CLINICAL STUDY

Gamma knife stereotactic radiosurgery of Nelson syndrome

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Abstract

Objective: Gamma knife radiosurgery (GKR) can be used as primary or adjuvant therapy for the treatment of an ACTH-producing pituitary tumor after bilateral adrenalectomy, called Nelson syndrome (NS). We have examined the effect of GKR on tumor growth and ACTH-hypersecretion, and characterized the adverse events of this treatment in patients with NS.

Design: Cross-sectional follow-up study. First, retrospective data pre- and post-GKR were collected. Patients then underwent a predefined survey including radiological, endocrinological, ophthalmological, and neurosurgical evaluation.

Subjects: Ten patients treated with GKR for NS after previous bilateral adrenalectomy. The mean follow-up was 7 years. No patient was lost to follow-up.

Results: Tumor growth was stopped in all patients. The ACTH levels declined in eight patients, and normalized in one patient. There was a significant drop in ACTH levels, with a half-time of 2.8 years. No patient developed visual field defects or any other cranial nerve dysfunction as a result of treatment. Four patients started hormone substitution therapy during the follow-up period. The substitution therapy of three pituitary axes present at GKR treatment could be stopped during the same period. One patient developed a glioblastoma in the left parieto-occipital region 14 years after GKR, far from the field of treatment. As the radiation level was below 1Gy to this area, it is unlikely that the GKR treatment itself induced the malignant tumor.

Conclusion: In patients with NS, GKR is an effective adjuvant treatment, carrying relatively few adverse effects. Although the risk of developing a secondary neoplasia after GKR is present, it is probably extremely low.

European Journal of Endocrinology 160 143–148

Introduction

Cushing's disease caused by an ACTH-producing pituitary tumor is, untreated, a deadly and highly mutilating disease. Treating this condition is difficult. In 10–50% of patients operated transsphenoidally, the disease recurs (1). Repeated surgery has a lower efficiency rate, and may have a higher rate of complications (2–4), therefore, adjuvant radiotherapy is often used. Treatment by gamma knife radiosurgery (GKR) or fractionated conventional radiotherapy may stop tumor growth, and over some years cause cessation of the hypersecretion. In the meantime, however, the patient will suffer from hypercortisolism, which may be devastating in aggressive forms.

In some cases, where the ACTH-secreting tumor has not been found or has not been treated efficiently

by transsphenoidal surgery, bilateral adrenalectomy can be carried out. This leads to immediate cessation of hypercortisolism, but also lifelong dependence on cortisol and mineralocorticoid replacement therapy. However, this may lead to increased growth in the ACTH-secreting pituitary tumor combined with hyperpigmentation called Nelson syndrome (NS). These tumors often exhibit a more aggressive phenotype than other pituitary adenomas (5).

Repeated surgery, conventional fractionated radiotherapy and stereotactic radiosurgery are being used as treatments for pituitary tumors in NS. We have evaluated patients treated with GKR for NS where transsphenoidal surgery has failed or not been an option. There are relatively few reports on the effect of this treatment regarding hypersecretion, tumor volume, and adverse effects. The patients underwent a

detailed survey similar to our recently published study on 55 patients treated with GKR for acromegaly (6).

Subjects and methods

Study population

The gamma knife unit in Norway is located at Haukeland University Hospital, Bergen. Patients are referred from the 4.6 million population of Norway. From January 1989 to December 2002, 127 patients were treated for tumors in the pituitary region; ten of these had established NS with enlarging pituitary tumor after bilateral adrenalectomy, ACTH hypersecretion and hyperpigmentation. The study adhered to the tenets of the Declaration of Helsinki, and the protocol was approved without review by the Regional Medical Research Ethics Committee (patient characteristics in Tables 1 and 2).

Treatment

Radiosurgery was performed with a 201-source Co⁶⁰ Leksell model C gamma knife (Elekta Instruments, Stockholm, Sweden) as described previously (6). Patients accepted for treatment had visible tumors on imaging, with a minimum distance to the optic nerve or chiasm of at least 3 mm. For treatment planning magnetic resonance imaging (MRI) was used routinely from 1996. CT imaging was, therefore, used in four cases and MRI in the remaining six cases. The dose plan aimed at delivering at least 25 Gy to the tumor periphery at the 50% isodose. This was achieved in seven patients. In the remaining the dose to the periphery of the tumor was 12 Gy in one and 20 Gy in two patients. The optic pathways received less than 10 Gy in all cases (Table 1).

Table 1 Population characteristics in ten patients with Nelson syndrome treated by gamma knife radiosurgery (GKR).

N (male)	10 (1)
Age	47 (27–64) years
Follow-up	7.0 (1.7–15.4) years
Follow-up > 5 years	6
Tumor volume at the time of GKR	1.1 (0.23–3.0) cm ³
Macroadenomas (> 1 cm)	6
ACTH at GKR	753 (138–3209) pmol/l
ACTH at survey	100 (2.0–278) pmol/l
Time from adrenalectomy until GKR	11.6 (5–22) years
Patients with previous transsphenoidal surgery	6
Patients with more than one procedure	2
Time from surgery to GKR	4.4 (0.5–6.7) years
GKR within 1 year after surgery	1
Treatment isodose (%)	49 (40–50) %
Treatment maximal dose (Gy)	53.4 (24–70) Gy
Dose to periphery (Gy)	26.2 (12–35) Gy
Tumor coverage dose (%)	87 (83–97) %
Dose to chiasm (Gy)	6.3 (3.5–9.0) Gy

For continuous variables mean values and ranges are stated.

Table 2 Overview of ten patients treated with gamma knife radiosurgery for Nelson syndrome.

Age	Sex	Years from GKR to survey	Years from adrenalectomy to GKR	Number of previous pituitary surgeries	Years from last pituitary surgery	ACTH level at GKR (pmol/l)	ACTH at survey (pmol/l)	Tumor volume at GKR (cm ³)	Tumor volume at survey (cm ³)	Max dose (Gy)	Peripheral dose (Gy)
53	F	12.5	11	1	5	282	29.4	0.79	0	70	35
49	F	2.4	15	2	2	≥275	25.9	0.70	0.48	60	30
55	M	13.5	18	0	NA	376	34.3	0.83	0.36	50	25
46	F	5.3	21	1	7	3209	278	3.00	0.56	24	12
36	F	1.7	15	2	1	138	152	1.70	0.67	50	25
57	F	6.6	13	0	NA	146	66.6	0.66	0	60	30
27	F	1.9	6	1	6	223	45.4	0.20	0	50	25
64	F	9.4	5	0	NA	288	92.6	0.95	0.40	50	20
33	F	11.7	5	0	NA	1291	2	0.23	0	70	35
48	F	2.9	5	1	6	≥275	≥278	1.70	1.84	50	20

Collection of data

Retrospective data Information regarding dose plans, radiological images, hormone substitutions, eye status, and hormone values were collected from the patients' medical journals. All patients were followed regularly by endocrinological and radiological examination according to clinical routine in the referring centers in the interval between GKR and survey. The patients were given adrenal hormone substitution with fluorocortisone (0.05–0.15 mg/day) and cortisone (25–50 mg/day), or prednisolone (10 mg/day). No patient received any medical therapy targeting tumor growth.

Data were analyzed using independent and paired sample Student's *t*-tests and Kaplan–Meier statistics. In addition, to analyze the dynamics of ACTH secretion, we collected all ACTH values obtained from GKR throughout the survey. The kinetics of reductions in ACTH levels were analyzed by a linear mixed effects model for log transformed ACTH by time since GKR using the R package name (7). Half-times for ACTH were calculated from the models' fixed effects estimates. For all statistical analysis SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and R (The R Foundation for Statistical Computing, Vienna, Austria) were used.

Cross-sectional data All patients underwent a 2-day survey including MRI, hormone evaluation, and clinical examination by a neurosurgeon, an endocrinologist and an ophthalmologist. One patient underwent survey according to the protocol outside Haukeland University Hospital. The protocol, which has been described in detail previously, is briefly given below (6).

Endocrinological examination A clinical evaluation of symptoms of pituitary dysfunction was performed. Laboratory analysis included morning urine- and serum osmolality and morning serum hormone levels. Reference values at Haukeland University Hospital: GH <13 mIU/l, insulin-like growth factor 1 IGF1 19–30 years; 15–63 nmol/l, 31–55 years; 11–40 nmol/l, >55 years; 7–29 nmol/l, ACTH 2.0–11.6 pmol/l, TSH 0.3–3.6 mIU/l, free T4 7.6–19.7 pmol/l, FSH 0.7–11.1 IE/l (21.7–153 IE/l in menopausal women), LH 0.8–7.6 IE/l, estradiol females 14–50 years; 80–2100 pmol/l, >50 years; 6–100 pmol/l, testosterone males 9.5–40.0 nmol/l, and prolactin 53–360 mIU/l. Gonadotrope, thyrotrope, and ADH deficiencies were defined as described previously (Vik-Mo *et al.* 2007). Pituitary deficiency in this study was defined by the finding of hormone levels below reference values. The GH secretion was evaluated by using basal GH values. In addition, patients already on substitution were scored as being deficient. Survey ACTH was measured using the Immulite 2000 ACTH (Siemens Medical Solutions, Llanberis, UK) assay.

MRI and ophthalmological examination In order to determine tumor volumes, MRI scans obtained at survey were compared with treatment scans. Volumes were estimated by measuring three orthogonal diameters that were multiplied by the formula $v = x \times y \times z \times 0.4$. In CT baseline images, the dose plan volume estimates were used for comparison with survey MRI. The measurements were carried out in an unblinded fashion by a pituitary neurosurgeon (ML-J). All patients underwent detailed ophthalmological testing and pre-GKR perimetries were compared with those obtained at survey.

Results

Radiological examination

Pre- and post-GKR MRI images were obtainable for comparison in nine cases (Fig. 1). The tumor volume had a reduction to a mean of 32 (range 0–69) % of initial volume, in only one patient was the tumor volume unchanged. Overall, there was a significant

Figure 1 MRI of the pituitary region in a patient with Nelson syndrome treated with GKR showing a reduction of the tumor volume after treatment. (A) Tumor (arrows) at the time of treatment. (B) Tumor (arrows) 22 months after GKR.

reduction in tumor volume (paired sample *t*-test, $P=0.019$). No cases of temporal lobe necrosis or other adverse effects were found.

Endocrine hypersecretion

One patient had normal ACTH at survey. Compared with initial values, eight out of the ten patients had a reduction of ACTH levels. ACTH levels were log transformed before a linear mixed effects model was estimated. The model included a possible decline and a random difference for the initial values between patients. The overall decline was significant ($P<0.001$) with a half-life of 2.76 years (95% CI 2.17–3.76 years; Fig. 2).

Adverse effects

Cranial nerves Pre-GKR and survey perimetry examinations were both normal in eight patients. In the remaining two patients, a visual field defect was diagnosed prior to GKR but perimetry at survey was normal. No patient reported diplopia or trigeminal symptoms.

Pituitary failure At the time of GKR two patients received hormone replacement therapy for thyrotrope axis failure, and one patient had diabetes insipidus after previous surgery and was treated with desmopressin. During the follow-up period, four additional patients developed a need for hormone replacement due to failure in one pituitary hormone axis (two somatotropin-, one thyrotrope-, and one gonadotropin axis), while the three patients receiving hormone substitution at GKR all had this stopped. The actuarial survival rate free from any new substitution therapy was six out of

the eight patients at 5 years and three out of the four patients at 10 years post-GKR (Fig. 3).

Neoplasia One patient (male, 55 years of age at GKRS) underwent survey with normal contrast MRI 14 years after GKR. Approximately 1 year after survey, he presented with a short history of cognitive decline and was diagnosed with a glioblastoma in the left parieto-occipital region (Fig. 4). The lesion was treated with surgery and irradiation, but the time from diagnosis until death was only 3 months. In the area, where the tumor emerged 14 years later, no tissue volume received more than 1 Gy.

Discussion

The number of patients reported in the literature treated with stereotactic irradiation for ACTH-secreting pituitary adenomas is steadily increasing. As GKR is a fairly new treatment modality, reliable long-term follow-up data are needed. Fortunately, only few patients with Cushing disease have to undertake bilateral adrenalectomy. Thus, relatively few cases of NS have been reported. Four other centers have previously (5, 8–10) reported a total of 33 cases, and only six cases, in one study, have a follow-up for more than 5 years. Only two papers state their definition of cure ((9, 10) – both with $\text{ACTH} < 50 \text{ pg/ml}$). Our ten patients have been followed for a longer mean period than that reported in other studies, and thus add significant data for this group of patients.

Wolfenbittel *et al.* (8) described one patient where GKR (maximum dose 40 Gy, peripheral dose 12 Gy) lead to growth control and a reduction in ACTH levels at a follow-up for more than 2 years.

Figure 2 Kinetics of ACTH decline in patients with Nelson syndrome ($n=10$) treated with GKR. Model-based estimates.

Figure 3 Actuarial survival free from new hormone replacement therapy in ten patients with Nelson syndrome treated with GKR.

Figure 4 (A) Dose plan of pituitary at treatment. Beyond the outer circle, referring to the 10% isodose line, less than 5 Gy is delivered. Inside this circle the dosage rapidly increases to 50 Gy at the maximum point in the center. (B) Glioblastoma MRI picture (T2 with gadolinium contrast) of one patient that developed a glioblastoma outside the dosage field.

Kobayashi *et al.* (9) reported on six patients with NS and 19 with cluster of differentiation treated with GKR (maximum dose 55 Gy, peripheral dose 40 Gy), the mean follow-up was 5.3 years. They concluded that the results were 'less gratifying' for NS than in cluster of differentiation patients. Growth cessation occurred in four cases but ACTH decrease in only two cases.

Pollock and Young (5) described 11 cases (maximum dose 40 Gy, peripheral dose 20 Gy) with a median follow-up of 37 months. Tumor growth control was achieved in nine cases. Ten patients had a decrease in ACTH levels (from 920 to 225 ng/ml) with a

normalization of the values in four (value not stated). Two patients died, one due to local tumor growth, while in another patient death was caused by extracranial metastasis – emphasizing the aggressive nature of these tumors. A high level of adverse effects were described (diplopia ($n=2$), ipsilateral blindness ($n=1$), testosterone and GH deficiency ($n=1$), and asymptomatic temporal lobe necrosis ($n=1$)), in patients having received conventional fractionated radiotherapy prior to GKR.

Mauermann *et al.* (10) reported that out of the 22 patients treated with GKR (maximum dose 50 Gy, peripheral dose 25 Gy), 12 had a decrease and eight had no change in tumor volume. Ten out of the 15 patients with elevated ACTH levels prior to GKR showed a decrease in ACTH levels after a median of 50 months of follow-up, and three of these had normalized ACTH levels (<50 pg/ml). Ten patients were evaluated for pituitary function and new failing axes were found in four. Two patients died because of tumor progression.

The primary goal of treatment in NS patients is to prevent further tumor growth. The experience obtained from GKR treatment of other hormone secreting pituitary tumors is that tumor growth arrest is seen in nearly all cases. In measuring tumor volumes we had to rely on estimates and in some cases of CT on dose plan volumes. In addition, the measurements were done unblinded, which may give observer bias. Nevertheless, in the clinical follow-up, no case of tumor retreatment following GKR was carried out, and there was no case of definite tumor volume enlargement. As evaluated from our study and the work by others, this also seems to be achievable in a majority of NS patients. However, the two deaths reported by Pollock *et al.* together with occasional cases where tumor growth continued despite GKR, indicate that NS tumors may have a more aggressive course than other pituitary adenomas.

All of our patients had large declines in their ACTH levels, but normal levels were only seen in one case. The drop in ACTH levels occurred more rapidly than what we have previously shown for GH and IGF1 in patients treated for acromegaly (half-life of 2.8 years versus 7.4 years), but slower than in patients with acromegaly also receiving somatostatin analogs (1.1 years) (6).

That four out of the ten patients started hormone substitution therapy during the follow-up period makes this more frequent than in the 13% we found for acromegalic patients (6). But still the fractions of patients developing loss of pituitary axes following GKRS seems to be lower than reported for conventional radiotherapy (50–100%) (11, 12). We have not found any papers describing the effect of repeated transsphenoidal surgery for NS on pituitary function. It is reasonable, however, to compare with the results from repeated transsphenoidal surgery in cluster of differentiation or acromegaly where loss of pituitary axis is seen in 41–50% (2–4). No adverse effect was found on any cranial nerves. Some patients received GH substitution

treatment. Although it may be feared, no study has shown increased incidence of tumors or neoplasia during GH treatment. Instead, in 100 patients on GH treatment followed prospectively because of sellar tumors, initial tumor growth was found only in one. In this patient, GH replacement was continued, and there was no further enlargement (13).

The current study uses a radiation dose similar to the studies by Pollock & Young (5) and Mauermann *et al.* (10). We do not find the serious side effects reported by the first group, and all over the effect- and side-effects reported here are more similar to the results reported by the latter group.

Following irradiation, there is a risk of pituitary failure, which has a negative impact on health and life quality. In addition, only half of patients undergoing bilateral adrenalectomy develop a growing pituitary tumor (14). Thus, we do not advocate irradiating the sellar area routinely in order to prevent tumor development following adrenalectomy. Instead, MRI scans and ACTH analysis should be carried out with regular intervals to detect any raise in activity.

One patient developed a glioblastoma at a distant site from the treatment field. There is a risk for development of neoplasia after radiotherapy, but only very few cases have been reported (15). In our case, the tumor was far from the therapeutic field, and the level of irradiation at this point was below 1 Gy. Thus, a direct induction of tumor, as a result of GKR treatment seems unlikely. Although a coincidental development of this tumor is possible, further vigilance in monitoring the frequencies of such cases is important.

Conclusion

GKR is an effective and relatively safe treatment option for patients with NS. Growth arrest was obtained in every case in our study. Most patients have a large decline in hypersecretion, although very few reach normal levels. The main aim of the therapy is, however, control of tumor growth. The need for new hormone substitutions is lower than previously reported for conventional fractionated therapy and comparable or lower than that reported for repeated transsphenoidal surgery.

Declaration of interest

The authors wish to declare that they have no conflict of interest.

Funding

The study was supported by a grant from the Western Norway Regional Health Authority (Helse Vest).

Acknowledgements

We are grateful to study nurse Monica Finnkirk for skillful organization and patient handling during the survey and in the collection of data.

References

- 1 Liu JK, Fleseriu M, Delashaw JB Jr, Ciric IS & Couldwell WT. Treatment options for Cushing disease after unsuccessful transsphenoidal surgery. *Neurosurgical Focus* 2007 **23** E8.
- 2 Ram Z, Nieman LK, Cutler GB Jr, Chrousos GP, Doppman JL & Oldfield EH. Early repeat surgery for persistent Cushing's disease. *Journal of Neurosurgery* 1994 **80** 8037–8045.
- 3 Friedman RB, Oldfield EH, Nieman LK, Chrousos GP, Doppman JL, Cutler GB Jr & Loriaux DL. Repeat transsphenoidal surgery for Cushing's disease. *Journal of Neurosurgery* 1989 **71** 520–527.
- 4 Benveniste RJ, King WA, Walsh J, Lee JS, Delman BN & Post KD. Repeated transsphenoidal surgery to treat recurrent or residual pituitary adenoma. *Journal of Neurosurgery* 2005 **102** 1004–1012.
- 5 Pollock BE & Young WF Jr. Stereotactic radiosurgery for patients with ACTH-producing pituitary adenomas after prior adrenalectomy. *International Journal of Radiation Oncology, Biology, Physics* 2002 **54** 839–841.
- 6 Vik-Mo EO, Oksnes M, Pedersen PH, Wentzel-Larsen T, Rødahl E, Thorsen F, Schreiner T, Aanderud S & Lund-Johansen M. Gamma knife stereotactic radiosurgery for acromegaly. *European Journal of Endocrinology* 2007 **157** 255–263.
- 7 Pinheiro JC & Bates DM. *Mixed-Effects Models in S and S-PLUS* New York: Springer, 2000.
- 8 Woffenbutter BH, Kitz K & Beuls EM. Beneficial gamma-knife radiosurgery in a patient with Nelson's syndrome. *Clinical Neurology and Neurosurgery* 1998 **100** 60–63.
- 9 Kobayashi T, Kida Y & Mori Y. Gamma knife radiosurgery in the treatment of Cushing disease: long-term results. *Journal of Neurosurgery* 2002 **97** 422–428.
- 10 Mauermann WJ, Sheehan JP, Chernavsky DR, Laws ER, Steiner L & Vance ML. Gamma Knife surgery for adrenocorticotrophic hormone-producing pituitary adenomas after bilateral adrenalectomy. *Journal of Neurosurgery* 2007 **106** 988–993.
- 11 Zierhut D, Flentje M, Adolph J, Erdmann J, Raue F & Wannenmacher M. External radiotherapy of pituitary adenomas. *International Journal of Radiation Oncology, Biology, Physics* 1995 **33** 307–314.
- 12 Becker G, Kocher M, Kortmann RD, Paulsen F, Jeremic B, Müller RP & Bamberg M. Radiation therapy in the multimodal treatment approach of pituitary adenoma. *Strahlentherapie und Onkologie* 2002 **178** 173–186.
- 13 Frajese G, Drake WM, Loureiro RA, Evanson J, Coyte D, Wood DE, Grossman AB, Besser GM & Monson JP. Hypothalamo-pituitary surveillance imaging in hypopituitary patients receiving long-term GH replacement therapy. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 5172–5175.
- 14 Assié G, Bihurel H, Coste J, Silvera S, Kujas M, Dugué MA, Karray F, Dousset B, Bertherat J, Legmann P & Bertagna X. Corticotroph tumor progression after adrenalectomy in Cushing's disease: a reappraisal of Nelson's syndrome. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 172–179.
- 15 Rowe J, Grainger A, Walton L, Silcocks P, Radatz M & Kemeny A. Risk of malignancy after gamma knife stereotactic radiosurgery. *Neurosurgery* 2007 **60** 60–65.

Received 3 November 2008

Accepted 4 November 2008