

STEREOTACTIC RADIOSURGERY USING GAMMA KNIFE FOR ITSENKO-CUSHING'S DISEASE

**Bakirzhan M.A.¹, Kozhemzharova M.K.¹, Kuanyshbaeva G.S.¹,
Kamitbekova Z.U.², Bazarova A.V.¹**

¹ Astana Medical University Astana, Kazakhstan

² Multidisciplinary City Hospital No. 1, Astana, Kazakhstan

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Bakirzhan M.A.

<https://orcid.org/0009-0007-1898-9282>

Kozhemzharova M.K.

<https://orcid.org/0000-0002-7667-6889>

Kuanyshbaeva G.S.

<https://orcid.org/0000-0002-4738-0296>

Kamitbekova Z.U.

<https://orcid.org/0009-0006-3918-9703>

Bazarova A.V.

<https://orcid.org/0000-0002-6518-7174>

Annotation

Stereotactic Gamma Knife radiosurgery is becoming the treatment of choice for patients with Cushing's disease that cannot be cured by surgery. The chances of 5-year remission are 65-75%, and control of tumor growth reaches more than 90%. However, the development of hypopituitarism (15% to 36%) is a common side effect, and severe neurological complications are rare. Relapse of the disease occurs in 16-18% of patients, but the reasons for this are unclear. Stereotactic Gamma Knife radiosurgery is effective as second line therapy in surgically untreated patients. The purpose of the study is to evaluate the effectiveness of stereotactic gamma knife radiosurgery as an adjuvant treatment for Cushing's disease, and also to consider possible complications and undesirable effects associated with the use of Stereotactic Gamma Knife radiosurgery in the treatment of Cushing's disease. The authors analyzed the published results of international, multicenter and retrospective cohort studies on the use of Stereotactic Gamma Knife radiosurgery in patients with. According to published data, the average time to achieve remission after Stereotactic Gamma Knife radiosurgery in patients with Cushing's disease was 16-17 months, while remission was maintained for 10 years in 60-80% of patients. Tumor growth control was achieved in 95% of cases. Our article suggests that radiosurgery is a safe and well-tolerated procedure and can provide long-term control of hypercortisolism in the majority of patients with Cushing's disease. However, given the likelihood of relapse after initial normalization of cortisol levels and the manifestation of hypopituitarism, long-term endocrine monitoring after radiosurgery is necessary. Ultimately, radiosurgery may be considered a reasonable primary treatment option for carefully selected patients who cannot have another treatment.

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Author for correspondence:

Bakirzhan M.A.

5th-year student in the specialty "General Medicine", JSC "Astana Medical University" 010020, Astana, Syganak str., 43. 87052192099, e-mail: madina.b29@mail.ru

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Introduction

Itsenko-Cushing's disease (ICD) is the most common cause (80-85%) of organic hyperproduction of cortisol-endogenous hypercorticism. In 10-20% of cases, endogenous hypercorticism develops as a result of primary pathology of the adrenal glands, and in 5-10% of cases, adrenocorticotropic hormone (ACTH) is produced by a carcinoid tumor of any extrapituitary localization (e.g., medullary thyroid cancer, islet cell cancer of Langerhans, chromaffinoma, ovarian cancer, testicular cancer, prostate cancer; carcinoid of the lungs, bronchi, thymus, appendix, tumors of the gastrointestinal tract, bladder, parotid and salivary glands, etc.).¹ About 80-90%

of these adenomas are microadenomas (<1 cm), which in approximately 40% of cases are not visible on magnetic resonance imaging (MRI) of the sella turcica. Symptoms of the disease include weakness, high blood pressure, diabetes, menstrual irregularities, and mental changes. Physical signs of elevated cortisol include a moon face, buffalo hump, bruising, abdominal stretch marks, obesity, facial flushing, and hirsutism.²

With the natural course of ICD (without treatment), the five-year survival rate is 50%, but it improves significantly even with palliative treatment—bilateral adrenalectomy increases survival up to 86%. With timely diagnosis and treatment in a highly specialized center, re-

mission can be achieved in 80% of cases, and the mortality rate in patients in remission does not differ from that of the general population.¹ The first line of treatment for ICD is transsphenoidal surgery (TSS) with selective resection of the adenoma (adenomectomy), the goal of which is to completely remove the adenoma while preserving normal pituitary function. In some cases, complete removal of the adenoma is not possible. This occurs when the adenoma invades the cavernous sinus and dura mater, has significant extrasellar extension, or cannot be detected during surgery despite a thorough pituitary examination.³ TSS is still the gold standard of treatment, demonstrating remission rates of 59% to 97%. However, even with initial remission, 50% of patients experience relapses 30 years after surgery. This poses a major challenge for the long-term management of ICD.⁴

Studies from 1999 and 2017 compared microscopic and endoscopic TSS methods. The complication rates for both approaches were approximately the same. Thus, 79% of TSS complications were temporary disturbances in blood sodium levels. Less common complications included diabetes insipidus, carotid artery injury, nosebleeds, sinusitis, cerebrospinal fluid leakage, and deep vein thrombosis.⁵

The aim of this study was to evaluate the efficacy of HF radiosurgery as an adjunctive treatment for Cushing's disease and to review potential complications and adverse effects associated with the use of radiosurgery in the treatment of Cushing's disease.

There are various approaches to delivering radiation therapy (RT) to patients with Cushing's disease. Conventional fractionated beam RT has been used for many decades and can result in the remission of hypercortisolism after an indefinite period, sometimes exceeding ten years. Several types of equipment are available for stereotactic RT, such as the Gamma Knife (which uses photons from a radioactive cobalt source),⁶ the CyberKnife or other devices (which use photons generated by a linear accelerator), and proton beam therapy (which produces protons in a cyclotron or synchrotron). One of the advan-

tages of stereotactic RT over traditional RT is the ability to complete treatment in a single session ("stereotactic radiosurgery," SRS), which is considered safe when the tumor is at least 3–4 mm from the optic nerve.⁷ Single-session treatment is usually perceived by patients as more convenient since traditional RT requires multiple sessions over 5–6 weeks. An additional advantage of proton beam therapy is the ability to precisely distribute the radiation dose to a complex three-dimensional target with minimal damage to healthy tissue due to the physical properties of proton beams (Bragg effect).⁷

Regardless of the chosen RT method, the duration of hypercortisolism varies from several months to several years, requiring temporary drug therapy to control cortisol levels. Risks associated with RT include the development of anterior hypopituitarism (in 35–60% of patients 5 years after RT), optic neuropathy (1–2%), and other cranial neuropathies (2–4%). Modern radiosurgery units can use frameless techniques that allow for repeated treatment sessions. Early models of GN SRS used single-session procedures only, but recent models, such as the ICON Gamma Knife with an attached CT scanner, allow frameless techniques and multiple treatment sessions (hypofractionated therapy).⁸ The usual prescribed radiation dose for the treatment of ACTH-producing pituitary adenomas is 23 Gy and can range from 15 to 25 Gy. The close proximity of the pituitary to critical neural and vascular structures must be carefully considered. To avoid optic neuropathy, it is recommended to limit the radiation dose to ≤ 8 Gy to 12 Gy, preferably maintaining a distance of 3 mm between the superior edge of the adenoma and the optic nerve/optic chiasm. The cranial nerves of the cavernous sinus can withstand significantly higher doses of radiation, and damage to the cavernous segment of the internal carotid artery is extremely rare.⁹

Materials and methods

An online search of journal articles related to the topic was performed using PubMed databases from 2014 to 2024 by entering the key terms "gamma knife stereotactic radiosurgery", "gam-

ma knife therapy”, “pituitary adenoma”, “Cushing’s disease”. Articles were limited to English language. Cited references in articles were also searched for subject matter relevant to the topic. A systematic literature review was performed according to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. The initial result identified 114 articles, which were subsequently confirmed. Inclusion criteria were observational: retrospective or prospective case

series of at least 15 patients, studies of radiosurgery using the Gamma Knife technique alone. On the other hand, the following exclusion criteria were applied: incident reports, letters to the editor, comments and expert opinions were excluded; studies involving patients with different pituitary tumors, with limited information, and with a follow-up period of less than 6 months.

The method for selecting sources for the literature analysis is shown in Figure1.

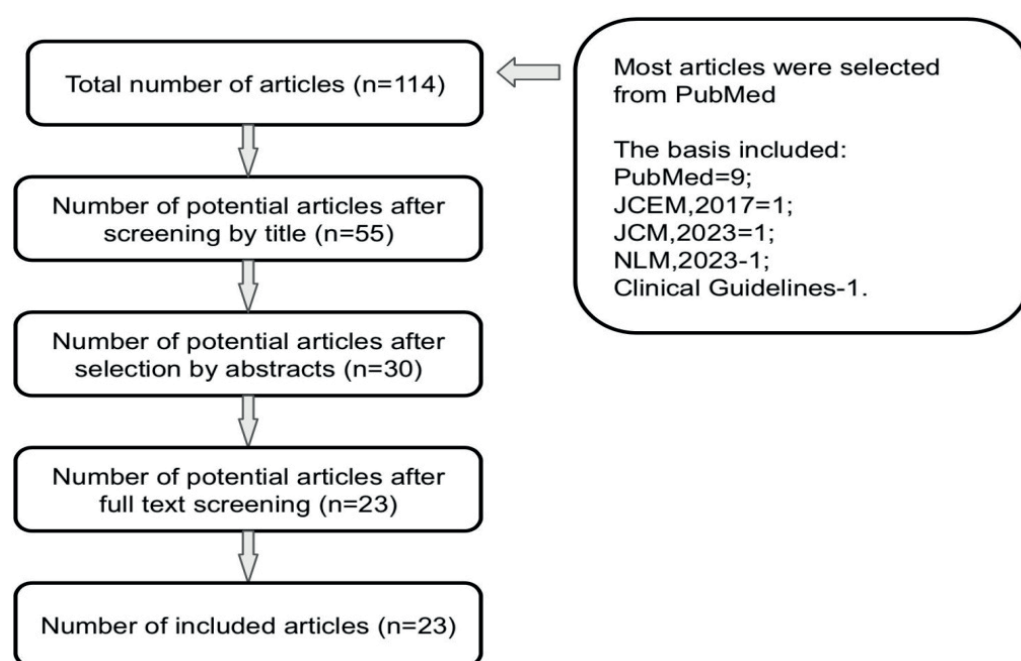


Figure 1. The method for selecting sources for the literature analysis

Results

Table 1 below lists the various inter-

national multicenter studies and retrospective cohort analyses of the articles.

Table 1.
Comparative analysis of multicenter studies on Gamma Knife Therapy for Cushing's disease

Authors of the articles	Therapy method	Patient sample	Prescribed radiation dose	Average time to achieve remission	Tumor control (%)	Biochemical remission (%)
Gao Y., et al. ¹⁰	SRS on GN	A total of 31 patients were included. The average age was 38.6 years old and 77.4% were female.	28Gy	20 months	100%	72.21%
Balossier A., et al. ¹¹	SRS on GN	A total of 26 patients were included	28.5Gy The average maximum dose received by the visual apparatus is 5.3Gy, the pituitary stalk is 13.5Gy.	36 months (median 24, range 6-98)	In 42% of patients, tumors remained stable, i.e. their size did not change.	77.6%
Mehta G.U., et al. ¹²	SRS on GN	A total of 278 patients were included, the average age was 41.4 years old and 80% of patients were female.	23.7Gy	14.5 months	In 53% of patients, tumors decreased in size. In 5% of patients, tumors increased in size.	69%
Abdali A., et al. ¹³	Stereotactic radiosurgery using CyberKnife	This is a retrospective study that included 41 patients (36 females and 5 males) who underwent BIC surgery from 2009 to 2019.	25Gy	14 months	95.12%	60.97%
Yanar E.A., et al. ¹⁴	Treatment included surgical removal of the pituitary adenoma in 69% of cases (63 of 91) and radiation therapy in 31% of cases (28 of 91).		The radiation dose during proton therapy was 40–85Gy, and during gamma knife radiosurgery it was 20–35Gy.	6 months or more	82%	After surgical treatment, remission was achieved in 71% of patients. After radiation therapy, remission was achieved in 82% of patients.

<p>Shrivastava A. et al.¹⁵</p>	<p>18 patients underwent SRS for GN after failed TLC, and in 6 patients the initial treatment was SRS for GN. The mean interval between TLC and SRS for GN was 10 months</p>	<p>24 patients with ICD were included in the study, 10 of them were male and 14 were female, the mean age was 18.32 years (range 10-21)</p>	<p>The marginal dose and maximum dose were 25 Gy (range 12.90-27.1 Gy) and 50 Gy (range 33-80 Gy), respectively.</p>	<p>At a median follow-up of 52 months after GKRS, 17 of 24 patients (70.8%) achieved endocrine remission at a median time of 12 months (range 2-42 months).</p>	<p>At a median follow-up of 46 months after GKRS, tumor control was achieved in 87.5% of patients (21/24). Fourteen patients had an initial volume reduction of >30% with a median time of 20 months.</p>	<p>At a median follow-up of 52 months after SRS for GN, 17 of 24 patients (70.8%) achieved endocrine remission. Two patients (8.3%) experienced normalization during medical treatment. Four of these 17 patients (23.5%) relapsed at a median interval of 9.5 months (range 6-16 months) after normalization. Four patients failed to achieve remission and underwent additional TLC. One of them died despite all treatments; he did not achieve remission and died 94 months after the initial SRS for GN</p>
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Sheehan J. P. et al. ¹⁶	SRS for GN. Most patients (93.6%) had undergone at least one previous tumor resection. Interestingly, 41.5% had a history of more than 1 previous resection.	The clinical series included 512 patients [226 [44%] female and 286 [56%] male]. The mean age of patients at the time of SRS for GN was 53 years (range 16-88 years).	the mean dose was 16 Gy	After Gamma Knife treatment, the median follow-up was 36 months, mean 47.1 months.	Tumor control was achieved in 93.4% of patients.	Progression was observed in 6.6% of patients. Actuarial progression-free survival was 98% at 3 years, 95% at 5 years, and 85% at 10 years after radiosurgery. Predictors of progression: In univariate analysis, tumor volume and radiation dose were found to be significant risk factors for tumor progression. Patients with tumors larger than 5 cm ³ had an increased risk of progression, as did patients with suprasellar tumor extension. Higher radiation dose (≥ 16 Gy) was associated with a lower risk of progression
Esene I. N. et al. ¹⁷	SRS for GN	16 cases with ICD were included in the study. The mean age \pm was 34.81 \pm 10.10 years. The male to female sex ratio was 1:3.	9 Gy	The median time to hormone normalization was 23 months.	Tumor volume control was achieved in all cases, while tumor shrinkage was achieved in (10 cases) 62.5%. The median time to shrinkage was 13 months.	Normalization of hypersecretion after 2 years was achieved in 13 cases (81.3%).

Gupta A. et al. ¹⁸	SRS for GN	46 patients were in- volved, 21 with ICD and 25 with acromegaly.	Patients received a mean tumor dose of 25 Gy (range 12–40.0 Gy) at a mean isodose of 50%.	The median endocrine follow-up was 69.5 months (range 9–246 months).	Tumor volume noted during follow-up was stable in 18 (39%) and decreased in 28 (61%) patients. There was no significant difference (p = 0.5) in tumor control rates after prior use of SRS on GN in patients with ICD or acromegaly.	Endocrine remission was achieved in 51% of the entire cohort, with 28% remission in acromegaly and 81% remission in patients with NIC at a 5-year interval. Patients with NIC achieved remission earlier than patients with acromegaly (p = 0.0005). In patients after SRS for GN, pituitary adenoma remained stable (39%) or decreased (61%) in size.
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In the vast majority of cases, radiotherapy was used as a second-line treatment in patients with persistent or recurrent disease after pituitary surgery. All studies examined patient outcomes, including tumor control, remission of hypercortisolism, and complications. It should be noted that the criteria used to define biochemical remission varied across studies, making comparisons difficult.

In Gao's study, 31 patients with CD received Gamma Knife SRS. Fewer patients (32%) underwent GKT after failed pituitary surgery. In the majority (67.7%), GKT was the initial treatment. Biochemical remission of CD was defined based on normal 24-hour urinary cortisol or serum cortisol ≤ 50 nmol/L after a 1 mg dexamethasone suppression test (1 mg DST). An increase in tumor volume $\geq 20\%$ was defined as tumor progression, while a decrease in tumor volume $\geq 20\%$ was defined as tumor regression. Tumor control was based on radiographic stability or regression by volumetric analysis after follow-up magnetic resonance imaging (MRI). Patients were followed for 22 months. Fourteen patients (45.1%) experienced control of hypercortisolism in the absence of pharmacologic treatment, and the 1, 2, and 3 years after GN SRS were 18.9%, 55.3%, and 72.21%, respectively. The overall complication rate was 25.8%, and the mean duration from GN SRS to hypopituitarism was 17.5 months. The new hypopituitarism rates at 1, 2, and 3 years were 7.1%, 30.3%, and 48.4%, respectively.¹⁰

In the study by Balossier E., there was a retrospective review of 26 patients from the University Hospital of Lille, France. The mean follow-up was 66 months. Eighteen (69.2%) patients had endocrine remission in the absence of any pharmacological therapy at a mean of 36 months (median 24, range 6-98). The actuarial probability of endocrine remission was 59% at 3 years and 77.6% at 7 years, which remained stable until 10 years. Tumor control was achieved in all cases. In seven patients (27%), new pituitary failure developed after SRS with GN.¹¹

In the article by Mehta U., patient selection was performed among 10 institutions, and 327 patients with NIC were

treated with a single session of SRS to GN. Forty-nine patients were excluded from the study due to insufficient data and insufficient follow-up time (less than 6 months), leaving 278 patients available for analysis. Most patients (80%) were women and had undergone previous resection (92%), while only 8% received SRS to GN as the primary treatment for NIC. SRS to GN was performed for residual tumor in 221 patients (79%) and tumor recurrence in 34 patients (12%). Sixteen patients (6%) had received fractionated radiotherapy before SRS. The mean endocrine follow-up after SRS was 5.6 years (median, 4.3 years; range, 0.5 to 20.5 years). Eighty-seven patients (31%) were taking medications to control hypercortisolism immediately before SRS. Of these patients, 85 were taking ketoconazole, 1 patient was taking mitotane, and 1 patient was taking metyrapone. In 59 patients, this medication was continued during SRS, but in 28 patients, it was stopped 2-3 weeks before SRS.^{8,12}

Control of Hypercortisolism:

- In 54 patients (19%), hypercortisolism was not controlled after SRS.
- In 31 patients (11%), hypercortisolism was controlled with medications.
- In 193 patients (69%), hypercortisolism was controlled without medications.

Efficacy Analysis: According to Kaplan-Meier analysis (a method of estimating survival or disease control over time), hypercortisolism was controlled in 59% of patients at 2 years after SRS, 77% at 5 years, and 80% at 10 years. The median time to normalization of urinary cortisol levels was 14.5 months, but this varied among patients.^{6,12}

Recurrence: After initial normalization of cortisol levels, 18% (35 of 193 patients) experienced recurrence of hypercortisolism. Recurrence-free survival after cortisol normalization was 89% at 2 years, 81% at 5 years, 70% at 10 years, and 66% at 15 years. The median time to recurrence after cortisol normalization was approximately 38-44 months.^{12,13}

Risk Factors for Recurrence: Both lower and higher doses of radiation were significant risk factors for recurrence. However, they did not show statistical significance in more complex analysis models.

Long-Term Control of Hypercortisolism: Fifteen years after treatment, 57% of patients maintained long-term control of hypercortisolism. The percentage of patients with long-term control of hypercortisolism was 48% at 2 years, 62% at 5 years, and 64% at 10 and 15 years.¹³

Efficacy of SRS in Different Groups:

- Among patients who received SRS as the primary treatment, 68% had stable control of hypercortisolism

- Among patients with normal urinary cortisol levels at the time of SRS, 74% had stable control of hypercortisolism.

- Among patients who were undergoing drug therapy at the time of SRS, 47% had long-term control of hypercortisolism.

Additional Procedures: Patients who failed to achieve biochemical control underwent additional procedures such as pituitary surgery, bilateral adrenalectomy, or repeat SRS.

Imaging Results: Imaging showed that tumors remained stable in 42% of patients, decreased in size in 53%, and increased in 5%.

In the study by Abdali A., unlike other studies in the table, a different radiation method was used, called CyberKnife. CyberKnife and Gamma Knife are two different devices used in stereotactic radiosurgery, and they differ in their operating principles, radiation types, and areas of application. Gamma Knife, unlike CyberKnife, uses gamma rays generated by radioactive cobalt-60. CyberKnife, in turn, uses x-rays generated by a linear accelerator and does not require rigid fixation, as the system automatically adjusts the direction of the beams in real-time, tracking the patient's position. CyberKnife is more versatile and is used to treat tumors in different parts of the body, including the spine, lungs, and liver.¹¹⁻¹³

The study by Abdali A. involved 41 patients (36 women and 5 men) who underwent NIC surgery from 2009 to 2019. Of the 41 cases, 34 had microadenomas and 7 had macroadenomas. These patients had recurrence or persistence of hypercortisolism after surgery. The treatment results are as follows: The remission rate in the study was 60.97% with a me-

dian follow-up of 79.03 months. The median time to biochemical remission was 14 months. Tumor growth control was achieved in 95.12%. Hypopituitarism of various axes was observed in 34.14% of patients. Secondary hypothyroidism was the most common pituitary insufficiency (34%), followed by secondary hypogonadism in 17%.¹³

In the study by E.A. Yanar, conducted from 1992 to 2020, 91 children with Itsenko-Cushing's disease (ICD) were observed. In 59% of them, pituitary adenoma (tumor) was detected, and in 41%—pituitary heterogeneity (abnormal changes without obvious tumors). Treatment included surgical removal of the pituitary adenoma in 69% of cases (63 of 91) and radiation therapy in 31% of cases (28 of 91). Remission was achieved in 71% of patients (45 of 63) after surgery and in 82% of patients (23 of 28) after radiation therapy. There was no significant difference in remission achievement depending on tumor characteristics on MRI ($P = 0.21$ after surgery and $P = 0.83$ after radiation therapy).¹⁹

Relapse of the disease was recorded in 11 patients, but the relationship between MRI characteristics and the time of its occurrence was not significant ($p = 0.055$). At the same time, the timing of relapse varied depending on the method of treatment: after surgical treatment, relapses occurred on average after 3.3 years, while after radiation therapy - after 6 years ($p = 0.022$). It was also found that patients with hypocorticism (low cortisol levels) in the early postoperative period had earlier relapses ($p = 0.04$). The study included children less than 18 years of age with confirmed central genesis of endogenous hypercorticism. The treatment was divided into two main groups: 1) transnasal adenomectomy (tumor removal), 2) radiation therapy (proton therapy or radiosurgery on a gamma knife). Until 2006, the main treatment method was proton therapy, after 2006, the main method was surgical treatment using stereotactic radiosurgery on a gamma knife if the surgery was ineffective.¹²

Proton therapy was administered to 30 patients (27 at the first stage of treatment and 3 at the second stage), and treatment on the gamma knife was

administered to 6 patients (5 at the second stage). The radiation dose for proton therapy was 40–85 Gy, and for gamma knife radiosurgery, 20–35 Gy.

Disease remission was achieved in 85% of patients (23 out of 27) who received radiation therapy. In 11 out of 18 patients who did not achieve remission after the first stage of surgical treatment, repeated removal of the pituitary adenoma led to remission in 73% of cases (8 out of 11). Six patients after ineffective first stage surgery received radiotherapy, which resulted in remission in all (100%).^{9,19}

Of the 27 patients who received radiotherapy in the first stage, it was ineffective in 4 patients. Three of them underwent repeated radiotherapy, and all achieved remission. One patient after ineffective radiotherapy underwent surgery, which also resulted in remission.^{17,18}

Patients were divided into three subgroups depending on the size of the adenoma: 1) non-visualizable adenoma, 2) microadenoma (<10 mm), 3) macroadenoma (>10 mm). Recurrence occurred in 5% of patients with non-visualizable adenoma, in 12% of patients with microadenoma, and in 23% of patients with macroadenoma. The differences in the recurrence rate among these subgroups were not statistically significant ($p=0.055$).²⁰

Analysis of the recurrence timing showed that patients who underwent only surgical treatment had recurrences in 14% of cases (8 of 55), while patients who received radiation therapy at one of the stages of treatment had recurrences in 6% of cases (2 of 35). The recurrence timing was significantly different, with a longer interval before recurrence after radiation therapy ($p=0.007$).^{10,21}

An analysis of the recurrence timing was also conducted depending on the development of hypocorticism after surgical treatment. Patients with hypocorticism in the early postoperative period had earlier recurrences ($p=0.04$).¹⁸

The findings of the study show that MRI characteristics of corticotropinoma cannot be used as a reliable predictor of therapy effectiveness in children with ICD. The choice of treatment method affects only the timing of recurrence,

but not its probability. The incidence of hypopituitarism was higher after radiation therapy than after surgery. Based on the data from all the above studies, it can be concluded that the average time to achieve remission was 16–17 months, after which remission continued for 10 years in 60–80% of patients, and tumor growth control was 95%. These data indicate that radiosurgery can provide long-term control of hypercortisolism in most patients with BIC, representing a safe and well-tolerated procedure in general.^{7,21}

Discussion

Surgical treatment is preferable in situations where rapid improvement of the patient's condition is required (e.g., in severe progressive disease or in the presence of significant complications such as osteoporosis with spontaneous fractures or malignant hypertension) and when the pituitary tumor is clearly visible on MRI. In cases of protracted disease, when the patient's condition allows a long wait until remission occurs, or when MRI shows only indirect signs of the adenoma or its size is too small for surgical intervention, radiosurgery can be chosen as the main method of treatment.^{8,16}

Most researchers note that stable remission in NIC after surgical removal of the adenoma is achieved in approximately 80–90% of cases, which significantly increases the effectiveness of treatment, especially in severe cases of the disease.^{15,18}

However, European experts studying NIC have shown that the recurrence rate after microsurgical removal of adenoma can reach 20%, and the risk of postoperative complications is 15%. Common complications of radiation therapy include post-radiation encephalopathy (5–20%) and hypopituitarism.¹⁹ Complications such as visual impairment or other cranial nerve problems after SRS for GN are rare and occur in only 3% of patients. After proton irradiation of the pituitary gland, thyroid-stimulating hormone deficiency (TSH) is often detected (35–42%), less often - ACTH (30–39%) or gonadotropin deficiency (15–29%).²² The process of decreasing the level of tropic hormones includes primary deficiency of somatotrophic hormone and gonadotropic

function, and then gradual impairment of ACTH and TSH secretion. Predicting the risk of developing hormonal deficiency after radiation is difficult, since different patients with the same radiation doses may have different results.^{3,10}

Limitations. Some of the studies included in this review are updates of previously published papers that included the same cohort of patients. To avoid duplication of data, each of these articles was carefully reviewed for new information on treatment outcomes or possible complications. Only those publications that contained the most up-to-date data with expanded information and the largest number of included patients were included in the final analysis.

Conclusions.

GN-SRS is an effective and safe treatment for PIH, reducing pituitary adenoma size and normalizing cortisol levels in most patients. GN-SRS should be considered in patients with persistent

hypercortisolism after pituitary surgery and as a first-line treatment for those who are not candidates for surgery. Further studies are important to more fully evaluate long-term outcomes and compare GN-SRS with other treatments.

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