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Abstract

Purpose: The aim of the study was to investigate the incidence of and risk factors for hypopituitarism after gamma knife radiosurgery (GKRS) for pituitary adenoma.

Methods: We conducted a retrospective analysis of the pituitary function of 90 patients who underwent GKRS for pituitary adenoma at the University Hospital Centre Zagreb between 2003 and 2014. Twenty seven of them met the inclusion criteria and the others were excluded from the study due to pituitary insufficiency which was present before GKRS. Eighteen patients had non-functioning and 9 patients had secretory adenomas. Median patients' age was 56 years (24-82). GKRS was performed using the Leksell gamma knife Model C. The median prescription radiation dose was 20 Gy (15-25) and the median tumor volume size was 3.4 cm^3 (0.06-16.81). New onset hypopituitarism was defined as a new deficit of one of the three hormonal axes (corticotroph, thyreotroph or gonadotroph) ≥3 months following GKRS. SPSS was used for statistical analysis, with the significance level at $P<0.05$.

Results: During the median follow-up period of 72 months (range 6-144), 30% of patients developed new hypopituitarism after GKRS. This corresponds to incidence of one new case of hypopituitarism per 15 patient-years. The median time for the development of the first pituitary axis insufficiency was 41.5 months (range 3-96). Age, gender, tumor function, tumor

volume or prescription dose of radiation were not predictive factors for the development of hypopituitarism.

Conclusions: In our cohort of patients with pituitary tumors who underwent GKRS, 30% developed new hypopituitarism during the follow-up period.

Keywords: hypopituitarism, gamma knife, radiosurgery, pituitary adenoma.

Introduction

Gamma knife radiosurgery (GKRS) represents the treatment of choice for patients with pituitary adenoma in the case of incomplete tumor resection, tumor recurrence and persistent hormone hypersecretion, or in those patients who, due to comorbidities, are not candidates for surgery [1,2].

Hypopituitarism is one of the most common complications of GKRS. The data on its incidence and possible prognostic/risk factors are rather variable among studies [3-11] and highly dependent on the definition of endocrine dysfunction that has been used [12-15]. The incidence of hypopituitarism also depends on several factors, such as the type and extent of surgery prior to GKRS, duration of follow-up, tumor volume, tumor function, prescription dose of radiation and preexisting pituitary function [4,16]. Long-term follow-up is crucial to assess new pituitary deficits. Typically, hypopituitarism presents within the first 2-4 years after the treatment with GKRS [17-19], but the risk of pituitary insufficiency increases to up to 80% after 10-15 years [20,21]. Reports on the highest incidence of new onset hypopituitarism also mentioned the longest follow-up period [22]. Long-term studies on the complications of GKRS are scarce.

This paper reports on our 12-year experience in performing GKRS in patients with pituitary adenomas. The aim of the study was to assess the incidence and time of occurrence of new onset hypopituitarism after GKRS performed for pituitary adenoma as well as to analyze possible prognostic/risk factors associated with the development of new onset pituitary deficits.

Materials and methods

Study design, selection criteria and subjects

This retrospective study investigated 90 patients with pituitary adenoma who were treated with GKRS at the Centre for Neuroendocrinology, University Hospital Centre Zagreb, Croatia, between 2003 and 2014. Sixty-three out of 90 patients had complete pituitary hormone insufficiency before GKRS and were therefore not included in the study. Twenty seven patients with at least one preserved pituitary hormone axis before GKRS and the minimum follow-up period of 6 months after GKRS, were enrolled in the study. The study was approved by the Ethics Committee of the University Hospital Center Zagreb.

Radiotherapeutic application

GKRS was performed using the Leksell Gamma knife Model C. Magnetic resonance imaging (MRI) with a stereotactic head frame was used when planning the treatment of each case. The radiation prescription dose to the target volume varied from 15 to 25 Gy at 50% isodose. This depended on the tumor volume size, distance to the optic apparatus and tumor functionality (secretory adenomas received higher doses of radiation).

Evaluation of the follow-up data

Pituitary function assessment and radiological evaluation were performed at baseline, three months after GKRS and then yearly afterwards. In the assessment of pituitary function, three hormonal axes were evaluated for each patient, i.e. the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-thyroid axis, and the hypothalamic-pituitary-gonadal axis. The low-dose short ACTH test (1 mcg) and/or the test of insulin-induced hypoglycemia were used for the evaluation of the *hypothalamic-pituitary-adrenal axis*. The cortisol level <550 nmol/L was diagnostic for the corticotroph cell insufficiency. Low fT4 level, accompanied by an

inappropriately low/normal TSH level were diagnostic for the *hypothalamic-pituitary-thyroid axis* insufficiency. Low testosterone levels in males, amenorrhea in premenopausal women, and inappropriately low/normal FSH and LH levels in postmenopausal women indicated the *hypothalamic-pituitary-gonadal axis* insufficiency. Somatotroph cell function was tested only in patients in whom growth hormone replacement therapy was planned (n=8). Due to the low number of such patients, those results were not reported in the manuscript.

New onset hypopituitarism was defined as a new deficit of one of the hormonal axes in the period of at least 3 months after GKRS. Ten patients (37%) had partial pituitary hormone deficiency prior to GKRS with the total of 15 insufficient pituitary hormone axes. Six patients had corticotroph deficiency, 4 thyreotroph deficiency and 5 gonadotroph cell deficiency. Accordingly, a total of 66 pituitary hormone axes were available for this study.

Statistical analysis

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) ver. 17.0 for Windows. Variables were described as median (range). The difference between two independent numerical variables was tested using the Mann-Whitney U test and between two categorical variables using the $\chi 2$ test. Pituitary axis event curves using the Kaplan-Meier method were performed. If insufficiencies of multiple axes were found in the same patient, the first axis insufficiency was used for the event curve analysis. Significance level was set at $P<0.05$.

Results

The patients' characteristics are summarized in Table 1. There were 18 clinically non-functioning adenomas (66%): 12 null-cell adenomas, 3 silent gonadotropinomas, 2 silent

corticotropinomas and one silent plurihormonal (GH+PRL+TSH) adenoma. Of the 9 secreting adenomas, there were 6 patients with acromegaly, 2 patients with Cushing's disease and one patient with prolactinoma. The median patient age at the time of GKRS was 49 years (23-74 years) while the median age at the study data collection was 56 years (24-82 years). Fifteen patients (55%) were males. The median follow-up period was 72 months (6-144 months).

The median tumor volume size was 3.41 cm^3 (0.06-16.81), whereas the median margin dose of radiation was 20 Gy (15-25). There was a significantly larger median tumor volume in clinically non-functioning adenomas, 4.73 cm^3 (0.06-16.81), compared to the median tumor volume of 1.1 cm^3 (0.1-5.02) in the secretory adenomas, P=0.014, z=-2.469. The median margin dose of radiation was significantly higher in the secretory adenomas (24 Gy (15-25 Gy)) than in the clinically non-functioning adenomas (19.5 Gy (18-23)), (P=0.046, z=-1.993).

Before GKRS, in the study group of 27 patients, there were 66 preserved pituitary hormone axes. At the end of the follow-up, 8 out of 27 patients (30%) developed insufficiency of 9 hormone axes. Insufficiency of one hormone axis was found in seven patients, and one patient (no. 15^0) developed insufficiency of two hormone axes (after 25 and 31 months). Altogether we observed 9/66 of new pituitary deficits during follow-up, which equals one new pituitary axis deficiency per 15 patient-years.

Four out of 21 patients with normal corticotroph cell function prior to GKRS developed corticotroph insufficiency (19%), two out of 24 patients with normal thyreotroph cell function prior to GKRS developed thyreotroph insufficiency (8%), whereas three out of 22 patients with normal gonadotroph cell function prior to GKRS developed gonadotroph cell insufficiency (14%). The median time to the occurrence of the first hormone insufficiency was 41.5 months (3-96 months).

The total cumulative incidence of new onset hypopituitarism was 42%, whereas the cumulative incidence during the first 2 years after GKRS was 13%, as shown by the Kaplan-Meier analysis (Figure 1.).

No correlations were found between the prevalence of new onset pituitary insufficiency on the one side, and age at GKRS, gender, tumor function, tumor type, preexisting pituitary function, duration of follow-up, tumor volume or the dose of radiation on the other (Table 2.).

Discussion

Hypopituitarism is the most prevalent complication of GKRS [3]. The reported incidence of pituitary insufficiency is highly heterogeneous across studies and it ranges between 11.6 and 39% depending mainly on the duration of follow-up [7,9,23,24]. For example, the study with one of the longest follow-up periods published by Gopalan *et al*. [7] reported the greatest incidence of new pituitary deficits after GKRS for non-functioning pituitary adenoma (39%). In our study we found 30% patients with new endocrine deficits after GKRS, after the median follow-up of 72 months. A number of factors have been evaluated in order to assess the risk of hypopituitarism after GKRS. The studies published so far showed that the prescription dose of radiation and the tumor volume size are major risk factors for new pituitary hormone insufficiency [25,26]. It was shown that the 5-year risk of developing new pituitary deficits was higher for tumors with a volume higher than 4 cm^3 (58% *vs* 18%) [16]. The most recent systematic review and meta-analysis which included 925 patients from 17 studies showed that patients with non-functioning pituitary adenomas and tumor volume size >4 ml were associated with 22% of GKRS induced hormonal deficits, significantly higher compared to the patients with tumor volume size <4 ml [27]. In our study, 12/27 patients (44%) had tumor

volume size >4 ml, which could explain the relatively high incidence of new onset hypopituitarism.

Functionality of the tumor has also been shown to play an important role in the development of hypopituitarism [4,16]. Numerous studies which examined functional adenomas reported higher incidence of new onset hypopituitarism in the group of patients with functional adenoma when compared to non-functioning pituitary adenomas. The incidence of hypopituitarism was 42% in prolactinoma [28], 50% in growth hormone secreting adenoma [29] and 66% in adrenocorticotropic secreting adenoma [30], with the median follow-up period of 60, 114 and 204 months, respectively. Another comprehensive review, which included 12 studies with non-functioning adenomas, 17 studies with prolactinomas, 26 studies with acromegaly and 17 studies with Cushing's disease, showed variable incidence of new onset pituitary deficits of 0-38%, 0-42%, 0-50% and 0-66%, respectively [22]. In our study, we did not find significantly higher incidence of pituitary insufficiency after GKRS in the group of functional adenomas. That result might be explained by the relatively large volumes of the clinically non-functioning adenomas enrolled in the study requiring relatively high radiation doses.

With regard to the timing of the development of hypopituitarism, it has been reported that pituitary insufficiency after GKRS may develop as early as after three months, but it also sometimes develops after as long as 10 years of follow-up [20,21]. One study reported the median period of 48 months from GKRS to the development of new onset hypopituitarism, with the first pituitary insufficiency occurring 14 months after GKRS and the last one 84 months after GKRS [23]. In our study, the median time from GKRS to the development of the first hormone insufficiency was 41.5 months. The period between GKRS and the development of the pituitary insufficiency ranged from 3 months to 96 months. The

cumulative incidence of developing new onset pituitary insufficiency during the first 2 years after GKRS in our study was 13%.

The major strength of our study is based on the fact that all the patients were followed-up in the same tertiary center with the standardized medical protocol. On the other side, the small sample size and a rather heterogeneous group of patients in terms of the size and tumor functionality represent major study limitations. Another limitation may be the lack of the data on somatotroph cell function, which was evaluated only in few patients and was therefore not reported in the manuscript.

In conclusion, in our cohort of the patients with pituitary tumors who underwent GKRS, 30% of them developed new hypopituitarism, which corresponds to the incidence of one new hypopituitarism per 15 patient-years. The first pituitary hormone insufficiency could appear as soon as 3 months after GKRS and the last after many years of follow-up. Neither the tumor size nor the radiation dose were prognostic factors for the development of hypopituitarism after GKRS in our study group. Further studies with a larger number of patients stratified by tumor volume, tumor function and radiation dosage are needed to address this issue.

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Compliance with Ethical Standards:

Conflict of interest: Author Karin Zibar declares that she has no conflict of interest. Author Tina Dušek declares that she has no conflict of interest. Author Ivana Kraljević declares that she has no conflict of interest. Author Zdravko Heinrich declares that he has no conflict of interest. Author Mirsala Solak declares that she has no conflict of interest. Author Ana Vučinović declares that she has no conflict of interest. Author David Ozretić declares that he

has no conflict of interest. Author Sergej Mihailović Marasanov declares that he has no conflict of interest. Author Darko Kaštelan declares that he has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figure Legends

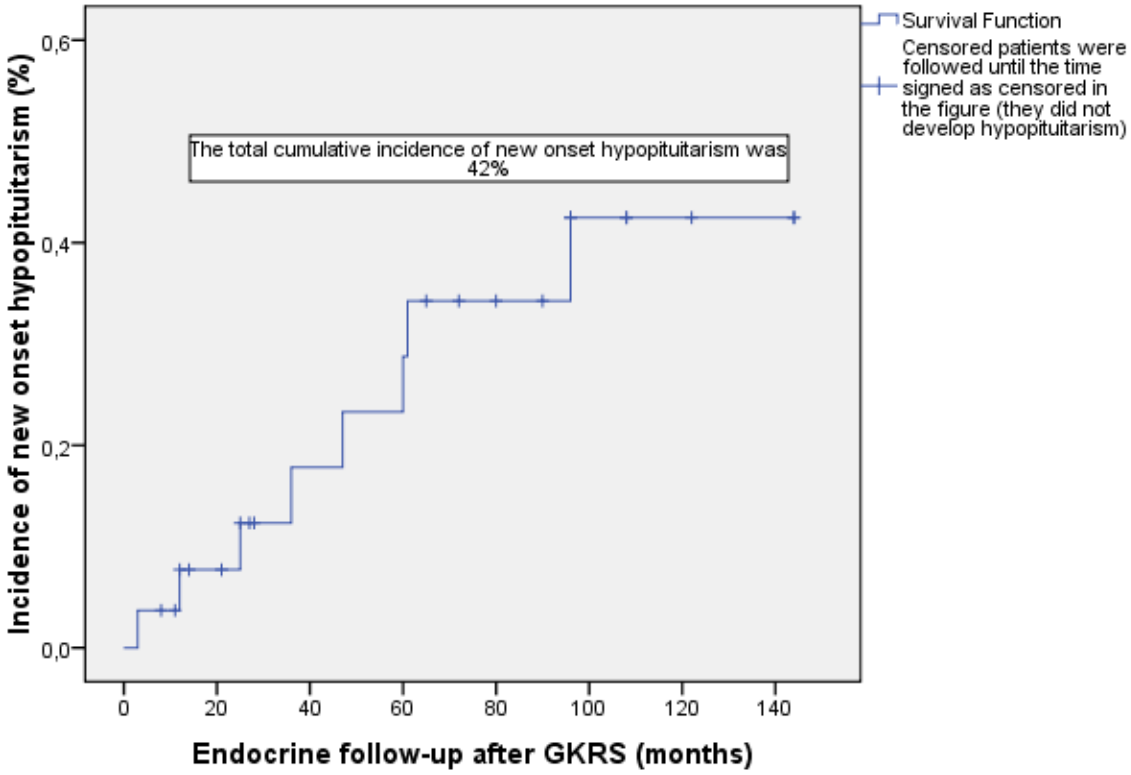

Figure 1. The incidence of new onset hypopituitarism after gamma knife radiosurgery (GKRS) for pituitary adenoma (Kaplan-Meier analysis).

Tables

Table 1. Patients' characteristics.

Case no.	**Age (years)**	**Sex**	**Tumor function**	**Tumor type**	**Hypopituitarism before GK**	**Follow-up period (months)**	**Prescription dose (Gy)**	**Tumor volume (cm^3)**	**Time to the first insufficiency (months)**
1	57	Female	Secretory	Acromegaly	Corticotroph+ thyreotroph	144	20	0.6	None
2	46	Male	Secretory	Acromegaly	Corticotroph +gonadotroph	144	15	2.2	None
3	53	Female	NF	Null-cell adenoma	No	122	18	0.7	None
4	54	Female	NF	Null-cell adenoma	No	122	18	0.06	96
5	55	Female	NF	Null-cell adenoma	No	108	18	4.29	None
6	49	Male	Secretory	Acromegaly	Corticotroph	108	16	3.4	None
7	47	Female	Secretory	Prolactinoma	No	96	25	0.99	12
8	75	Male	NF	Null-cell adenoma	No	96	20	0.9	None
9	82	Male	NF	Null-cell adenoma	No	96	19	2.17	36
10	59	Male	NF	Silent gonadotropinoma	No	96	23	2.5	None

11	66	Female	Secretory	Cushing disease	Corticotroph	90	25	0.1	None
12	80	Male	NF	Null-cell adenoma	No	80	22	3.35	None
13	73	Male	NF	Null-cell adenoma	Thyreotroph+ gonadotroph	72	18	8.94	60
14	46	Female	NF	Silent corticotropinoma	No	72	18	16.81	None
15	80	Female	NF	Null-cell adenoma	No	69	20	6.8	25 and 31
16	61	Male	NF	Silent gonadotropinoma	No	65	22	5.59	None
17	41	Male	NF	Null-cell adenoma	Corticotroph + thyreotroph	61	18	4.82	61
18	32	Female	Secretory	Acromegaly	Thyreotroph	48	25	5.02	47
19	75	Male	NF	Silent gonadotropinoma	Gonadotroph	28	22	5.47	None
20	64	Male	NF	Null-cell adenoma	No	27	22	3.61	None
21	66	Male	NF	Silent corticotropinoma	Corticotroph + gonadotroph	25	18	9.4	None
22	47	Female	NF	Null-cell adenoma	Gonadotroph	21	20	5.38	None
23	50	Femal	Secreto	Cushing	No	14	24	1.5	None

		e	ry	disease					
24	56	Male	NF	Null-cell adenoma	No	12	18	6.13	None
25	56	Femal e	Secreto ry	Acromegaly	No	11	25	0.75	None
26	65	Male	NF	Silent plurihormonal (GH+PRL+TS H)	No	8	20	4.64	None
27	24	Male	Secreto ry	Acromegaly	No	6	24	1.1	3

*GK= gamma knife, NF= non-functioning, GH= growth hormone, PRL= prolactinoma, TSH= thyroid-stimulating hormone.

Table 2. Influence of different prognostic factors on new onset pituitary insufficiency.

Prognostic factor	**New onset insufficiency**	**No insufficiency**	***P***	***Z or χ^2***
Age at GKRS (years)	40.5 (23-74)	53 (34-73)	0.457	-0.744
Sex (m/f)	4/4	11/8	0.706	0.142
Tumor function (yes/no)	3/5	6/13	0.766	0.089
Tumor type			0.35	3.286
Non-functioning (n=18)	5	13		
Cushing disease (n=2)	0	2		
Acromegaly (n=6)	2	4		
Prolactinoma (n=1)	1	0		
Hypopituitarism before GKRS (yes/no)	3/5	7/12	0.974	0.001
Follow-up period (months)	70.5 (6-122)	72 (8-144)	0.958	-0.053
Tumor volume (cm^3)	3.5 (0.06-8.94)	3.4 (0.1-16.81)	1	0
Margin dose of radiation (Gy)	19.5 (18-25)	20 (15-25)	0.745	-0.325

*Z value where Mann-Whitney U test was performed for and χ^2 value where $\chi 2$ test was performed. *P* value <0.05 was considered statistically significant. †GKRS= gamma knife radiosurgery.