CLINICAL STUDY

Gamma knife surgery for patients with volumetric classification of nonfunctioning pituitary adenomas: a systematic review and meta-analysis

Yong Chen*, Zhi Feng Li*, Fei Xiang Zhang, Jian Xian Li, Lin Cai¹, Qi Chuan Zhuge¹ and Zhe Bao Wu^{1,2}

Department of Neurosurgery, Yueyang Second People's Hospital, Yueyang 414000, China, ¹Department of Neurosurgery, First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China and ²Department of Neurosurgery, Huashan Hospital, Fudan University, No. 12, Wulumuqi Middle Road, Shanghai 200040, China

(Correspondence should be addressed to Z B Wu at Department of Neurosurgery, Huashan Hospital, Fudan University; Email: zhebaowu@fudan.edu.cn)

*(Y Chen and Z F Li contributed equally to this work)

Abstract

Objective: The aim of this study was to scrutinize the literature to determine the efficacy and safety of gamma knife surgery (GKS) for the treatment of nonfunctioning pituitary adenomas (NFPAs) with volumetric classification.

Methods: Electronic databases including MedLine, PubMed, and Cochrane Central were searched. The literature related to patients with NFPAs treated with GKS was collected. Eligible studies reported on the rate of tumor control (RTC), the rate of radiosurgery-induced optic neuropathy injury (RRIONI), the rate of radiosurgery-induced endocrinological deficits (RRIED), and other parameters.

Results: A total of 17 studies met the criteria. Based on the tumor volume, NFPAs were divided into three groups: the RTC of group I (93 patients) with tumor volumes <2 ml was 99% (95% CI 96–100%), the RRIONI was 1% (95% CI 0–4%), and the RRIED was 1% (95% CI 0–4%). The RTC of group II (301 patients) with volumes from 2 to 4 ml was 96% (95% CI 92–99%), the RRIONI was 0 (95% CI 0–2%), and RRIED was 7% (95% CI 2–14%). The RTC of group III (531 patients) with volumes larger than 4 ml was 91% (95% CI 89–94%), the RRIONI was 2% (95% CI 0–5%), and the RRIED was 22% (95% CI 14–31%). There were significant differences in the RTC and in the RRIED among the three groups ($P < 0.001$), indicating that there were higher RRIED and lower RTC with the increase of tumor volume.

Conclusions: NFPAs, according to tumor volume classification, need stratification for GKS treatment. GKS is the optimal choice for the treatment of group II NFPAs. Patients with residual tumor volumes of <4 ml will benefit most from GKS treatment.

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Introduction

Pituitary adenomas (PAs) represent 10–20% of all primary brain tumors (1). Clinically nonfunctioning PAs (NFPAs) make up approximately one-third of the PAs. Patients with NFPAs generally experience anterior pituitary hormonal deficits, visual loss, headaches, or less frequently, apoplexy. The goals of treatment are to achieve an adequate reduction of tumor volume and to preserve pituitary function.

The primary treatment for patients with NFPAs is pituitary microsurgery with a transsphenoidal or transcranial approach to achieve a rapid reduction of tumor volume and decompression of the optic apparatus. Incomplete resection because of regional tumor invasion into the surrounding structures (especially the cavernous sinus) may be associated with long-term recurrence rates in as many as 67% of

the patients (2, 3). Although additional resection may be attempted for recurrent tumors, complete resection may remain difficult to achieve, and the risks associated with repeat surgery are greater than those for the initial operation (4).

Conventional fractionated radiotherapy (FRT) has been used after subtotal resection to reduce recurrence rates in patients with residual tumors or even in some patients after gross total resection (2, 5, 6, 7, 8). FRT is thought to achieve tumor control rates of 90–97% and to significantly reduce the rate of recurrence with a reported progression-free survival of 75–90% at 20 years (9, 10, 11, 12). However, there is concern that FRT carries an increased risk of later toxicity. This is most commonly observed in the form of hypopituitarism, occurring in 30–88% of the patients at 10 years (9, 10, 11). Hypopituitarism requires lifelong hormone replacement therapy with a significant impact on

quality of life and has additionally been reported to be associated with increased respiratory, cerebrovascular, and cardiovascular mortality (13, 14, 15). A less common finding is the development of radiation-induced neoplasia including meningiomas and glial tumors, with a reported incidence of 2% at 20 years (9). Furthermore, concern has arisen over the long-term neurocognitive impact of radiotherapy. Taken together, FRT provides adequate tumor control, but it poses a small risk of serious late-term sequelae.

Recently, gamma knife surgery (GKS) has been more commonly used in the management of PAs, either as adjuvant therapy after surgical resection or rarely as a primary treatment modality in select cases. It has improved upon standard FRT by enabling the delivery of targeted therapy in a single session, with a steeper dose gradient that minimizes irradiation to the surrounding structures. Theoretically, this provides increased precision with a minimization of toxicity, but we lack long-term safety and efficacy data for GKS with regard to optimal eligibility criteria and there is little information to assess the efficacy of GKS for the treatment of NFPAs of differing sizes and stages. However, the reports (16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32) concerning the efficacy of GKS for the treatment of NFPAs are limited by small sample sizes, retrospective and nonrandomized study designs, heterogeneous patient populations, and varying definitions of outcomes. There is no multi-center meta-analysis summarizing the evidence regarding the knowledge of the efficacy and safety of GKS for the treatment of NFPAs with delineation of prognostic factors associated with poor outcomes for NFPAs that would help to formulate clinical practice guidelines.

In this study, NFPAs were divided into three groups according to the tumor volume (0–2, 2–4, and > 4 ml) at the time of GKS treatment. We wanted to clearly understand the efficacy and safety of GKS for the treatment of NFPAs through a systematic review and to gain reliable evidence to recommend eligibility criteria for the use of GKS for the treatment of NFPAs.

Subjects and methods

Search strategy

English literature papers published in MedLine, PubMed, and Cochrane Central databases from 1966 to January 2012 were systematically searched using the following terms: 'Gamma Knife surgery', 'radiosurgery', 'non functional pituitary tumors', 'nonfunctioning pituitary adenomas', 'nonfunctioning pituitary adenoma', 'non-function pituitary tumors', 'non-secreting pituitary adenomas', 'non-secreting pituitary adenomas', and 'non secreting pituitary adenomas'. The 'related articles' function was used to obtain any relevant articles. Additionally, the references cited

in the articles included in the analysis were reviewed for any other citations. The search was carried out independently by two members of the study team: Y Chen and Z F Li. Hand-searching was conducted using references from papers acquired using the computer searches.

Inclusion/exclusion criteria

Inclusion criteria included NFPAs for which GKS was carried out with or without surgical removal. These studies can provide the parameters of GKS for the treatment of NFPAs, such as the median/mean target volume, the tumor control rate, the actuarial tumor control rates (ATCRs) at 5 and 10 years, the rate of radiosurgery-induced optic neuropathy injury (RRIONI), the rate of radiosurgery-induced endocrinological deficits (RRIED), and the actuarial RRIED rates (ARIEDRs) at 2, 5, and 10 years. Eligible study designs included retrospective and prospective analyses.

Data from the articles obtained were extracted independently by two co-authors and reviewed by the corresponding author. Data collected from the articles included the number of patients, study design (retrospective vs prospective), the median follow-up period, the median/mean target volume, the tumor control rate, the ATCRs at 5 and 10 years, the RRIONI, the RRIED, the ARIEDRs at 2, 5, and 10 years, the median marginal radiation dose, and the median optic radiation dose. If articles could not provide the parameters directly, we indirectly extracted these parameters from the Kaplan–Meier curves of their articles. We contacted authors for missing data when needed. If no data were reported on a certain variable of interest, they were recorded as not available.

Evaluation of the quality of studies

This study adhered to the reporting guidelines of meta-analysis (33, 34) and used the GRADE approach to rate the quality of evidence (35). To assess the methodological quality of the studies, we determined items such as the period of inclusion of the patients, ascertainment of outcomes, follow-up protocol, definition of the decrease or increase in size, definition of pituitary insufficiency, radiosurgical technique, and calculation of tumor volume (36).

Statistical analyses

Weighted summaries were determined using meta-analysis models if a given result was reported by three or more studies. Tests for heterogeneity were carried out for each meta-analysis using the I^2 statistic ($I^2 < 25\%$ and $I^2 > 50\%$ reflect small and large inconsistencies respectively). If the Q value ($P > 0.01$) is not significant in the tests for heterogeneity, it indicates the heterogeneous nature of the research, so we used fixed-effects

models or random-effects models. We used the Pearson's χ^2 test for the comparative groups. The variance test was used to analyze the dose-related complications. The R meta package from the R statistical language for Windows and SPSS 12.0 were used to carry out these analyses (37). A P value ≤ 0.05 was considered to be statistically significant.

Results

Search results

The data abstraction process is shown in Fig. 1. The search identified 584 candidate references, of which 28 were studies deemed to be eligible (16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48). We excluded six studies (42, 44, 45, 46, 47, 48) because the stereotactic radiosurgery was carried with a CyberKnife or linear accelerator. One study had few patients ($n=3$) who underwent GKS (43). Additionally, we excluded four studies from this analysis because of poor quality assessment (38, 39, 40, 41).

Study characteristics

A total of 17 studies met the inclusion criteria, and the total number of patients included in this meta-analysis was 925 (summarized in Table 1 and Supplementary Table 1, see section on supplementary data given at the end of this article). These studies were longitudinal observational cohort studies, including prospective (seven studies) and retrospective (ten studies) designs. All patients with NFPAs had undergone GKS. These studies mainly analyzed the tumor control rate, the RRIONI, and the RRIED. NFPAs were divided into three groups according to the tumor volume at the time of GKS treatment, summarized in Supplementary Table 2. There were stratified data available for a total of

93 patients with tumor volumes of < 2 ml, 301 patients with tumor volumes ranging from 2 to 4 ml, and 531 patients with tumor volumes > 4 ml.

Meta-analysis

Random-effects models and fixed-effects models were computed for the parameters according to the tests for heterogeneity, with probability values of < 0.01 or above, as summarized in Table 2. The NFPAs were divided into three groups according to the volume of tumor tissue at the time of treatment: the tumor control rate of group I tumors (93 patients) with volumes < 2 ml was 99% (95% CI 96–100%), the RRIONI was 1% (95% CI 0–4%), and the RRIED was 1% (95% CI 0–4%). The tumor control rate of group II tumors (301 patients) with volumes from 2 to 4 ml was 96% (95% CI 92–99%), the ATCR at 5 years involving four studies with 166 patients was 91% (95% CI 88–93%), the RRIONI was 0% (95% CI 0–2%), and the RRIED was 7% (95% CI 2–14%). The tumor control rate of group III tumors (531 patients) with volumes larger than 4 ml was 91% (95% CI 89–94%), the ATCR at 5 years involving five studies with 394 patients was 94% (95% CI 91–97%), the ATCR at 10 years involving three studies with 299 patients was 80% (95% CI 72–87%), the RRIONI was 2% (95% CI 0–5%), the RRIED was 22% (95% CI 14–31%), and the ARIEDRs at 2, 5, and 10 years were 16% (95% CI 13–20%), 31% (95% CI 25–37%), and 49% (95% CI 44–55%) respectively.

The pooled tumor control rate was 95% (95% CI 92–97%). The pooled ATCRs at 5 and 10 years were 93% (95% CI 90–95%) and 80% (95% CI 72–87%) respectively. The pooled RRIONI was 1% (95% CI 0–3%). The pooled RRIED was 11% (95% CI 6–18%). The pooled ARIEDRs at 2, 5, and 10 years were 16% (95% CI 13–20%), 31% (95% CI 25–37%), and 49% (95% CI 44–55%) respectively.

Figure 1 Study selection process.

Pearson's χ^2 test

We used the Pearson's χ^2 test to analyze the difference in the efficacy and safety of GKS among the three groups of NFPAs, summarized in Table 3. Significant differences in the tumor control rates were found among the three groups ($P < 0.001$), especially between groups II and III and between groups I and III, which indicated that there was a statistical trend in these inter-groups ($P = 0.04$). There was a statistically significant difference in the RRIED among the three groups ($P < 0.001$) and between two groups ($P < 0.0125$), which showed that the RRIED was more common with the increase in tumor volume. There was a statistically significant difference in the RRIONI between groups II and III ($P = 0.003$), but no significant differences were found between the other groups.

Table 1 The original data in 17 studies before 2012.

Study references	Case no.	Follow-up time (months)	Tumor volume (ml)	Maximal dose (Gy)	Marginal radiation dose (Gy)	Optic radiation dose (Gy)	Tumor control rate	ATCR			ARIEDR		
								At 5 years (%)	At 10 years (%)	Optic neuroptathy injury	Endocrinological deficits	At 2 years (%)	At 5 years (%)
(16)	125	50.4	5.6	38.6	18	2.5	113/125	97	87	16/117	37/122	NA	NA
(17)	126	62	4.5	27.9	13	7.7	112/125	94	76	1/125	21/125	15	28
(18)	48	95	5.1	41.3	18.4	3.7	8/48	88	77	0	19/48	12.5	31.4
(19)	43	36	Small size	NR	18.2	10	43/43	NA	NA	0	0	NA	NA
(20)	14	42	1.3	NR	12.5	3.4	14/14	NA	NA	0	0	NA	NA
(21)	23	78	1.1	50	20	5.1	23/23	NA	NA	0	0	NA	NA
(22)	62	64	4	34.5	16	9.5	60/62	95	NA	0	11/41	17	32
(23)	79	60	3.45	40	20	7	79/79	NA	NA	0	2/30	NA	NA
(24)	82	44.9	4.8	41.5	18.5	2.5	75/82	NA	NA	0	12/61	16	22
(25)	31	59.8	2.5	NR	14	8	27/31	93	NA	0	2/31	NA	NA
(26)	51	40.6	2.4	NR	16.5	8	49/51	89.8	NA	NA	NA	NA	NA
(27)	54	41.1	2.3	33.2	16.6	6.1	52/54	88.2	NA	0	7/54	NA	NA
(28)	33	43	5	36	16	9.5	32/33	97	NA	0	5/18	18	41
(29)	56	36	2.3	30	15	6.3	56/56	NA	NA	0	0	NA	NA
(30)	29	31.2	Macroadenomas	32	16.2	7	28/29	NA	NA	2/29	0	NA	NA
(30)	13	31.2	Microadenomas	32	16.2	7	13/13	NA	NA	0	0	NA	NA
(31)	30	55	2.3	28.9	16	NA	2/30	93	72.5	0	3/30	NA	NA
(32)	27	20.7	4.4	28.5	13.8	8.1	23/24	NA	NA	0	6/22	NA	NA

NA, not available; ATCR, actuarial tumor control rate; ARIEDR, actuarial radiosurgery-induced endocrinological deficit rate.

Radiation dose and dose-related complications

We analyzed the difference in doses among the three groups, including the maximal dose, the marginal radiation dose, and the optic radiation dose. There was no significant difference in radiation doses among the three groups (Supplementary Table 3, see section on supplementary data given at the end of this article).

The pooled maximal dose was 36 (95% CI 32–39) Gy, the pooled marginal radiation dose was 17 (95% CI 15–18) Gy, and the pooled optic radiation dose was 7 (95% CI 0.6–0.8) Gy (Supplementary Figure 1A–C). Based on the pooled maximal dose and the pooled marginal radiation dose, these studies were also divided into two groups respectively (<36 vs ≥ 36 Gy and <17 vs ≥ 17 Gy). A significant difference in endocrinological deficits was found between the two groups ($P < 0.01$, Table 4). However, there was no significant difference in the tumor control rate between the two groups (Table 4).

Quality of studies

During the period of inclusion of patients ranging from 1987 to 2012, the Leksell Gamma Knife Unit model was different and included models U, B, C, 4C, and Perfexion. Neuroimaging and clinical follow-up were carried out in a different period. Additionally, the majority of studies did not provide adequate information or definition regarding pituitary insufficiency. The calculation of tumor volume among these studies was done using different methods. Lastly, the definition of the decrease or increase in size among these studies was not uniform (e.g. the volume change exceeded 10, 15, 20, 25, and 50% or a difference of 2 mm or more in multiple planes). The above-mentioned aspects might contribute to study inconsistency.

We carried out a sensitivity analysis by including five unqualified studies (38, 39, 40, 41) to determine whether the inclusion of these studies would affect the study conclusions (summarized in Supplementary Table 1). The pooled tumor control rate was 95% (95% CI 91–98%); the pooled RRIONI was 5% (95% CI 2–10%); and the pooled RRIED was 4% (95% CI 1–9%).

Discussion

Principal findings

To the best of our knowledge, this is the first systematic review on the efficacy of GKS for the treatment of NFPAs related to volumetric classification. Because different types of stereotactic radiotherapy as well as follow-up strategies for this condition lack evidence from randomized studies, the results of this meta-analysis will help clinicians make informed decisions as to which relative volumes of tumor treated with GKS had high tumor

Table 2 Incidence of the efficacy parameters.

	Incidence (%) and 95% CI	I ² (%)	P
Tumor control rate			
Group I	99 (96–100)	0 (0; 0)	0.9725
Group II	96 (92–99)	66.8 (21; 86.1)	0.01
Group III	91 (89–94)	22.3 (0; 64.1)	0.2521
Overall	95 (92–97)	62.6 (37.7; 77.5)	0.0002
ATCR at 5 years			
Group I	NA	NA	NA
Group II	91 (88–93)	0 (0; 77.7)	0.5594
Group III	94 (91–97)	50.7 (0; 81.9)	0.0873
Overall	93 (90–95)	42.7 (0; 73.6)	0.0827
ATCR at 10 years			
Group I	NA	NA	NA
Group II	NA	NA	NA
Group III	80 (72–87)	59.4 (0; 88.4)	0.085
Overall	80 (72–87)	59.4 (0; 88.4)	0.085
Optic neuropathy injury			
Group I	1 (0–4)	0 (0; 0)	0.9725
Group II	0 (0–2)	0 (0; 0)	0.9969
Group III	2 (0–5)	79.5 (60; 89.5)	<0.0001
Overall	1 (0–3)	60 (32; 76.5)	0.0008
Endocrinological deficits			
Group I	1 (0–4)	0 (0; 0)	0.9725
Group II	7 (2–14)	68.2 (18; 87.7)	0.0135
Group III	22 (14–31)	79.4 (59.8; 89.4)	<0.0001
Overall	11 (6–18)	86.2 (79.4; 90.8)	<0.0001
ARIEDR at 2 years			
Group I	NA	NA	NA
Group II	NA	NA	NA
Group III	16 (13–20)	0 (0; 30.6)	0.8783
Overall	16 (13–20)	0 (0; 30.6)	0.8783
ARIEDR at 5 years			
Group I	NA	NA	NA
Group II	NA	NA	NA
Group III	31 (25–37)	54.9 (0; 83.4)	0.0644
Overall	31 (25–37)	54.9 (0; 83.4)	0.0644
ARIEDR at 10 years			
Group I	NA	NA	NA
Group II	NA	NA	NA
Group III	49 (44–55)	0 (0; 0)	0.9117
Overall	49 (44–55)	0 (0; 0)	0.9117

NA, not available; ATCR, actuarial tumor control rate; ARIEDR, actuarial radiosurgery-induced endocrinological deficit rate.

control rates and low RRIONI and RRIED and which should be the best candidates for GKS.

In this study, NFPAs were divided into three groups according to the tumor volume at the time of treatment. In group I tumors with volumes ranging from 0 to 2 ml, the tumor control rate was 99% (95% CI 96–100%) and both the RRIONI and the RRIED were 1% (95% CI 0–4%). It seems that the efficacy of GKS for the treatment of NFPAs is very nearly ideal. Our recent study (49) has found that the mean residual tumor volume doubling time of NFPAs is 3.4 years (95% CI 2.4–4.5 years); that is, the majority of these tumors grow very slowly. The small-volume tumors in this group might not reach a large enough volume to impair patients' health during their lifetime, which would lead to an extensive and safe follow-up span. Furthermore, if the tumor volume increased to the volume of group II

tumors, the rate of tumor control (RTC) with GKS was not significantly different from that observed for group I tumors. So, a comprehensive management plan of close follow-up and timely intervention is the optimal choice for these groups of NFPAs in order to minimize the side effects of radiation therapy. Because of the small volumes and slow growth rate, it is not necessary for group I patients to undergo GKS immediately after operation.

In group II tumors with volumes ranging from 2 to 4 ml, the tumor control rate was 96% (95% CI 92–99%) and the RRIONI and the RRIED were 0% (95% CI 0–2%) and 7% (95% CI 2–14%) respectively. This shows that the RTC is high and that the possibility of radiosurgery-induced complications such as optic neuropathy injury and endocrinological deficits is low. GKS appears to be the optimal choice for the treatment of this medium-volume group of NFPAs.

Table 3 Pearson's χ^2 test results for the comparative groups.

Group	Pearson's χ^2 value	P
Tumor control rate	15.655	<0.001
Groups I vs II	3.17	0.075
Groups II vs III	8.26	0.04
Groups I vs III	8.494	0.04
Optic neuropathy injury	12.056	0.002
Groups I vs II ^a		
Groups II vs III	8.809	0.003
Groups I vs III	3.297	0.069
Endocrinological deficits	49.082	<0.001
Groups I vs II	6.801	0.009
Groups II vs III	25.645	<0.001
Groups I vs III	27.288	<0.001

^aStatistical significance is not available.

In group III tumors with volumes >4 ml, the tumor control rate was 91% (95% CI 89–94%), the RRION and the RRIED were 2% (95% CI 0–5%) and 22% (95% CI 14–31%) respectively, and the ATRCs at 5 and 10 years were 94% (95% CI 91–97%) and 80% (95% CI 72–87%) respectively. The ARIEDRs at 2, 5, and 10 years were 16% (95% CI 13–20%), 31% (95% CI 25–37%), and 49% (95% CI 44–55%) respectively. With the increase in tumor volume, the RTC was significantly decreased and the RRIED was significantly increased. In addition, it seems that GKS may not have a long-term efficacy for the treatment of group III tumors and the RTC decreases with time. Furthermore, the ARIEDRs increase with time and reach values as high as 49% at 10 years. These results need to be confirmed by increasing the follow-up time and patient numbers.

Effect of tumor volume to assess efficacy

Some studies have found that tumor volume is the major factor predictive of tumor growth (16, 17, 18). Gopalan *et al.* (18) found that tumor volume was a significant predictor of imaging outcome in long-term follow-up and tumor volumes >5 ml were significantly associated with a faster rate of tumor growth after GKS. Park *et al.* (17) found that larger tumors were more likely to progress. A target volume of <4.5 ml was an independent factor for a better progression-free survival. Starke *et al.* (16) reported that a tumor volume >5 ml was the only factor predictive of tumor growth in a multivariate analysis.

These data suggest that large tumors are more resistant to treatment with GKS. There are several reasons for the initial tumor volume influencing the outcomes of GKS in the treatment of NFPAs. For one thing, tumor volume may be a reflection of the involvement of the surrounding structures. Additionally, larger tumor volumes may reflect proximity to critical structures and make it difficult to deliver an ideal radiation dose to the target volume. In this

meta-analysis, there was a significant difference in the tumor control rate and in the RRIED among the three groups. The reason for this might not be the radiation dose, because there was no significant difference in radiation doses among the three groups. This indicates that there is a statistical trend that the larger the tumor volume, the worse the control rate. Furthermore, the RRIED was significantly more common when there was an increase in tumor volume. However, there were radiation dose-related endocrinological deficits if the maximal dose or the marginal radiation dose was more than 36 or 17 Gy respectively.

Effect of the radiation dose to assess efficacy

A significant difference in endocrinological deficits was found between the two groups (<36 vs ≥36 Gy and <17 vs ≥17 Gy). Previous reports have suggested that the radiation dose delivered to the pituitary stalk or functioning gland may be associated with radio-surgically induced hypopituitarism (50, 51). The dose delivered to the pituitary gland is important, as it depends on the distance between tumor and pituitary gland, than on the marginal dose to the tumor. In the 17 studies, we did not find data about the radiation dose delivered to the pituitary gland; however, there was one report about the dose delivered to structures such as the oculomotor nerve and the brain stem (19). The reason for this might be the difficulty involved in defining the distance between the tumor and the pituitary gland because of their proximity. On the other hand, the definition of endocrine deficits in the majority of studies is 'a condition requiring hormone replacement' and the incidence of hypopituitarism is not assessable after GKS. Thus, the reported lower incidence of hypopituitarism after GKS compared with that observed after the use of other radiation techniques remains to be demonstrated.

The optic apparatus is generally believed to be the most radiosensitive to GKS. Recently, the dose threshold for the development of radiation-induced optic neuropathy has been questioned. Radiation tolerance for the optic nerve has been reported to range from 8 to 12 Gy and depends on the volume treated in single-dose radiosurgery (52, 53, 54, 55). Ideally, most studies suggest a maximum dose of 8 Gy and a minimum dose of 2–5 mm between the tumor and the optical apparatus to keep the risk of optic neuropathy close to

Table 4 Pearson's χ^2 test results for the different dose groups.

Group	Pearson's χ^2 value	P
Tumor control rate		
<36 vs ≥36 Gy	2.102	0.147
<17 vs ≥17 Gy	0.174	0.677
Endocrinological deficits		
<36 vs ≥36 Gy	12.471	<0.001
<17 vs ≥17 Gy	8.316	0.004

0 (56, 57). In our meta-analysis, the pooled optic radiation dose was 7 Gy (95% CI 06–08), which may be the safe radiation dose threshold for the optic nerve.

Limitations

From Table 1, it becomes evident that the average duration of follow-up in all studies is limited to only 20.7–95 months after GKS (49.49 ± 18.19 months, mean 4.12 years). This indicates that a mean follow-up period of ~4–5 years is, therefore, sufficient to outline the results of GKS in the short term and midterm, but real control of tumor growth in the long-term necessitates the continuation of the follow-up of these patients. The same caveat holds true for some side effects of GKS, in particular, the probability of new pituitary insufficiency seems to increase with time after GKS.

On the other hand, the nonrandomized, observational nature of the available literature is associated with several methodological issues, including publication bias, reporting bias (not all the outcomes were reported in all the papers), and lack of standardization in the study design (34). These issues highlight the inherent limitations in any meta-analysis based on observational data and the need for future large prospective studies.

Clinical implications

In light of very low-quality evidence (35) and the resulting uncertainty, it is suggested that clinical studies on this issue be prospective and use clear and explicit criteria for inclusion, objective outcome definitions and assessment, and uniform follow-up. Four suggestions should be considered: first, neuroimaging and clinical follow-up should be carried out at 6-month intervals for the first 2 years and yearly thereafter (19, 22, 28), and long-term follow-up is necessary; second, uniform calculation of tumor volume and the Leksell Gamma Unit model are needed; third, a standard definition of pituitary insufficiency and the decrease or increase in size should be used; and lastly, NFPAs should be resected to the maximum extent during the operation in order to reduce the residual tumor volume to <4 ml.

Conclusion

NFPAs, according to the tumor volume at the time of treatment, need stratification for GKS treatment. According to the small volumes and slow growth rate of group I NFPAs, comprehensive treatment including close follow-up and timely intervention is the reasonable choice in order to further optimize the risk:benefit ratio of GKS. GKS is the optimal choice for the treatment of group II NFPAs. The optimal treatment strategy for group III patients is still a challenge. Clinicians are

suggested to remove tumor volume to the maximum extent during the operation in order to reduce the residual tumor volume to <4 ml, by which patients will further benefit from the postoperative GKS treatment.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-13-0400>.

Declaration 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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