference between each pair of data.

IGF1 data IGF1 fell by a mean of 32% at 12 months, 38% at 24 months and 44% to the latest follow-up post GK (Figs 1b and 2). IGF1 levels fell to within the age- and gender-related reference range in 50% within 12 months, but by the latest follow-up, 80% had normalised, with five patients now off all treatments (mean follow-up 38.5 months, mode 36 months, range 6–78 months) (Fig. 1b). A 19% increase in IGF1 was observed in one patient; however, he exhibited a fall in GH level over the same time period.

Satisfactory control was achieved in three out of ten patients as evidenced by both a normal age- and gender-related serum IGF1 level and a mean GH <1.8 ng/ml (one off all the medical treatments), with a further five out of ten patients achieving a satisfactory serum IGF1 on treatment for the first time (Fig. 1).

Imaging There has been no interval change documented in any of these patients.

Pituitary function Five out of ten patients with acromegaly were panhypopituitary prior to receiving GK: two out of five sustained a partial loss of pituitary function following GK, one remained partially hypopituitary and two remained eupituitary following GK (mean follow-up of these five patients was 31.4 months, range 6–55 months).

Cushing's disease and Nelson's syndrome The clinical details of all patients with corticotroph adenomas are listed in Table 2. One of the two patients with Nelson's syndrome was treated with 10 Gy, and showed excellent long-term control: a 61% fall in plasma ACTH and disease stabilisation on MRI (follow-up 5 years). The other had very aggressive disease invading the clivus, skull base and subsequently extracranial soft tissues. She received 20 Gy GK on two occasions to two distinct areas of disease (patient 15, Table 2). She showed a temporary response for 12 and 18 months respectively, though she subsequently progressed and has recently received temozolomide chemotherapy (21). Out of the four patients with Cushing's disease, one showed an improvement in cortisol excess – mean cortisol fell by 37% – and stable disease on imaging to date (12 months). A second patient showed a promising early response with an initial fall in mean cortisol of 88%, but relapsed within 12 months. Two patients showed no response, requiring bilateral adrenalectomy at 9 and 10 months. Again, no direct relationship between radiosurgical dose and clinical response was apparent in this small group. Five out of six patients were panhypopituitary prior to GK, with one remaining eupituitary at 36 months of follow-up. No other adverse events were detected.

Prolactinoma

This 75-year-old patient showed a 75% reduction in her PRL level from 3740 to 790 mU/l, with a 30% volume reduction on MRI scanning at 24 months. She was panhypopituitary before receiving GK and developed no other adverse events (follow-up 42 months).

Non-functioning pituitary adenomas

All patients with NFPA underwent GK due to regrowth of previously stable visible disease. Six of eight patients have responded. Two showed a reduction in tumour size

on serial imaging, and had received 8 and 14 Gy. Four showed disease stabilisation and had received between 10 and 20 Gy (mean follow-up 44.6 months, range 12–96 months). The remaining two patients showed tumour control for 36 and 66 months but with subsequent re-growth requiring further surgery (Table 2). These two had received comparatively low radiosurgical doses of 9 and 12.5 Gy. It is possible but not proven that higher radiosurgical doses may achieve a better long-term control. Seven out of the eight patients were panhypopituitary prior to receiving GK, with one losing further anterior pituitary function following GK; no other adverse events were detected.

Adverse events

The treatment was well tolerated by all subjects, with none reporting headache or other immediate complications. The group is small and follow-up is ongoing; however, no new tumours have been detected in the radiotherapy field on serial imaging, and no neurological, cerebrovascular or psychological disturbance has been detected on detailed clinical review of all subjects to date (median follow-up 36 months, range 6–96 months). No new visual field or acuity losses have been detected to date. Out of 25 patients, 18 were panhypopituitary prior to GK, while 3 out of the remaining 7 patients (43%) developed partial anterior hypopituitarism following GK. Three patients remain eupituitary, and one with partial hypopituitarism developed no further loss post GK.

Four patients complained of headache prior to GK, of which one improved following GK. Four patients with cavernous sinus disease also complained of diplopia prior to GK. Two with cavernous sinus syndrome experienced complete resolution of their diplopia at 2 and 18 months post GK. The others with isolated III and IV nerve palsies had no change in their symptoms.

Discussion

This is the first report of the use of GK radiosurgery exclusively in patients who had previously undergone CRT. These data confirm that GK radiosurgery is effective in acromegaly. These data also suggest an improved control in patients with recurrent NFPAs, although a true increase in actuarial progression-free survival or local disease control cannot be confirmed in such a limited number of patients with limited follow-up. GK was demonstrated to be well tolerated with an excellent safety profile although the follow-up period remains short. Our recorded instance of 43% new pituitary failure is higher than that observed in the series using GK as a treatment in non-irradiated pituitaries, but it is compatible with other series of repeat pituitary radiotherapies (6), with the majority

of such heavily pre-treated patients already being panhypopituitary. We have observed no other significant adverse events to date.

Acromegaly

The largest patient group treated with GK in the current series had a diagnosis of acromegaly. Controversy exists as to the definition of 'cure' in acromegaly. Most recent consensus statements suggest that attempts should be made to achieve both a normal age- and gender-related IGF1 and a nadir GH below 0.4 ng/ml following an oral glucose tolerance test (22, 23). However, in this group of patients with ongoing biochemical disease and macroadenomas, cure rates are invariably low. In such a population, already on medical therapy, or intolerant of it, and with previous exposure to CRT, we consider any further reduction in disease activity and sparing of the need for expensive or poorly tolerated medical treatments to be worthwhile aims. We have therefore assessed disease activity by comparing the mean of serial serum GH levels before and after treatment, and have taken the percentage fall in activity to be the primary outcome of treatment. Normal survival is associated with the reduction in mean serum GH levels below 5 mIU/l (which converts to <1.8 ng/ml) and a normalisation of the age- and gender-related serum IGF1 level, and so we have taken this to be a satisfactory disease control, though this was not always possible to achieve in this series (24, 25). Furthermore, although all patients were deemed to be stable before considering GK, inevitably some would have been within the phase of slow decline observed following CRT as discussed above. We propose that GK accelerated the fall in biochemical activity in these highly active and poorly controlled tumours allowing biochemical control to be achieved much earlier than otherwise predicted. Controversy also exists as to the possible radioprotective effect of somatostatin analogue treatments (10, 26). It was not possible to stop all the medical treatments prior to GK in this series, and the numbers are too small to draw any conclusions on this point. Those patients on treatment are indicated in Table 1 (six out of ten patients).

By analysing this group according to the biochemistry that was presented, it was found that 100% of the patients presenting with IGF1 less than twice the upper limit of their normal age- and gender-related reference range achieved normal levels, 50% within the first year. A total of 75% patients presenting GH levels less than twice the upper limit of normal (<3.6 ng/ml) also achieved a satisfactory disease control within 12 months of GK. These data strongly support the use of GK for a biochemically mild disease, and are in keeping with previous reports that the best predictor of GK effectiveness is the initial tumour activity (1, 24–28). This is also in line with other series of surgeries, CRT and medical treatments, all of which show optimal

outcomes in patients with a biochemically mild disease, usually corresponding to small tumour size on imaging (29, 30).

Examining the responses in terms of percentage fall, we report a 49% fall in GH and a 32% fall in serum IGF1 at 1 year. This fall is in addition to the previously observed fall following CRT, and this is expected to continue with continued follow-up. In our unit, mean GH is predicted to fall by ~50% at 2 years, and in this series there had been a 62% fall in GH since CRT in patients for whom data were available. In these four patients, modal interval between CRT and GK was 13.3 years, (range 1.5–43 years in the complete group) (14). There are very few reports of such refractory acromegaly with which to compare these data.

Other pituitary tumours

This series also includes 15 patients with non-somatotroph pituitary adenomas, which were also heavily pre-treated.

A previous report of 100 patients with NFPAs treated with GK reported tumour stabilisation or shrinkage in 92%, with 25% anterior pituitary failure and no other side effects (31). These data are comparable to standard radiotherapy or linear accelerator-based radiosurgery given in the early post-operative period: 95–100% local control rate at 10 years compared to 6–46% control rate at 10 years with no post-operative irradiation (32–34). Our data indicate that GK can also be safely used in the 5% of the patients who escape control post surgery and CRT. An alternative option for these tumours is to consider a repeat course of standard radiotherapy. In one series, reirradiation of 42 Gy was delivered to similarly aggressive and recurrent tumours at a median of 10 years after a median initial dose of 41 Gy (6). Overall, control was good considering the nature of this group of patients: 50% improvement and 50% stabilisation of visual loss, with local disease control in 12 out of 15 cases. In that series, temporal lobe injury was observed in 2 out of 15 patients, disease progression occurred in 3 out of 15 and all patients who were not already panhypopituitary subsequently became so. A recent review also highlights the unpredictable natural history of NFPAs, and stresses that treatment should be considered for those with visual field deficits and large or growing remnants post surgery only (34). We would therefore advocate that repeat surgery is the safest first-line treatment in NFPA escaping control despite initial conventional surgery and radiotherapy. Where this is not feasible, GK or CRT should be considered on an individual case basis.

Several groups have reported success with GK in Cushing's disease. GK has been used as an alternative to CRT following non-curative surgery, with an early remission rate of 63% in one series (35). GK and linear accelerator-based radiosurgery have also been used as the primary treatments with good results:

42–49% remission rates which are similar to that of neurosurgery alone (36). In this context, our observed response to GK radiosurgery as a salvage treatment is disappointing. GK treatment was, however, well tolerated, with an excellent safety profile, and it provided at least a modest short-term response in four out of six patients, making it an option worth considering in patients with a very severe disease in whom there is currently little else to offer. Other groups have reported success with GK as an alternative to CRT in prolactinomas (37), though there are no previous reports of its use in previously irradiated patients to our knowledge.

Adverse events

There are multiple reports of complications such as cognitive problems, visual loss, second brain tumours and cerebrovascular disease following pituitary radiotherapy (29, 30, 38, 39). It has been suggested that the rates of anterior pituitary failure and other complications may be lower following pituitary radiosurgery than those following CRT due to the ability to closely map radiation exposure to the target rather than to the pituitary fossa as a whole (8, 40). The patients in this series are not comparable to those in other published GK series due to their previous exposure to CRT, and the relatively low radiosurgical doses used (mode 10 Gy). However, in this context, the safety profile is notable, although the median follow-up remains short: 36 months.

Finally, while safety concerns remain about the repeat application of CRT (6, 7), and there are no published reports of CRT following radiosurgery to date, this represents the second series demonstrating the safety and efficacy of radiosurgery following CRT, with no significant adverse effects being detected to date (15).

Conclusions

In summary, we demonstrate that in severe pituitary disease that is resistant to conventional treatments, including radiotherapy and previous surgery, GK represents a safe salvage treatment. In this series, GK led to an accelerated fall in GH excess and stabilisation of NFPAs in the majority of cases.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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