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Gamma Knife Radiosurgery (GKRS) for Patients with Prolactinomas: Long-Term Results From a Single-Center Experience

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Statistical Analysis C
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Background: The aim of this study was to review outcomes of gamma knife radiosurgery (GKRS) for prolactinoma and report our experience with it.

Material/Methods: We reviewed the patient database in our center and identified 24 patients with prolactinoma who underwent GKRS from 1993 to 2016. Complete endocrine, clinical, and radiological data were available on these individuals before and after GKRS.

Results: Data from 5 males and 19 females with a median age of 30.5 years (range, 18.1 to 51.1) were reviewed. The median follow-up was 109.3 months (range, 23.2–269.3). The median margin dose of GKRS was 15 Gy (range, 10.5 to 23.6). In total, prolactin (PRL) normalization after GKRS was achieved in 66.7% of patients. Endocrine remission (normal PRL levels after discontinuation of dopamine agonists) was achieved in 10 patients (41.7%), and endocrine control (normal PRL levels while taking dopamine agonists) was achieved in 6 patients (25.0%). All of the patients showed tumor control. New-onset hypopituitarism post-GKRS occurred in 4 patients (16.7%). No new visual dysfunction or cranial nerve dysfunction were observed after GKRS.

Conclusions: For treatment of prolactinomas, GKRS may provide relatively high rates of endocrine remission and tumor control, as well as a low rate of new-onset hypopituitarism. GKRS may be an effective and safe treatment for prolactinomas.

MeSH Keywords: Hypopituitarism • Prolactinoma • Radiosurgery

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Background

Prolactinomas, which secret prolactin (PRL), are the most common type of functional adenomas and consist of around 40% of pituitary adenomas [1]. The majority of prolactinomas are microadenomas (80%) and men more commonly present with macroadenomas. Prolactinomas usually cause gonadal and sexual dysfunction due to hyperprolactinemia, and other symptoms related to tumor expansion occur as well. The ultimate goals of treatment for prolactinomas are threefold: 1) recovery of gonadal and sexual function through normalization of excessive serum prolactin; 2) relief of symptoms associated with visual and cranial nerve function through control of the tumor volume; and 3) preservation of or improvement in residual pituitary function and prevention of hypopituitarism [2]. Medical therapy with dopamine agonists (DAs) is safe and effective for prolactinomas, and in most cases, results in clinical improvement, including control of tumor volume control and normalization of serum PRL levels [3].

Bromocriptine and cabergoline are the 2 DAs most commonly used to treat prolactinomas. Cabergoline, a long-acting DA, offers advantages over bromocriptine. With the drug, 75% to 96% of patients become normoplactinemic [4,5], even some with tumors resistant to bromocriptine. Because cabergoline is not available in mainland China, cabergoline is the drug of choice for most patients there who have prolactinomas. For patients resistant to or intolerant of bromocriptine or other DAs, surgical resection and gamma knife radiosurgery (GKRS) can be considered. Some biologically aggressive prolactinomas can invade the cavernous sinus. In those cases, which are less responsive to DAs, surgical resection usually fails and there are increased risks of complications such as internal carotid artery injury and bleeding [6,7]. Restoration of serum PRL level is difficult with surgical resection alone. In some patients with prolactinomas, both DA therapy and surgical resection may fail. GKRS is an alternative for management of invasive prolactinomas and for patients who are resistant to or intolerant of DAs. Hypopituitarism is the most frequent adverse effect associated with GKRS, and has been reported in up to 42% of patients [8–10] It is a highly conformal and selective therapy for prolactinomas, but many questions regarding its efficacy and associated complications remain to be considered and explored.

In the present study, we reviewed the database of patients with prolactinoma who were treated with GKRS in our clinical center from 1993 to 2016 and analyzed information from 24 of these cases. We also evaluated outcomes with PRL normalization, tumor control, and complications, as well as prognostic factors associated with PRL normalization and new-onset hypopituitarism after GKRS.

Material and Methods

Patients

Records for patients with pituitary adenoma who had been treated with GKRS in the Department of Radiotherapy at the Second Affiliated Hospital of Guangzhou Medical University between December 1993 and December 2016 were reviewed. Our retrospective analysis included 24 patients with prolactinoma (5 male, 19 female) with median age 30.5 years (range, 18.1 to 51.1), who had complete clinical and endocrine evaluation before and after GKRS. The median follow-up was 109.3 months (range, 23.2 to 269.3 months). Patients were diagnosed with prolactinoma based on presenting with a serum prolactin higher than 200 ng/mL [8,11]. The two indications for GKRS were resistance to DAs and were intolerance to the drugs' side effects (severe gastrointestinal side effects of nausea and vomiting). Informed consent was obtained from each participant. All procedures were approved by the institutional committee of the Second Affiliated Hospital of Guangzhou Medical University.

Endocrine and imaging evaluations

Endocrinological assessment of all patients before and after GKRS consisted of measurements of free triiodothyronine (FT3), free thyroxine (FT4), serum PRL, cortisol and adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and testosterone and estradiol. PRL normalization was defined as serum PRL level <18.9 ng/mL (normal range, 0 to 18.9 ng/mL). Endocrine remission was defined as normoprolactinemia after discontinuation of DAs after GKRS. Endocrine control was defined as normoprolactinemia while taking DAs after GKRS. PRL normalization was defined as endocrine remission and endocrine control [9]. Hypopituitarism was defined asymptomatic anterior pituitary deficiency with laboratory examination [12]. TSH deficiency was diagnosed by low FT4 (normal range, 12.00 to 22.00 pmol/L) without regard to TSH level. A morning (08: 00) cortisol level >400 nmol/L excluded ACTH deficiency. ACTH deficiency was defined as a morning (08: 00) cortisol level <100 nmol/L [9,12]. Gonadotrophin deficiency in men was defined by low serum testosterone levels (normal range, 0.18 to 0.78 nmol/L) without elevated FSH and LH levels. Gonadotrophin deficiency in women was diagnosed based on amenorrhea with low levels of serum estradiol and gonadotrophins in premenopausal women, and without high gonadotrophins in postmenopausal women [12,13]. Pituitary hormones were measured using commercial kits. Chemiluminescence was used to analyze PRL (ADVIA Centaur, Bayer, Tarrytown, New York, United States). Serum cortisol levels were measured using a radioimmunoassay kit (Immunotech, Marseille, France). Levels of FT3, FT4, TSH, FSH, LH, testosterone, and estradiol were measured with chemiluminescence analysis (Roche Diagnostics, GmbH).

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Routine hormonal follow-up was performed every 6 months in our center. Clinical evaluations and magnetic resonance imaging (MRI) were carried out every year after GKRS as part of follow-up. Cavernous sinus invasion was defined as Knosp grade 3 or 4 [14]. Maximal tumor diameter <10 mm was defined as microadenoma and >40 mm was defined as giant adenoma. Tumor dimensions were measured in 3 orthogonal planes: anteroposterior (AP), craniocaudal (CC), and transverse (TR). Volumes of pituitary adenomas were calculated based on the formula: V=(ϖ×[TR×AP×CC])/6 [15]. Unfortunately, the digital data from the Leksell Gamma Knife model B in Gamma plan were missing. Therefore, we had to estimate tumor volume based on tumor diameters. Definitions of tumor control included tumor shrinkage (>20% tumor volume increase) and tumor stability (<20% reduction from the pre-GKRS measurement). Tumor progression was defined as >20% increase in tumor, or tumor regrowth [11].

GKRS technique

The Leksell Gamma Knife, model B, was used before April 2014 and the Perfexion Unit (Elekta Instrument, Inc., Stockholm, Sweden) was used thereafter. A stereotactic frame placement was done under local anesthetic. MRI with administration of intravenous contrast material was performed. GKRS planning was done by a radiation oncologist, neurosurgeon, and medical physicist. Dosage of GKRS was based on patient history of previous radiotherapy, distance to the optic nerve and chiasm, and tumor volume. The maximal dose to the lateral wall of the cavernous sinus was restricted to 15 Gy, and to the optic nerve and chiasm was restricted to 9 Gy. Collimators measuring 4 mm and 8 mm were mainly used to achieve better conformality.

Statistical analysis

Descriptive statistics and frequency distributions were calculated for all variables. Univariate analysis of potential prognostic factors associated with PRL normalization and new-onset hypopituitarism was performed using log-rank test statistics and a Cox proportional hazards regression model was used to calculate a likelihood ratio. Kaplan-Meier analysis was performed to assess PRL normalization and new-onset hypopituitarism. $P<.05$ was considered statistically significant. SPSS software (version 21.0) was used for statistical analyses.

Results

Population and characteristics

In this study, the median tumor volume was 0.716 cm^3 (range, 0.019 to 6.53). There were 13 patients (54.2%) with macroadenomas and 1 patient (4.2%) with a giant adenoma. Twenty patients (83.3%) were resistant to DA treatment, and 4 patients (16.7%) were intolerant to DAs. Twenty-two patients (91.7%) had taken bromocriptine before GKRS, and only 2 patients (8.3%) had used cabergoline before the procedure. Six patients (25.0%) had suprasellar extension and 4 patients (16.7%) had cavernous sinus invasion. Hypopituitarism occurred in 16 patients before GKRS, including gonadotrophin deficiency (n=15), ACTH deficiency (n=1), and TSH deficiency (n=5). Four patients (16.7%) had visual dysfunction before GKRS. No patients had cranial nerve dysfunction before GKRS. The baseline characteristics of these patients are summarized in Table 1.

GKRS characteristics

In this series, the median margin dose was 15 Gy (range, 10.5 to 23.6) (Table 2). The median maximum dose was 33.2 Gy (range, 24.0 to 66.6). The median prescription isodose was 40% (range, 30% to 60%).

Outcomes of GKRS

Endocrine remission was achieved during post-GKRS follow-up in 10 of 24 patients (41.7%) who had high levels of serum PRL before the procedure. The median time to endocrine remission after discontinuation of DAs was 71.7 months (range, 25.2 to 106.5). Endocrine control while taking DAs was achieved in 6 patients (25.0%), with median time of 62.7 months (range, 27.9 to 70.8). Eight patients (33.3%) had persistent hyperprolactinemia after GKRS. Figure 1 shows the development of PRL levels. Table 3 summarizes PRL levels before and after GKRS, according to achievement of hormonal normalization. In total, 66.7% of patients demonstrated PRL normalization, whether DA was discontinued or continued after GKRS. The median time to PRL normalization was 62.7 months (range, 25.2 to 106.5) (Figure 2). Gonadotrophin deficiency resolved in 7 of the patients with baseline hypopituitarism prior to GKRS (29.2%) and TSH deficiency occurred in 1 case (4.2%) after GKRS. The overall incidence of new-onset hypopituitarism was 16.7% (n=4) after GKRS, including gonadotrophin deficiency (n=3) and TSH deficiency (n=1). The median time to new-onset hypopituitarism was 98.5 months (range, 53.2 to 125.3) (Figure 3). Of the 3 patients with new gonadotrophin deficiency, 2 presented with persistent hyperprolactinemia and 1 had endocrine control. Tumor shrinkage occurred in 23 patients (95.83%) and in 1 patient (4.2%), the tumor was stable. Therefore, tumor control was achieved in all the patients and none had tumor progression. GKRS improved visual dysfunction in 4 patients (Table 3). Furthermore, potential prognostic factors, including age, sex, suprasellar extension, cavernous sinus invasion, history of surgical resection, history of DA treatment, tumor margin dose, maximum dose, and tumor volume, were analyzed. In univariate analysis, no prognostic factors were significantly related to PRL normalization or new-onset hypopituitarism.

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Table 1. Patient baseline characteristics of pre-GKRS and GKRS parameters.

Characteristic	Value
Male/Female, n (%)	5/19 (20.8/79.2)
Median age, (range), years	30.5 (18.1–51.1)
Median follow-up time, (range), months	109.3 (23.2–269.3)
Median tumor volume, (range), cm^3	0.716 (0.019–6.535)
Tumor size, n (%)	
Microadenoma	10 (41.7)
Macroadenoma	13 (54.2)
Giant adenoma	1 (4.2)
Indication for GKRS	
Resistance to DA	20 (83.3)
Drug intolerance	4 (16.7)
Type of DAs	
Bromocriptine	22 (91.7)
Cabergoline	2 (8.3)
Suprasellar extension, n (%)	6 (25)
Cavernous sinus invasion, n (%)	4 (16.7)
pre-GKRS	
DAs treatment, n (%)	24 (100)
Surgical resection, n (%)	3 (12.5)
Hypopituitarism prior to GKRS, n (%)	16 (66.7)
Gonadotrophin deficiency	15 (62.5)
ACTH deficiency	1 (4.2)
TSH deficiency	5 (20.8)
Visual function, n (%)	
Normal	20 (83.3)
Visual dysfunction*	4 (16.7)
Cranial nerve dysfunction of pre-GKRS, n (%)	0
Median margin dose, (range), Gy	15 (10.5–23.6)
Median maximum dose, (range), Gy	33.2 (24–66.6)
Median isodose level, (range), (%)	40 (30–60)

GKRS – gamma knife radiosurgery; ACTH – adrenocorticotropic hormone; TSH – thyroid-stimulating hormone; DAs – dopamine agonist.
* Visual dysfunction consisted of visual field defect and/or visual acuity decrease.

Table 2. Outcomes of 24 patients who underwent GKRS.

Outcomes	No. (%)
Imaging outcome	
Tumor shrinkage	23 (95.8)
Tumor stable	1 (4.2)
Tumor progression	0
Endocrine outcomes	
Endocrine remission	10 (41.7)
Endocrine control	6 (25)
Persistent hyperprolactinaemia	8 (33.3)
Resolved hypopituitarism after GKRS	
Gonadotrophin deficiency	7 (29.2)
ACTH deficiency	0
TSH deficiency	1 (4.2)
New-onset hypopituitarism	4 (16.7)
Gonadotrophin deficiency	3 (12.5)
ACTH deficiency	0
TSH deficiency	1 (4.2)
Visual function	
Visual dysfunction improved*	4
Visual dysfunction worsen*	0
Cranial nerve dysfunction of after GKRS	0

GKRS – gamma knife radiosurgery; PRL – prolactin; ACTH – adrenocorticotropic hormone; TSH – thyroid-stimulating hormone; DAs – dopamine agonist. * Visual dysfunction including visual field defect or visual acuity decrease or both.

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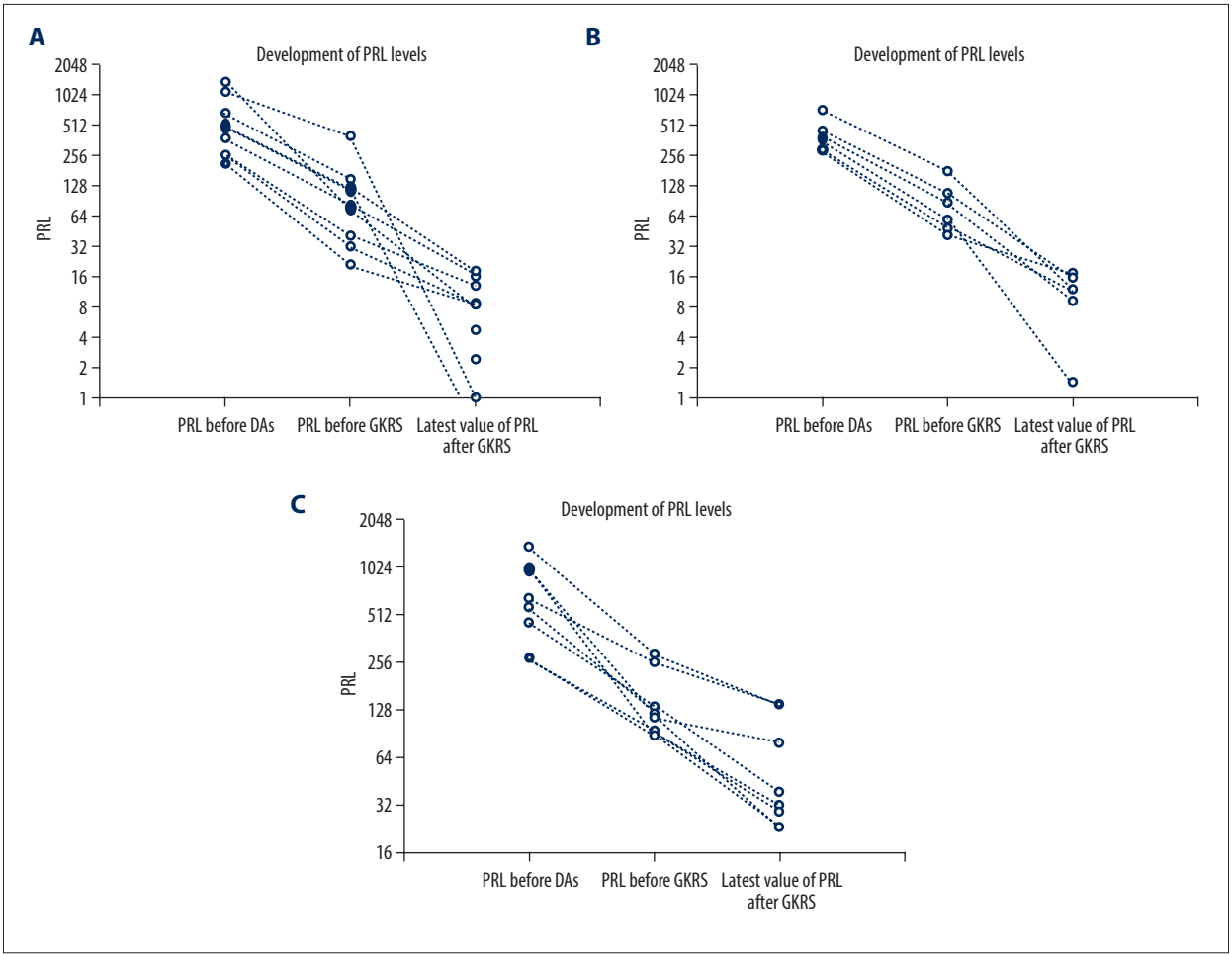

Figure 1. Development of Prolactin Levels. (**A**) Patients with endocrine remission after discontinuation of DA treatment. (**B**) Patients with endocrine control during DA treatment. (**C**) Patients with persistent hyperprolactinemia.

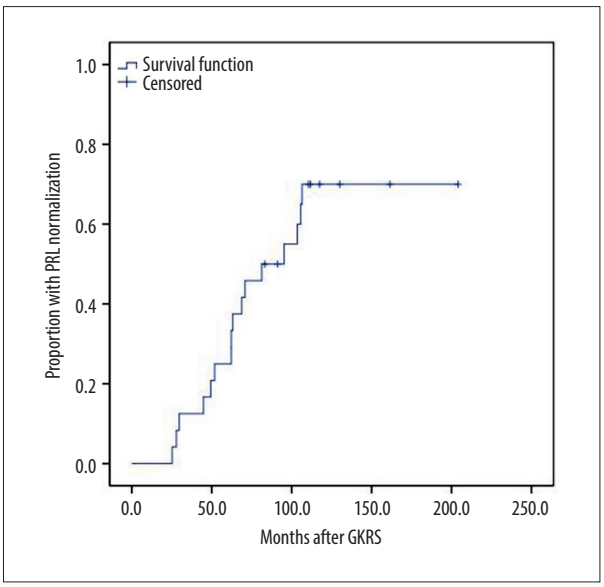

Figure 2. Kaplan-Meier curve of overall proportion of patients with PRL normalization.

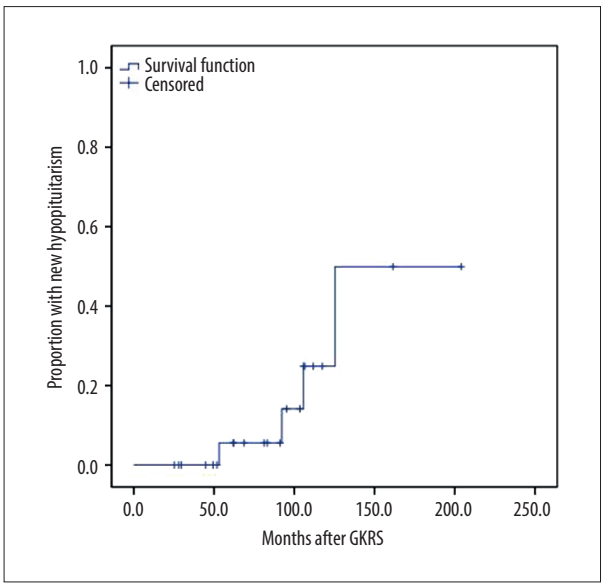

Figure 3. 0Kaplan-Meier curve of overall proportion of patients with new-onset hypopituitarism.

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Table 3. Prolactin levels before and after GKRS according to the achievement of hormonal normalization.

	Median PRL level before DAs (μg/L)	Median PRL level before GKRS (μg/L)	Median latest value of PRL after GKRS (μg/L)
Endocrine remission	483 (208–1376)	97.0 (21.2–400)	8.7 (0.5–17.9)
Endocrine control	382 (286–720)	72.9 (42.7–180)	11.8 (1.4–17.2)
Persistent hyperprolactinaemia	612 (269–1360)	117.5 (87–286)	35.7 (23.3–140)

GKRS – gamma knife radiosurgery; PRL – prolactin; DAs – dopamine agonist.

Discussion

GKRS is an alternative treatment for prolactinomas. In our department, we use it for patients who are intolerant or resistant to DAs.

Previous studies have reported long-term results with GKRS for treatment of prolactinomas. In a 2009 study by Jezkova et al. [16], endocrine remission was achieved in 37.1% of 35 patients with prolactinomas (16 drug resistant, 11 drug intolerant) after GKRS, with a median margin dose of 34 Gy (range, 20 to 49). The median time to hormonal remission after discontinuation of DAs was 96 months. In this study, 40% of patients were treated with cabergoline before GKRS. Tanaka et al. [13] reported a 17% 4-year actuarial rate of biochemical remission after GKRS without medication, with a median margin dose of 25 Gy in a group of 22 patients with prolactinomas. In 2019, Jezkova et al. published a study of 28 patients with prolactinomas who underwent GKRS.[9] Hormonal remission and control were achieved in 13 patients (46.4%) and 10 patients (35.7%), respectively. The median margin dose was 35 Gy and the median time to hormonal remission after discontinuation of DAs was 152 months. Two patients (8.3%) had hypopituitarism after GKRS. However, 93% of patients were treated with cabergoline before GKRS. In a study by Cohen-Inbar et al. [8], 38 patients with medically and surgically refractory prolactinomas underwent GKRS with a margin dose of 25 Gy. Hormonal remission and control were achieved in 50% and 35.7% of patients, respectively. The median time to hormonal remission after discontinuation of DAs was 15 months. The median time to hormonal control in patients treated with GKRS while taking DAs was 20 months. GKRS-induced hypopituitarism occurred in 30.3% of the patients. In a study by Kuo et al. [17], 15 patients with prolactinomas underwent GKRS with a margin dose of 15.2 Gy. The proportion of drug resistance or intolerance in this study was unknown. Hormonal remission was achieved in 73% of patients. The median time to hormonal remission was 42 months. In a study by Pouratian et al. [18], 23 patients were treated with GKRS with a margin dose of 18.6 Gy after failing to respond to medical and surgical intervention for prolactinomas. Hormonal remission was achieved in 26% of the patients. The median time to hormonal remission was 24.5 months. New pituitary hormone deficiencies occurred in 28% of the patients.

In previous publications [8,9,11,13,16–19], endocrine remission rates ranged from 4.5% to 83.0%. The margin dose ranged from 15 to 35 Gy. The median time of endocrine remission ranged from 15 to 152 months. In the present study, the endocrine remission rate was 41.7%, which was similar to other studies. The median time of endocrine remission was 71.1 months in the present study, which was shorter than in the Jezkova et al. studies from 2009 and 2019 [9,16], but longer than in other studies [8,11,13,17–19]. Success rates with GKRS for endocrine remission have varied widely because they are affected by several factors, such as the number of patients studied or the period of follow-up. In some studies, serum PRL level and tumor volumes before GKRS were associated with the rate of endocrine remission in univariate analysis [11]. In our study, we did not find a significant association between PRL normalization and potential prognostic factors. This is contrary to results in previous studies. We speculated that the main reason was the relatively small number of patients in our study or the limited power of this retrospective review. Because cabergoline is not available in mainland China, 91.7% of patients had to be treated with bromocriptine before receiving GKRS in the present study, which was a higher percentage than in the Jezkova et al. studies from 2009 and 2019 [9,16]. The mechanism of resistance to cabergoline and bromocriptine may differ. Therefore, patient heterogeneity may exist between the current study and the studies of Jezkova et al. [9,16]. The median margin dose of 15 Gy was relatively low compared with the doses used in the other studies. A high margin dose has been related to new hypopituitarism after GKRS [20,21]. The patients in our study were young, with a median age of 30.5 years. Therefore, to decrease the rate of new hypopituitarism after GKRS, we adopted a relatively low margin dose.

After GKRS, prolactinomas stopped growing or shrank in all patients in the present study. This is in accordance with previous studies, because success rates for tumor control, based on imaging, have been reported as 87% to 100% [22]. Visual dysfunction occurred in 4 patients (16.7%) in our study before exposure to GKRS. Visual dysfunction did not worsen in any of the patients, which is similar to outcomes in the previous study [18]. Similarly, in our study, we restricted the dose of radiation to the optic nerve to 9 Gy.

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Previous long-term studies suggested that new-onset hypopituitarism was the most common adverse effect of GKRS. The incidence of hormone deficiency varies between 4.5 and 42% [23,11]. In our study, after GKRS, new-onset hypopituitarism occurred in 4 patients (16.7%; gonadotrophin deficiency, n=3, and TSH deficiency, n=1), which was a lower incidence than in the other report [8]. Two of the 3 patients with new-onset gonadotrophin deficiency had persistent hyperprolactinemia and another patient achieved endocrine control after GKRS. Gonadal function may be inhibited by hyperprolactinemia. Therefore, new-onset gonadotrophin deficiency occurring in these 2 patients may be to blame for persistent hyperprolactinemia and/or GKRS. Many factors that may affect the incidence of new-onset hypopituitarism have been analyzed in different studies. In several studies, key prognostic factors in the success of GKRS have included median prescription isodose and prescription of an increased isodose line [9,24,25]. In our study, univariate analysis showed that no prognostic factors were significantly associated with new-onset hypopituitarism.

The present study has some limitations First, the small population probably limited its statistical power. Second, it was performed at a single center and patient selection may have introduced bias. In addition, the timeframe for collecting a combination of prospective and retrospective data was short. Finally, taking into account the irregular shape of the tumors, the tumor volume measurements were only a rough estimate of the actual tumor volumes in this study.

Conclusions

In conclusion, in patients with prolactinomas, it may be possible to achieve relatively high rates of endocrine remission and tumor control with GKRS, with a low rate of new-onset hypopituitarism following the procedure. GKRS may be an effective and safe treatment option for patients who have prolactinomas that are resistant to DAs or who cannot tolerate those drugs.

Conflict of interest

None.

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