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Role of gamma knife radiosurgery in the treatment of prolactinomas

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Abstract

Purpose Stereotactic radiosurgery is one of the treatment options for prolactinomas, the most commonly used being Gamma Knife Radiosurgery (GKRS). GKRS is indicated mainly in the treatment of dopamine agonist (DA)-resistant prolactinomas. In our study, we report on our experience in treating prolactinoma patients by GKRS.

Methods Twenty-eight patients were followed-up after GKRS for 26–195 months (median 140 months). Prior to GKRS, patients were treated with DAs and 9 of them (32.1%) underwent previous neurosurgery. Cavernous sinus invasion was present in 16 (57.1%) patients. Indications for GKRS were (i) resistance to DA treatment (17 patients), (ii) drug intolerance (5 patients), or (iii) attempts to reduce the dosage and/or shorten the length of DA treatment (6 patients).

Results After GKRS, normoprolactinaemia was achieved in 82.1% of patients, out of which hormonal remission (normoprolactinaemia after discontinuation of DAs) was achieved in 13 (46.4%), and hormonal control (normoprolactinaemia while taking DAs) in 10 (35.7%) patients. GKRS arrested adenoma growth or decreased adenoma size in all cases. Two patients (8.3%) developed hypopituitarism after GKRS. Prolactinoma cystic transformation with expansive behaviour, manifested by bilateral hemianopsia, was observed in one patient.

Conclusions GKRS represents an effective treatment option, particularly for DA-resistant prolactinomas. Normoprolactinaemia was achieved in the majority of patients, either after discontinuation of, or while continuing to take, DAs. Tumour growth was arrested in all cases. The risk of the development of hypopituitarism can be limited if the safe dose to the pituitary and infundibulum is maintained.

Keywords Gamma knife radiosurgery · Prolactinoma · Resistance · Hypopituitarism

Introduction

Prolactinomas are the most common type of pituitary tumour. Pharmacological therapy with dopamine agonists (DA) is the treatment of choice for prolactinomas. Other treatment modalities involve surgery and radiation therapy.

Pharmacological therapy is very effective and well tolerated. The most commonly used dopamine agonists are ergot-derived bromocriptine and cabergoline and non-ergot-derived quinagolide. Out of those DAs, cabergoline (CAB) is the most effective, as normoprolactinaemia is achieved in 75–96% of patients with prolactinomas [1, 2], even in cases resistant to the other dopamine agonists [2]. Tumour shrinkage is reported in 80% of patients treated with DAs [3]. Cabergoline is the best tolerated DA, as drug intolerance is observed in 3% of patients, compared to 12% of patients treated with bromocriptine, and 7% of patients treated with quinagolide [4–6].

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Resistance to dopamine agonists, specifically to cabergoline, is observed in 10% of patients with microadenomas and 18% of patients with macroadenomas [7, 8]. Resistant prolactinomas are more often found in men than in women [9]. Resistant prolactinomas are larger tumours, often present with cavernous sinus invasion. [10]. Prolactinomas occurring as a part of multiple endocrine neoplasia type 1 (MEN1) are considered to be more aggressive and resistant to DA treatment [11].

Neurosurgery is indicated in cases of DA-resistant prolactinomas, DA intolerance, cerebrospinal fluid fistulas or in emergency situations in patients presenting with pituitary apoplexy and rapidly progressing neurological and ophthalmological symptoms due to mass effect. Long-term hormonal normalisation is reached in 61.1% of microprolactinomas and 26.1% of macroprolactinomas after neurosurgery [12]. Neurosurgical treatment fails in cases of invasive giant prolactinomas, especially in those with significant cavernous sinus invasion.

Pharmacological therapy and neurosurgery may fail in the treatment of some prolactinomas. Therefore, in such cases, radiosurgery is used concerning primarily DA-resistant prolactinomas. Another indication can be DA intolerance or an attempt to reduce the dosage and/or shorten the length of DA therapy. The most common side-effect associated with stereotactic radiosurgery is the development of hypopituitarism, which was observed in up to 42% of patients in some studies [13, 14], while other side-effects such as optic neuropathy, cranial neuropathy, radionecrosis or vascular injury developed in exceptional cases [15–17].

In our previous study, we analysed a group of 35 prolactinoma patients treated by GKRS between 1993 and 2005 [18]. In the current study, we examined a group of 28 prolactinoma patients treated by GKRS. In the meantime, radiosurgical technique and focusing have improved and promised a more precise and safe therapy. The aim of this study was to assess whether the results of GKRS have changed and whether the development of hypopituitarism is reduced when the previously calculated maximum safe doses [19, 20] to the healthy pituitary gland tissue and distal infundibulum are maintained. We speculated whether the indication for GKRS for prolactinomas had changed after cabergoline has become the predominantly used DA in recent years.

Patients and methods

We retrospectively studied the results of GKRS treatment performed between 2001 and 2015 at the Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital. Our study group consisted of 28 patients (13 females and 15 males, aged 18–71, mean ± SD, 40.3 ± 13.7, median, 37.5 years) with prolactin secreting pituitary adenomas. Prior to GKRS, a total of 19 patients (67.9%) received only pharmacological therapy, while 9 (32.1%) underwent neurosurgery in addition to pharmacological therapy. The interval between neurosurgery and GKRS was 9–228 months (median 36 months). Cavernous sinus invasion was demonstrated in 16 patients. The follow-up period was 26–195 months (mean ± SD, 130.7 ± 49.6, median, 140 months).

GKRS was indicated due to (i) resistance to DA treatment (17 patients), (ii) drug intolerance (5 patients), or (iii) attempts to reduce the dosage and/or shorten the length of DA therapy (6 patients). Resistance to DA treatment was defined as a failure to achieve normoprolactinaemia on a cabergoline dose of 2 mg per week, if the patient was treated for at least 6 months. Complete resistance was defined as a failure to normalise prolactin level at a cabergoline dose of ≥ 3.5 mg weekly.

Patients resistant to DAs were treated with cabergoline at doses from 2.0 to 10.5 mg weekly (mean ± SD, 3.2 ± 2.2 mg weekly, median 2.5 mg weekly). Out of those, 14 patients were treated with cabergoline at doses ranging from 2 to 3 mg weekly, 3 patients were on cabergoline doses of ≥ 3.5 mg weekly.

In 22 patients (78.6%), administration of dopamine agonists was suspended for 4–8 weeks prior to GKRS. Out of those, in 11 patients cabergoline administration was suspended for 8 weeks.

During treatment with DAs before GKRS, the size of adenoma decreased < 50% of original size in 4 patients; adenoma size was stable in 2 patients, adenoma size increased in 1 patient.

Data concerning patient and tumour characteristics are summarised in Table 1.

The regular hormonal follow-up was carried out at a single centre (3rd Dept. of Medicine, 1st Faculty of Medicine, Charles University, Prague, Czech Republic). The tests were carried out every 6 months in order to establish (i) the normalisation of prolactin production, and (ii) the possible pituitary deficits after GKRS.

Hormonal activity in patients with prolactinomas was determined by prolactin level. The criteria for hormonal normalisation included the upper limit of the normal range for our method (PRL < 29.2 µg/l in fertile women, PRL < 20.3 µg/l in postmenopausal women, and PRL < 17.7 µg/l in men).

Serum-free thyroxin hormone level was used for evaluation of the pituitary-thyroid axis. In order to exclude a diagnosis of incident primary hypothyroidism, TSH level was measured. The activity of the pituitary–adrenocortical axis was assessed by measuring morning serum cortisol level (08:00). Hypocortisolism was excluded, if morning cortisol level (08:00) was > 400 nmol/l. Hypocortisolism was determined if morning cortisol level was < 100 nmol/l. In

Table 1 Patient and tumour characteristics

Characteristics	Values
Total no. of patients	28
Median age at GKRS (years)	37.5 (18–71)
Sex (male/female)	15/13
Median follow-up (months)	140 (26–195)
Indication for GKRS	
Resistance to DA	17
Drug intolerance	5
Attempt to reduce the dosage and/or shorten the length of DA therapy	6
Treatment prior to GKRS	
DA treatment	28
Surgical resection	9
Type of DAs	
Cabergoline	26
Terguride	2
Median dose of cabergoline before GKRS (mg)	2 (1–10.5)
Median prolactin level before initiation of DA treatment (µg/l)	967 (110–7.050)
Median prolactin level on DA treatment (µg/l)*	63 (2.9–372)
Hypopituitarisms before GKRS (No. of patients)	7
Total	4
Partial	3
Tumour features	
Median tumour volume (mm^3)	1.150 (79–13.200)
Cavernous sinus invasion (No. of patients)	16

*The assessment was performed 2 months before GKRS

all patients with morning serum cortisol levels between 100–400 nmol/l, stimulation tests, either insulin tolerance test (ITT) (0.1–0.2 IU/kg insulin–HM R i.v. as bolus; samples drawn at 0, 30, 60 and 90 min), or Synacthen test (1-24 ACTH (Synacthen) 10 µg/l administered intravenously with a 30- and 60-min serum cortisol measurement) were performed. Peak cortisol levels below 500 nmol/l at 30 or 60 min indicated hypocortisolism. The activity of the pituitary–gonadal axis was measured by determining luteinising hormone (LH), follicle-stimulating hormone (FSH) in all patients; in males by serum testosterone levels, and in females by serum levels of 17-β-oestradiol and the presence of regular menstrual bleeding.

Hormonal parameters were evaluated using commercial kits. Prolactin was determined by chemiluminescence immunoassay (Abbott), serum cortisol by chemiluminescence immunoassay (ADVIA Centaur), LH and FSH by chemiluminescence immunoassay (ADVIA Centaur), testosterone and oestradiol by chemiluminescence immunoassay (Architect Abbott), and fT4 by chemiluminescence immunoassay (Centaur Bayer).

Radiosurgery was performed between 2001 and 2009, using an LGK model C, since 2010 using LGK Perfexion (Elekta Instrument AB, Stockholm). Stereotactic imaging was performed by MRI (Siemens 1.5 T) using classic native TSE sequences in T2 weighting and in T1 weighting in axial and coronary cuts of 2 mm thickness, before and after contrast. In some patients, images were obtained by dynamic TSE T1 weighted sequence. The accuracy of MRI targeting was evaluated in a separate study [21]. Data concerning radiosurgical treatment characteristics are summarised in Table 2. Post-radiation MR scans were performed in all patients on a regular basis. To evaluate the size of adenoma, the volumetric measurement method for pituitary adenomas was used. The volumetric measurement method works on the following principle: software derives the volume of adenoma from its contouring on each slice of the coronal study and from the thickness of the slices. In macroadenoma patients, a volume change (decrease or increase) is evaluated if the difference in the volume is at least 20% compared to the original size.

Statistical analysis

All statistical analyses were performed using S.A.S. software release 8.2 (SAS Inc., Cary, NC, USA). The present study was a non-randomised clinical trial. The time-to-normalisation was estimated by the product limit-method (also called the Kaplan–Meier method). The association between time-to-normalisation and different influencing factors were

Table 2 GKRS characteristics

Patient receiving DA at the time of GKRS (No. of patients)	6
Target radiosurgical tumour volume (mm^3)	1.900 (450–14.600)
Median margin dose (Gy)	35 (20–36)
Median maximum dose (Gy)	70 (40–70)
Median maximal dose to the optic nerve (Gy)	5 (1–8)
Median dose to the pituitary gland (Gy)	12 (3–15)
Median maximal dose to the distal infundibulum (Gy)*	9 (3–20)

*The dose to the pituitary gland and to the distal infundibulum was determined in all 24 patients with normal pituitary function

investigated by univariate and multivariate Cox proportional hazard models. Relationships between nominal variables were analysed by means of a Chi square test. If one cell's expected size was below five observations, then the Fisher's exact test was used instead of the Chi square test. Descriptive statistics are also presented; categorical data are summarised by means of absolute and relative frequencies. Continuous data are presented by means of the following summary statistics: number of observations, arithmetic mean, standard deviation, minimum, median, and maximum.

All tested hypotheses were two-sided. The level of significance was selected as alpha = 0.05. In the results, p-values were rounded up to four digits. All tests of H0 versus H1 hypotheses were formulated prior to data sample selection and no downward adjustment of significance levels for multiple testing was used.

Results

Effects on hormonal activity

The mean prolactin level prior to the initiation of DA treatment was 2.051 ± 2.152 µg/l, median (min; max), 967 (110; 7.050) µg/l. Prior to GKRS, 26 (92.9%) patients were treated with cabergoline and 2 (7.1%) with terguride. Patients who had received terguride prior to GKRS started DA treatment at the time when cabergoline was not available on the market. Length of DA administration prior to GKRS ranged from 6 to 228 months (mean ± SD, 72.2 ± 64.9, median, 48 months). The mean prolactin level on DA treatment before GKRS (the assessment was performed 2 months before GKRS) was 87.8 ± 92.5 µg/l, median (min; max), 63 (2.9; 372) µg/l. Two patients, whose indication for GKRS was the attempt to reduce the dosage and/or shorten the length of DA therapy, had normal prolactin levels before GKRS (on DA treatment). The mean prolactin level at the end of follow-up was 15.3 ± 13.5 µg/l, median (min; max), 10.7 (2.6; 71) µg/l.

Prolactin levels before and after GKRS according to the achievement of hormonal normalisation are summarised in Table 3.

Hormonal remission (normal prolactin level after discontinuation of dopamine agonists after GKRS) was achieved in 13 (46.4%) patients. The median time to hormonal remission in the study group of 28 patients was 152 months, 95% CI (76 months, upper limit is not estimable due to low percentage of remissions) (Fig. 1). Hormonal control (normal prolactin levels while taking dopamine agonists after GKRS) was achieved in 10 (35.7%) patients. In total, hormonal normalisation was achieved in 82.1% of patients, either after the discontinuation of DA or while taking DA after GKRS irradiation.

None of the following factors–adenoma size before GKRS, tumour shrinkage after GKRS, prolactin levels before initiation of DA treatment, prolactin levels on DA treatment prior to GKRS, cavernous sinus invasion, marginal dose and discontinuation of DAs prior to GKRS–influenced statistically significantly the success rate of hormonal remission, as tested by univariate Cox proportional hazard model.

The impact of the discontinuation of dopamine agonist was analysed in a group of 22 patients, in which dopamine agonists were suspended for 4–8 weeks before GKRS, and

Table 3 Prolactin levels and tumour volume before and after GKRS according to the achievement of hormonal normalisation

	Median prolactin level before initiation of DA treatment (µg/l)	Median prolactin level on DA treatment (µg/l)	Median tumour volume before GKRS (mm^3)	Median prolactin level after GKRS at the end of follow-up (µg/l)	Median tumour volume after GKRS (mm^3)
Hormonal remission	936 (110–6.750)	35.8 (2.9–351)	990 (140–13.20)	9.6 (2.6–23.1)	460 (0–10.800)
Hormonal control	891 (445–7.050)	85.2 (6.2–372)	1.800 (590–11.200)	10.7 (4.5–20.2)	696 (200–3.640)
Persistent hyperprolactinaemia	1.406 (1.076–5.856)	77.3 (63–273)	1.260 (79–4.700)	32.9 (30.2–71)	840 (0–2.600)

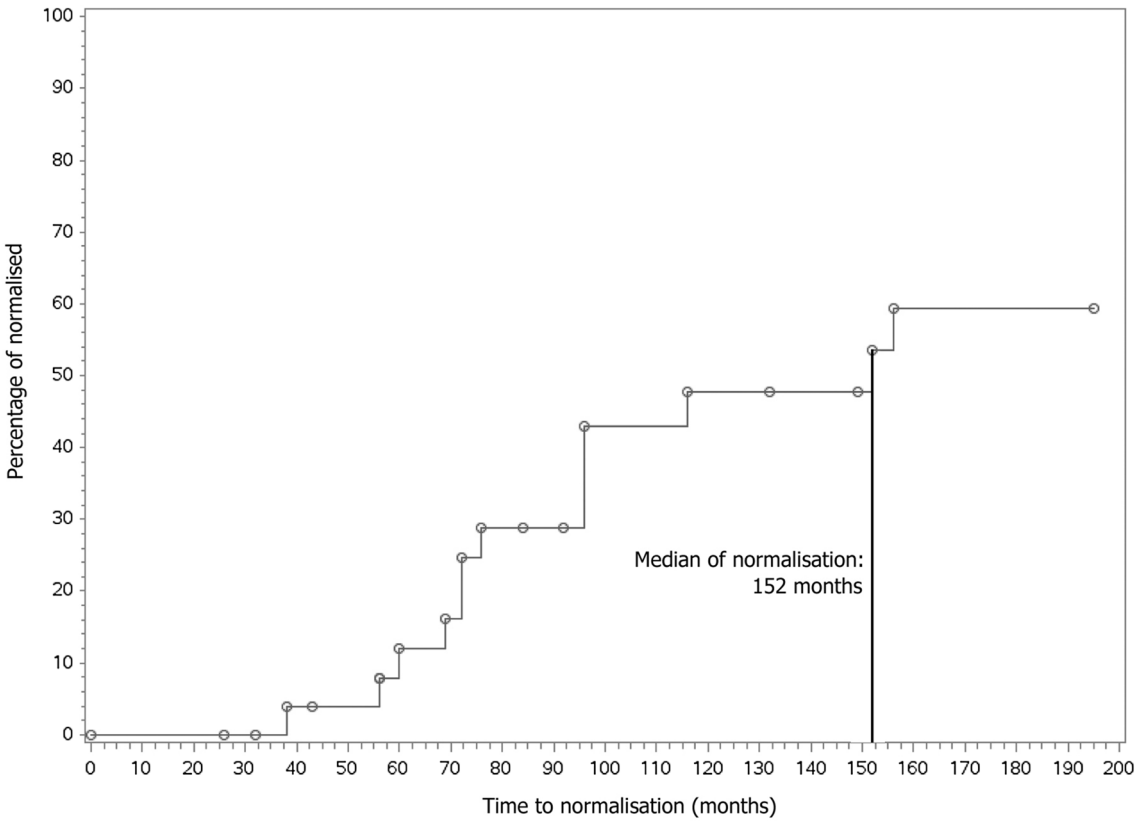

Fig. 1 Proportion of normalised patients (according to Kaplan–Meier method)

in a subgroup of 11 patients, in which cabergoline was suspended for 8 weeks before GKRS.

Eleven patients who achieved hormonal remission were followed up for at least 12 months after discontinuation of DAs (mean ± SD, 58.3 ± 31.5 months; median (min; max), 50 (12;118), months), and two patients were followed up for a shorter period. No relapse of hyperprolactinaemia was observed in any of these patients.

The outcomes of GKRS according to (i) indication for GKRS treatment and (ii) the presence of cavernous sinus invasion are summarised in Table 4.

In a group of 10 patients who achieved hormonal control, 7 patients were treated with a reduced dose of DA (cabergoline) compared to before GKRS, where the median dose of CAB before GKRS was 2 (1.5–3) mg and the median dose of CAB after GKRS was 0.25 (0.25–2) mg. One patient switched to cabergoline from terguride, 1 patient switched to bromocriptine from cabergoline due to symptoms of depression while taking cabergoline, 1 patient who developed secondary resistance to cabergoline was treated by an increased dose of cabergoline compared to before GKRS.

Four patients with persistent hyperprolactinaemia were treated with the same dose of DAs as before GKRS. A decrease of prolactin levels was observed in all of them. One of those patients who was treated with 10.5 mg of cabergoline weekly was recommended to undergo neurosurgery 3 years after GKRS.

Effects on adenoma size

In a group of 28 patients, 24 patients (86%) experienced a decrease in the size of adenoma, the adenoma was not visible on MRI in 2 patients (7%), while no change in the size of the adenoma was found in 2 patients (7%). The mean volume of adenoma before GKRS was 2.081 ± 2.983 mm^3, median (min; max), 1.150 (79; 13.200) mm^3, the mean volume of adenoma after GKRS was 1.186 ± 2.027 mm^3, median (min; max), 618 (0; 10.800) mm^3. Tumour growth was not observed. Tumour volumes before and after GKRS regarding the achievement of hormonal normalisation are summarised in Table 3.

Cystic changes in the adenoma were observed in 7 patients after GKRS. In 3 out of 7 patients, cystic transformation developed newly after GKRS. In 4 patients, cystic changes in the adenoma were already present before GKRS. In 2 patients, the extent of the cystic changes has not changed after GKRS. In 1 patient, cystic changes gradually resolved after GKRS. By contrast, in 1 patient, the cystic changes enlarged and led to the complete prolactinoma cystic transformation after GKRS. Of those 7 patients, only

Table 4 Outcomes of GKRS, prolactin and tumour volume before and after GKRS according to (i) indication for GKRS, (ii) the presence of cavernous sinus invasion

Indication for GKRS	No. of patients	Hormonal remission-No. of patients (%)	Hormonal control-No. of patients (%)	Persistent hyperprolactinaemia-No. of patients (%)	Median prolactin level on DA treatment before GKRS (μg/l)	Median tumour volume before GKRS (mm^3)	Median prolactin level after GKRS at the end of follow-up (μg/l)	Median tumour volume after GKRS (mm^3)
Resistance to DA	17	7 (41.2%)	7 (41.2%)	3 (17.6%)	82.1 (25–372)	1.260 (79–13.200)	9.6 (2.6–71)	500 (0–10.800)
DA intolerace	5	2 (40%)	2 (40%)	1 (20%)	63 (31–86.4)	700 (140–1.100)	20.2 (10.9–40.2)	390 (0–840)
Attempt to reduce the dosage and/or shorten the length of DA therapy	6	4 (66.7%)	1 (16.7%)*	0	15.8 (2.9–50)	2.000 (630–3.000)	12.8 (9.4–15.7)	915 (516–2.500)
Cavernous sinus invasion								
Yes	16	6 (37.5)	6 (37.5%) *	3 (18.8%)	69 (6.2–372)	1.650 (600–13.200)	11.6 (2.9–71)	925 (200–10.800)
No	12	7 (58.3%)	4 (33.4%)	1 (8.3%)	59.4 (2.9–350.8)	750 (79–2000)	9.7 (2.6–31.6)	309.5 (0–1.360)

*1 patient who had normal prolactin levels on DA treatment before and after GKRS was not evaluated

1 cystic lesion, which developed newly after GKRS, had expansive behaviour. In that case, 3 months after GKRS a posthaemorrhagic pseudocyst with a volume of 500 mm^3 developed. The cyst had suprasellar extension, manifested by bitemporal hemianopsia and was evacuated by stereotactic cyst aspiration. During the long-term follow-up of this patients, only the adenoma residue was observed (volume of adenoma at the time of GKRS 1.100 mm^3, 10 years after GKRS 120 mm^3).

Side-effects

Development of hypopituitarism

Seven patients suffered from hypopituitarism before GKRS. Of those 7 patients, 4 (3 males, 1 female) suffered from panhypopituitarism. These 4 patients had undergone neurosurgery before GKRS. Out of 3 patients who suffered from partial hypopituitarism, 1 patient developed central hypothyreosis as a result of the mass effect of pituitary macroadenoma. Two male patients developed central hypogonadism due to either the mass effect of macroadenoma or previous operation.

Six patients with peripheral hypothyreosis were treated with thyroid hormone replacement therapy before GKRS. The pituitary-thyroid axis was evaluated in 17 patients who were euthyroid before GKRS. One patient (5.9%) developed thyroid deficiency. The pituitary-adrenocortical axis was examined in 24 patients, of which 1 patient (4.2%) developed cortisol deficiency.

Gonadal function was influenced by the inhibitory activity of hyperprolactinaemia on the pituitary–gonadal axis. Following GKRS, a regular menstruation cycle was restored in 8 women with normoprolactinaemia and in two women with mild hyperprolactinaemia. In one female patient, gonadotropic functions had already been damaged post-operatively before GKRS. The other two patients were in menopause. None of the female patients developed hypogonadism after GKRS. Normalisation of serum testosterone levels was achieved in 8 of 15 male patients. Of the remaining 7 patients, 5 patients suffered from hypopituitarism before GKRS, either total (3 patients) or partial (2 patients). Two male patients developed central hypogonadism after GKRS.

In total, 2 patients (8.3%) developed hypopituitarism after GKRS. The first patient developed central hypogonadism, hypothyroidism and hypocortisolism 28 months after GKRS. In this case, the mean dose to the pituitary was 14 Gy and to the distal infundibulum 20 Gy. The second patient developed central hypogonadism, while the function of the pituitary-thyroid and pituitary-adrenal axis was not disturbed. Macroprolactinoma sized 22 × 20 × 30 mm was diagnosed 3 years before GKRS in the case of the second patient. At the time of GKRS, the size of the macroadenoma was 19 × 22 × 12 mm, thus showing a shrinkage during the treatment with cabergoline. The central hypogonadism developed 36 months after GKRS. The dose to the pituitary was 6 Gy and the dose to the distal infundibulum was 6 Gy.

Other side-effects

Prolactinoma cystic transformation with expansive behaviour, manifested by bilateral hemianopsia, was observed in one patient.

In one patient, who was indicated for GKRS due to resistance to medical treatment, an aneurysm of the right carotid artery in the sella region was revealed on MRI 9 years after GKRS. Because of the aneurysm growth, the patient underwent endovascular treatment 4 years later (13 years after GKRS).

No other side-effects were observed following GKRS.

Pregnancy

Three patients became pregnant following GKRS, 2 of whom became pregnant twice. Treatment with DAs had failed to allow these patients to become pregnant prior to receiving GKRS. In all cases, pregnancy was achieved after GKRS with concurrent DA treatment. The treatment with DAs was stopped after pregnancy was confirmed.

Discussion

Stereotactic radiosurgery is one of the treatment options for prolactinomas, the most commonly used being Gamma Knife Radiosurgery.

Stereotactic radiosurgery, defined as highly precise circumscribed delivery of radiation to a target in a single session, is performed by either gamma knife or another stereotactic modality. One of the most important determinants for the use of GKRS is the tumour size. Functioning pituitary adenomas with diameters of up to 25 mm and non-functioning pituitary adenomas with diameters of up to 30 mm are suitable for GKRS. The other important limitation for GKRS is the distance between the margin of the adenoma and the optic pathway, which should be at least 2 mm in the case of a functioning pituitary adenoma [22]. The criteria regarding adenoma size can be partially overcome by the fractionation of the dose delivered by a linear accelerator-based system. External beam radiation therapy (EBRT) remains an effective treatment option in selected cases involving large pituitary adenomas, typically greater than 3 cm in diameter, tumours with irregular anatomical margins including adenoma with diffuse local infiltration and extrasellar invasion, and for tumours in close proximity to the optic apparatus. EBRT may also be used for patients with pituitary carcinoma.

In our institution, GKRS was indicated in selected patients as an alternative treatment option to surgical resection for patients who were resistant or intolerant to dopamine agonists, or as an option to avoid long-term or life-long medical treatment with dopamine agonists. The majority of patients was treated between 2001 and 2010. Our indication for GKRS did not fully meet the criteria for using radiotherapy for prolactinoma stated in "Diagnosis and Treatment of Hyperprolactinaemia: An Endocrine Society Clinical Practice Guideline" published in 2011, where radiotherapy was recommended for patients who are cabergoline-resistant and who fail surgical treatment or who harbour aggressive or malignant prolactinoma [23].

Pharmacological therapy with dopamine agonists was the first-line treatment in all studied prolactinoma patients. If the treatment with dopamine agonists, i.e. cabergoline at a dose of 2 mg or more weekly, failed to normalise the prolactin level, or in the case of intolerance to dopamine agonists, GKRS was recommended in some cases as an alternative treatment option. The criteria for choosing GKRS depended on the following factors: primarily the inclusion criteria for GKRS had to be fulfilled, another important factor for GKRS being preferred to surgical resection was an extensive cavernous sinus invasion, further responsiveness of adenoma size to dopamine agonists (specifically the failure to reduce adenoma size $^{>}$ 50% on DA treatment), and patient's preference between neurosurgery or radiosurgery. Patient's preference was the most important factor when an attempt to reduce the dosage and/or shorten the length of DA therapy was the indication for GRSK.

In our current study of 28 prolactinoma patients, hormonal remission i.e. normoprolactinaemia after discontinuation of DAs, was achieved in 13 patients (46.4%) and hormonal control i.e. normoprolactinaemia while taking DAs, in 10 patients (35.7%). The median time to hormonal normalisation was 152 months. In our previous study of 35 prolactinoma patients, hormonal remission was reached in 13 (37.1%) and hormonal control in 15 (42.9%) patients. The median time to hormonal normalisation was 96 months [18]. Patient groups of previous and current studies are comparable regarding the radiation volume, radiation doses and prolactin levels before initiation of DA treatment (at the time of prolactinoma diagnosis). The only difference was the type of dopamine agonist the patients were treated with before GKRS. Due to the limited availability of cabergoline on the market, in the previous study 40% of patients with prolactinoma were treated by cabergoline before GKRS, compared to 93% of patients in the current study. Results concerning the success of the hormonal normalisation were similar in both studies. However, the time required for hormonal normalisation is longer in the current study. The efficacy of Gamma Knife Radiosurgery in the treatment of prolactinoma patients has been evaluated in several studies. The success rate of GKRS is reported to be as 4.5–83%. Results vary as they are affected by the number of studied patients and length of follow-up (Table 5). In comparison to other studies, both our studies (previous and current) proved a

Table 5 Prolactinoma: success rate of GKRS

Author (year)	Number of patients	Marginal dose (Gy)	Mean or median follow-up (months)	Hormonal remission (%)	Hormonal control (%)	Mean or median hormonal remission (months)
Lim (1998) [24]	18	25.4	25.5[a]	55.5	NR	NR
Hayashi (1999) [25]	13	23.9	16.2[a]	15.4	NR	NR
Kim (1999) [26]	18	28.7	26.9[a]	16.7	NR	NR
Mokry (1999) [27]	19	14.2	30.8[a]	21	29	30.8[a]
Pan (2000) [28]	77	31.2	33.2[a]	20.8	NR	NR
Landolt and Lomax (2000) [29]	20	25	NR	25	30	28.6[a]
Choi (2003) [15]	21	28.5	42.5[a]	23.8	NR	NR
Petrovich (2003) [30]	12	15	41[a]	83	NR	NR
Kuo (2004) [31]	15	15.2	42[b]	73	NR	42[b]
Pouratian (2006) [32]	23	18.6	58[b]	26	NR	24.5[a]
Ježková (2009) [18]	35	34	75.5[b]	37.1	42.9	96[b]
Castinetti (2009) [33]	15	86.2	NR	46.6	NR	24[b]
Tanaka (2010) [13]	22	25	60[b]	18	14	NR
Sheehan (2011) [14]	32	●	●	26	NR	NR
Liu (2013) [34]	22	15	36[b]	4.5	22.7	NR
Elshirbiny (2015) [35]	16	●	Range 18–22	56	NR	Range 12–36
Cohen-Inbar (2015) [36]	38	25	42.3[b]	50	31.6	15[b]

(●) Data reported from a series including other types of adenomas

NR not reported

[a]Mean

[b]Median

significantly longer time required for the achievement of hormonal normalisation. In our experience, prolactinomas respond the slowest to GKRS treatment, compared to other functioning pituitary adenomas, namely GH and ACTH secreting pituitary adenomas [37, 38].

Some studies proved that discontinuation of DAs prior to GKRS correlates with the success rate of hormonal normalisation [29, 32, 33]. Contrary to these studies, both our studies (previous and current) similarly to other studies [34, 36] did not find this correlation. In both our studies, the results could be influenced by the relatively small group of analysed patients.

Seventeen patients who were indicated for GKRS due to cabergoline resistance were treated with cabergoline at a weekly dose of 2.0 to 10.5 mg, 14 patients at a weekly dose of 2.0 to 3.5 mg, and 3 patients at a weekly dose of 3.5 mg or more. It has been reported that about 80% of patients with macroprolactinomas achieve prolactin normalisation with weekly doses of cabergoline ranging from 0.5 to 1.5 mg [10]. Most often, cabergoline resistance is defined as a persistence of hyperprolactinaemia on the maximal labelled dose of cabergoline, i.e. cabergoline dose of 2.0 mg per week. Those cases of resistance are often partial and the escalation of cabergoline dose up to 3.5 mg weekly permits prolactin normalisation in 75% of the cases [9]. Opinions on further escalation of CAB dose over 3.5 mg/week are not unanimous. In some cases, the successful increase of CAB dose up to 7 mg/week, exceptionally even up to 11 mg/week, has been reported [8, 23, 39, 40]. It is nevertheless necessary to consider that prolonged treatment with a high dose of cabergoline can be associated with the potential risk of cardiac valvular thickening and regurgitation [41, 42]. Alternatively, GKRS can lead to the overcoming of dopamine resistance, allowing for a decreased dose of DAs or withdrawal of DAs.

Resistant prolactinomas are often macroprolactinomas with cavernous sinus invasion [10]. In our prolactinoma group, cavernous sinus invasion was demonstrated in 16 patients. Of those, 6 patients achieved hormonal normalisation after the discontinuation of DAs and 6 did so while taking DAs.

MEN 1 associated prolactinomas are considered to be larger and less responsive to DAs [11]. In our study, two patients (mother and daughter) had prolactinomas as part of MEN I. In the first case (mother), hormonal control was achieved, i.e. normal prolactin levels while taking a low dose of cabergoline weekly (0.5 mg). Prolactinoma was not visible on MRI. In the second case (daughter), the patient underwent operation prior to GKRS. Four years after GKRS, the prolactin levels decreased (prolactin 80 µg/l) while taking

the same dose of DA (cabergoline 3 mg weekly). On MRI, prolactinoma was not visible.

None of the patients which were followed up for at least 12 months after achieving hormonal remission experienced disease relapse. This fact is important because, on the basis of meta-analysis (743 patients from 19 studies), the persisting normoprolactinaemia after dopamine agonist withdrawal was proved in only 21% of patients [43].

After GKRS, the adenoma stopped growing or decreased in size in all patients. This is in accordance with previously published data, since the success rate of adenoma size control has been reported to be between 87 and 100% [17]. In 3 patients, adenoma cystic transformation developed newly after GKRS, while in 4 patients, cystic changes were present before GKRS. Only in 1 case the cystic change was symptomatic, presenting signs of the mass effect, therefore stereotactic cyst aspiration was performed. Liu et al. [34] reported the case of a prolactinoma patient who was lost to initial follow-up and discontinued DA treatment after GKRS. Three years later, this patient noticed a right exophthalmos. MRI revealed a large lobulated pituitary tumour with a haemorrhagic cyst. The patient underwent stereotactic aspiration of the cyst, followed by external radiation therapy. Hayashi et al. [25] described a non-functioning pituitary adenoma extension in association with cystic change. The cystic changes may develop as a result of GKRS in conjunction with dopamine agonist treatment, although spontaneous occurrence is also known. Cystic change is thought to arise after the resolution of a preceding haemorrhage into the adenoma, or by the necrosis of the tumour [44].

Vasculopathy-related lesions were described as a late effect after conventional fractionated radiotherapy. The occurrence of de novo intracranial aneurysms following stereotactic radiosurgery was reported only in individual case reports (following GKRS of arteriovenous malformation, acoustic neuroma, cerebellopontine meningioma, vestibular schwannoma) [45, 46]. In our study group, an aneurysm of the right carotid artery in the sella region was revealed on MRI 9 years after GKRS. In a group of 1500 patients with pituitary adenomas treated by GKRS in the Department of Stereotactic and Radiation Neurosurgery at Na Homolce Hospital, this is the only case of arterial aneurysm to have been observed following GKRS. It is, however, not entirely clear whether GKRS was the cause for the development of the aneurysm.

Development of hypopituitarism

Hypopituitarism is reported as being the most common side-effect of GKRS. The incidence of a new hormone deficiency ranges between 4.5 and 42% [33, 34]. According to the multicentre study evaluating 1023 patients with nonfunctioning and functioning adenomas (acromegaly and Cushing disease, prolactinomas were not involved), hypopituitarism developed in 24.2% of patients, mostly within 5 years, while only 15.6% of the affected patients developed hypopituitarism after that time [47]. In our current study, hypopituitarism occurred in 2 patients (8.6%) 24 and 36 months after GKRS. Factors which may affect the development of hypopituitarism were analysed in different studies. The importance of the maximum safe dose to the pituitary and infundibulum, as well as the prescription of an increased isodose line was proved [20, 48–50]. In our previously published study [20], we determined that keeping the mean radiation dose to the pituitary under 15 Gy and the dose to the distal infundibulum under 17 Gy may prevent the development of hypopituitarism. In our current study, the dose to the pituitary gland and to the distal infundibulum was determined in all 24 patients with normal pituitary function before GKRS. The safe dose to the distal infundibulum was exceeded in only 1 patient. This patient developed panhypopituitarism after GKRS. The absence of investigation of GH axis after GKRS is a limitation of our study.

To avoid the side-effects after GKRS, the radiation tolerance of the surrounding critical structures must be taken into consideration during radiosurgery dose planning. The dose to the optic pathway should be kept under 8 Gy, the dose to the brain stem under 14 Gy, the mean dose to the normal pituitary gland under 15 Gy, and to the distal infundibulum under 17 Gy. In comparison to the stated structures, the other surrounding structures are more resistant [22].

In conclusion, Gamma Knife Radiosurgery is one of the treatment options for prolactinomas. In our experience, it is a safe and effective modality in the treatment of dopamine agonist-resistant prolactinomas or in patients who are intolerant to DAs. GKRS allows the achievement of normoprolactinaemia in the majority of prolactinoma patients, either after discontinuation of, or while continuing to take, DAs. Unless the withdrawal of dopamine agonists after GKRS is accomplished, a reduction of the DA dose is usually possible. Remission persists after the withdrawal of medical therapy. The indisputable disadvantage is the time required for the achievement of hormonal normalisation. GKRS successfully arrests adenoma growth. Although rarely, adenoma cystic transformation with expansive behaviour can develop. Hypopituitarism can be limited if the safe mean dose to the pituitary of $<$15 Gy and the maximal dose to the distal infundibulum of $<$17 Gy are maintained.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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