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Cyberknife radio-neurosurgery for secreting pituitary adenomas treated with single fraction radio-neurosurgery: A systematic review and *meta*-analysis

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ABSTRACT

Introduction: Stereotactic radiosurgery (SRS) is one of the treatment options for the management of residual or recurrent secreting pituitary adenomas (PA). While the role of radiosurgery (RS) by Gamma Knife (GK) has been clearly established, Cyberknife (CK) RS has been evaluated in fewer series.
Material and methods: To perform a systematic review of the literature and *meta*-analysis, with the aim of focusing on the effect of CK RS on secreting PA. Using PRISMA guidelines, we reviewed articles published between January 1994 and January 2024. The inclusion criteria contained: single fraction RS, biochemical remission, tumor control and complication appearance (hypopituitarism).
Results: We~~re~~ incorporated 8 studies including 152 secreting PA. Vast majority were treated in single fraction 115 (75.6 %), with an overall rate of 59.9 % ($p < 0.001$). Total remission was encountered in 44/108 patients, for an overall rate of 50.2 % ($p < 0.001$). Partial remission was inconsistently reported among studies for 25/55 patients, for an overall rate of 38.8 % ($p = 0.003$). Uncontrolled disease was encountered in 36/108 patients, for an overall rate of 32.7 % ($p < 0.001$). Tumor control was not separately reported for secreting or non-secreting PA, but attained overall high rates.
Conclusion: Single fraction CK radiosurgery is common practice for secreting PA. Our *meta*-analysis suggests high rates of both total and partial remission (as high as 89 % if both taken together), with a complete remission rate of 50.2 %. These results encourage the use of single fraction CK RS for secreting PA. To reach high rates of biochemical control, high doses of irradiation should be used.

1. Introduction

Pituitary adenomas (PA) stand as one of the prevailing primary CNS tumors, with an estimated prevalence of 17 %. Roughly half of PAs secrete distinct pituitary hormones (most often prolactin-PRL, growth hormone-GH, or adrenocorticotropic hormone-ACTH), leading to a significant morbidity and reduced lifespan [1]. Acromegaly, a rare endocrinological disorder, is usually engendered by GH-secreting PA, further leading to increased insulin-like growth factor 1 (IGF-1) levels [2,3]. Acromegaly is commonly associated with multiple medical comorbidities, further predisposing to premature mortality [4]. Normalizing GH secretion and IGF-1 levels is critical in mitigating theses risks [5]. Cushing disease (CD) stems from hypercortisolism, subsequent from an ACTH-producing PA, accounting for approximately 70 % of cases with Cushing syndrome [6–8]. Around 40 % of patients have a microadenoma or no visible tumor at presentation [9].

The majority of secreting PAs are macroadenomas (>10 mm)^3, with around 70 % of them infiltrating the surrounding structures, particularly the cavernous sinus, hence complete surgical resection would be feasible for just 20 % of cases [10,11]. Surgery is the primary treatment for both

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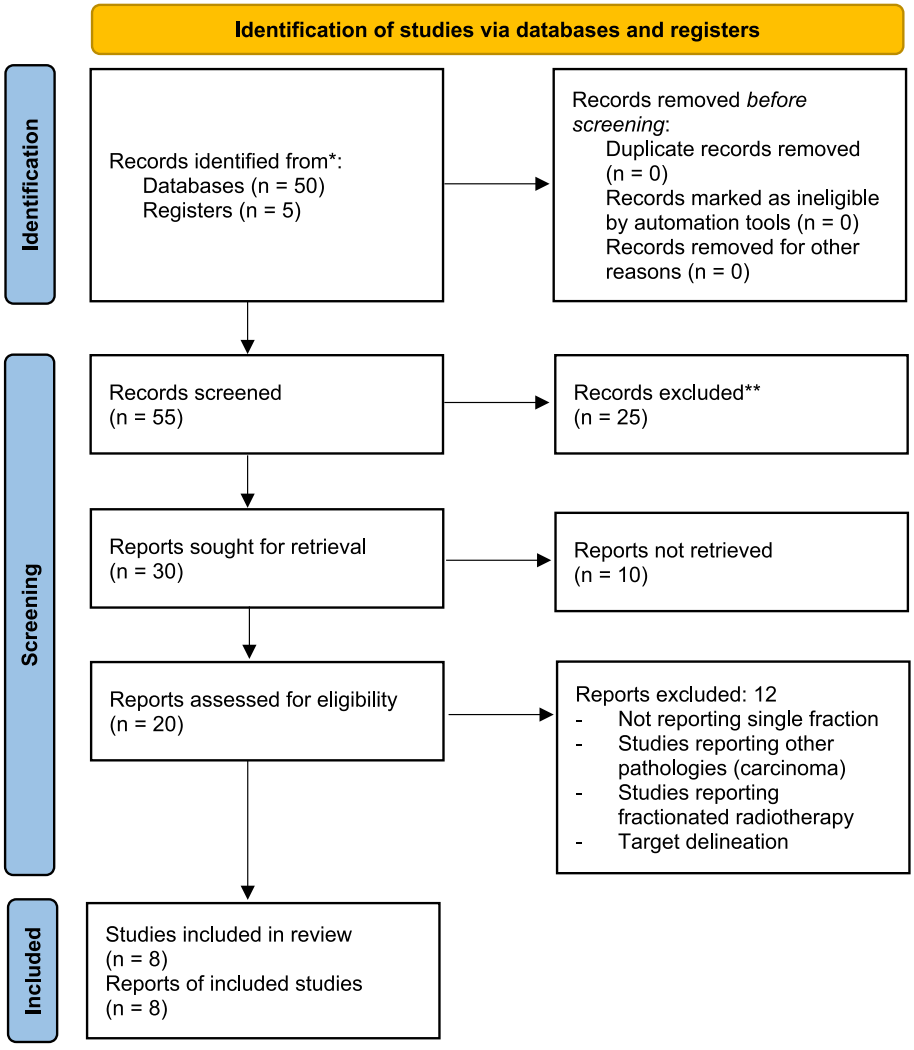
acromegaly and CD, with biochemical cure rates reaching around 50 % [12], ranging between 30–70 % for acromegaly [13] and around 60 % for CD [14]. Moreover, such is suggested between 46.5–94 % in microadenomas and 20–43 % in macroadenomas [15–17]. In the case of remanent tumor, there is a risk of persistent biologically active disease. After microsurgical resection, between 20–40 % of cases may not achieve complete biochemical remission [1,18]. In those patients, management options include lifelong medical therapy (IGF-1 lowering drugs) [18] as well as stereotactic radiosurgery (SRS) [19,20]. On the another hand, persistent and/or recurrent CD requires further treatments, including medical therapy, radiation [21–23] and/or adrenal surgery [24,25].



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram with study selection details.

Radiation may be indicated for residual disease following microsurgical resection and in patient's intolerant or unresponsive to medical therapy [26]. Historically, conventional radiation therapy (RT) was used as adjuvant treatment, with efficacy rates between 5–75 % [27,28] in acromegaly, while 28–86 % [29–31] in CD. Biochemical remission was attained as late as after several years and with the drawback of complications such as cranial nerve neuritis, visual field deficits, hypopituitarism (as high as 40 %), radiation brain necrosis or radiation induced gliomas [32–34]. Over the past five decades, SRS has become a valuable alternative [35], allowing to deliver high doses of radiation, with high conformity and selectivity [36]. Stereotactic radiosurgery can be delivered using various devices, of which the most common are the Gamma Knife (GK; Elekta Instruments, AB, Sweden), the Cyberknife (CK; Accuray, Sunnyvale, CA, USA) or the ZAP-X [37].

While the results of single fraction radiosurgery (RS) using the GK for secreting PA have been reported by numerous studies [1,19,38–41], CK RS −one of the technical branding of Linac RS- has scarcely been described in the current literature [42]. Moreover, it is yet unclear whether one can easily adopt the results of GK for CK, particularly for single fraction SRS. In this systematic review and *meta*-analysis, we reviewed the published literature on CK RS for secreting PA.

2. Materials and methods

2.1. Study selection

We searched for PubMed and Embase databases, for article entries between January 1994 (date of the appearance of the CK) and January 2024 using the following query guidelines: (radiosurgery) OR (Cyberknife) AND (pituitary adenoma) OR (acromegaly) OR (Cushing disease) OR (prolactin). The year 1994 was selected as the first published report of the CyberKnife system's application was in the early 1990 s, with a key study published in 1994. Search filters were set to English language articles only. The significance of the returned articles was evaluated by evaluating the titles, abstracts, or both. Inclusion criteria required that each article is a peer-reviewed clinical study or a case series of PA treated with the CK (particularly those treated in single fraction, Fig. 1). Only series reporting separate outcomes after CK treatments for single and hypofractionnated treatments for secreting PA were included. Demographic data can be found in Table 1. The follow-up period is also illustrated and is of a mean of at least 24 months for all studies.

2.2. Primary endpoints

Primary endpoints were biochemical remission and tumor control. Biochemical remission was defined by some authors and for acromegaly as a normalization of serum IGF-1 levels, using a gender and age-standardized normal range without concomitant use of medical therapy, such as dopamine agonist or somatostatin analog for at least 12 weeks [43]. Active disease was considered if IGF-1 levels remained increased despite medical therapy. Normalization of serum IGF-1 levels, using a gender and age-standardized normal range in association with a GH level greater than 1 mcg/L [44]. Patients were defined as cured if there was normal serum IGF-1 with concomitant medical therapy. For CD, such was defined as resolution of hypercortisolism [45]. Remission was further defined by both normalization of adrenal function and achievement of hypoadrenalism [45]. Normalization of the hypothalamic–pituitary–adrenal axis was defined as normal 24-hour free urine cortisol excretion and/or normal plasma cortisol response to overnight 1 mg Dexamethasone test without the requirement of glucocorticoid replacement [45]. Active disease was defined as persistent hypercortisolism (elevated 24-hour free urine cortisol excretion, elevated serum basal cortisol without suppression after overnight 1-mg Dexamethasone test, or late-night salivary cortisol) [46]. Time to biochemical remission was noted, whenever present (for details, please see Table 1 and 2).

Partial remission was considered as a significant reduction in the overproduction of hormones, but not to normal levels, leading to a decrease in clinical symptoms, but with hormone levels remaining above the normal range. Total remission was defined as a complete normalization of hormone levels after treatment, with clinical symptoms completely resolving, without the need of further meical therapy.

Tumor control was evaluated on serial follow-up MRI. Some authors evaluated as significant change in tumor size as increase or decrease in greatest diameter by more than 25 %[46], but the definition remained heterogenous. We considered tumor controlled if either stable and/or decreased, as commonly reported (Table 2).

2.3. Secondary endpoint

The secondary endpoint was complication appearance (hypopituitarism, visual).

2.4. Biologically effective dose aspects

The biologically effective dose (BED) was not uniformly reported in all studies. Some authors [43] used the linear quadratic model to calculate the biologically effective dose (BED) [47], as multiple fraction schemes were used together with single fraction. The alpha/beta was considered as being 3 (late responding tissue) [43] or 4 [44,45].

Table 1
Demographic data.

Study	Number of cases	Type	Male:female	Follow-up months Mean (median, range)	Previous surgery	Previous radiation
Kajiwara et al. (2005)	21	7/21 secreting: – PRL: 3/7 – GH: 2/7 – ACTH: 2/7 14/21 non secreting	07:14	35.3 (36; 18–59)	21/21 (10 operated on >=2)	Feb-21
Roberts et al. (2007)	9	GH: 9/9	04:05	25.4 (–; 6–53)	08-Sep	1/9 CK
Chul Bum Cho et al. −2009	26	9/26 secreting: – GH: 6/9 – PRL: 3/9 17/26 non secreting	14:12	30 (–; 7–47)	22/26	/
Sala et al. (2017)	22	GH: 22/22	10:12	43.2 (–; 6–153)	21/22	22 CK
Moore et al. (2018)	7	ACTH: 7/7	02:05	55.4 (–; 9–159)	07-Jul	/
Apaydin et al. (2020)	7	7/7 secreting	03:04	– (29; 5–61)	7/7 (3 operated on >=2)	0
Ehret et al. (2021)	50	50/50 secreting	28:22:00	57.3 (57.7; 6.1–171.9)	50/50	/
Abdali et al. (2021)	41	ACTH: 41/41	05:36	57.3 (48.8; 6–110)	41 (20 operated on >=2)	Feb-41

Table 2
Dosimetric data and outcomes.

Study	Single/ Fractionated	Single Secreting	Volume (mL) Mean (range) Standard deviation	Marginal dose (Gy) (Mean or/ and Range)	Optic nerve dose (Gy) Brainstem (Gy)	Tumor control	Biological control	Complications (hypopituitarism)
Kajiwara et al. (2005)	Single: 1/21	01-Jan	11.3 + -9.2 (0.2–34.9)	6.4–27.7	–	Decreased: 4/21	Secreting: hypersecretion improved in all cases after CK (Single Fraction: PRL improvement)	– 0/1 hypopituitarism for secreting PA (treated in single fraction)
	Fractionated (2–3-4–5): 20/21							– 2/21 cases treated in hypofraction showed hypofunction of pituitary anterior lobe and needed hormone replacement therapy (1 case non secreting et 1 ACTH (27 Gy)
			– Secreting:			Stable: 16/21	Non secreting:	
			7.5 + -8.9 (0.2–27.6)	– secreting: Mean: 17.5			underwent in 1 patient.	– One patient showed visual deterioration (case non secreting (an additional resection was performed
						Increased: 1/21		
			– Non-secreting:	– non-secreting			One PRL showed normalization of the PRL level and 1 ACTH-producing tumor with high-dose irradiation showed a decrease of the ACTH and cortisol levels to a less than normal range.	One was the case with an ACTH-producing tumor treated by high-dose irradiation (27.0 Gy), as described above, and the other was the case with a non-functioning adenoma.
			13.3 + -8.7 (2.1–34.9)	Mean: 12.6				
Roberts et al. −2007	Single: 5/9	05-May	2.46 (0.41–5.69)	21 (18–24)	–	Stable: 5/5	– biochemical remission: 4/9 (3/4 single fraction)	1/5 new panhypopituitarism
	Fractionated (2–3): 4/9						– controlled: 1/9 (single fraction)	
							– unchanged: 4/9	
Chul Bum Cho et al. −2009	Single: 5/ 26Fractionated (3): 21/26	03-May	2.6 (0.20–7.89)	19 (14–24)	–	–	4/9: normalization	0/5 no hormone deficiency
							9/9: improved	2/26 visual acuity worsened (No fractional Cases)
Sala et al. (2017)	Single: 14/22	14/14	1.64 (0.4–26.6)	24 (18–30)	Dmax to optic chiasm: 7.88 (1.5–22.7)	Decrease: 3/22	All had a reduction in their IGF-1 levels	1/14 (GH deficiency)
	Fractionated (2–3-5): 8/22							
				Single fraction:	Dmax for left and right ON: 7.35 (0–24.6) and 7.65 (0–18.7)	Stable: 19/22	Cured: 9/22	
				20–30				
							4/22: others demonstrated biochemical control of acromegaly	
Moore et al. (2018)	Single: 4/7	04-Apr	1.18 (0.27–3.4)	25 (21–35.5)	Dmax: 6.1 (0–28.5)	Decrease or	Normalization of hypercortisolism: 4/7 (including 2 single fraction)	1/4 (panhypopituitarism)
	Fractionated (3–5): 3/7				Dmax left&right ON: 4.2 (0–24.5) and 9.2 (3.8–25)	Stable: 7/7		
					Dmax brainstem: 9.2 (0–24.3)		unchanged: 3/7 (including 2 single fraction)	
Apaydin et al. −2020	Single: 4/7	04-Apr		28		Decrease: 2/7	2/7 achieved biochemical remission	2/7 hypopituitarism (not specified if for single or hypofractionnated)
	Fractionated: 3/7					Stable: 5/7		

(*continued on next page*)

Table 2 (*continued*)

Study	Single/ Fractionated	Single Secreting	Volume (mL) Mean (range) Standard deviation	Marginal dose (Gy) (Mean or/ and Range)	Optic nerve dose (Gy) Brainstem (Gy)	Tumor control	Biological control	Complications (hypopituitarism)
Ehret et al. (2021)	Single: 50/50	50/50	2.07 (0.13–12)	18 (14–24)	Dmax ON: 6 (1.1–15.5) Dmax brainstem: 5.7 (0–17.6)	Decrease: 9/50	9/50: biochemical remission 24/50: showed biochemical disease control 14/50: persistent uncontrolled disease	19/50: hypopituitarism(2 G, 2 ACTH, 3 TSH, 11GH, 1 ADH) Retreatment: 1/48
Abdali et al. (2021)	Single: 34/41 Fractionated (3–5): 7/41	34/34	3.8 (0.8–7.20) Single: mean 28	26.38 (16–30.1)	<8	Decreased: 6/41 Stable: 33/41 Increased: 2/41	25/41 (60.97 %): remission (including 21 single fraction) 16/41 (39.02 %): not achieved remission (including 13 single fraction)	19/348 (G), 8 (TSH), 2 (GH), 1 (pan)

2.5. Statistical analysis

Because of high variations in study characteristics, a statistical analysis using a binary random-effects model (DerSimonian–Laird method) was performed using OpenMeta analyst software (Agency for Healthcare Research and Quality). Weighted summary rates were determined using *meta*-analytical models. Heterogeneity was tested for each *meta*-analysis; pooled estimates were obtained for all outcomes.

Results of series concerning the local control and complications (hypopituitarism) were compared using a *meta*-regression with a random effect. P values < 0.05 were considered statistically significant.

3. Results

3.1. Study selection

Were included 8 studies including 152 secreting PA [42–45,48–51]. Of these 152, were treated in single fraction 115 (75.6 %).

3.2. Patient population

Cavernous sinus invasion was reported in as high as 86.3 % of cases as suggested by Sala et al. [44] or as high as 100 %[45] in other series.

3.3. Incidence of patients treated in single fraction

Overall use of single fraction in all series including patients with secreting PA was 115 out of 152 patients, for an overall rate of 59.9 % (range 38.8–81.1 %, $I^2 = 92.07$, p heterogeneity $= 0.001$, $p < 0.001$, Fig. 2). The prescribed dose in single fraction SRS was heterogenous, as high as 30 Gy (range 20–30) [44], or even 33.9 (mean 27.2; median 28.9, range 16–33.9) [48].

3.4. Structures at risk

Ehret et al. [42] have given maximal doses to the optic nerve of 6 Gy (range 1.1–15.5), while to the brainstem 5.7 Gy (range 0–17.6). Other authors prescribed a median dose to the chiasm of 7.36 Gy (range 1–5-9.1), or to the optic nerve as high as 18.7 Gy for single fraction [44].

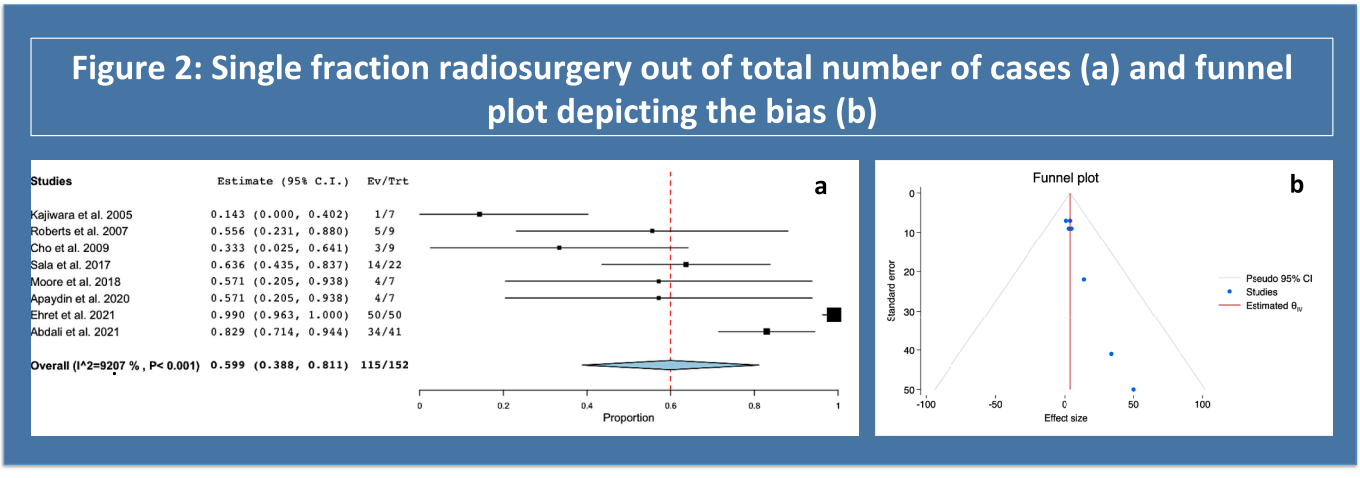

Fig. 2. Overall rates of single fraction CK radiosurgery out of the total number of secreting PA treated cases and the corresponding funnel plot with the effect size and standard error.

Some authors [48] kept the maximal dose inferior to 8 Gy.

3.5. Continuation of medication before SRS

Ehret et al. [42] have had 92 % of the patients continuing medication while receiving irradiation, similar as in the others CK series.

3.6. Outcomes: Biological control

Total remission was attained in 44 out of 108 patients, for an overall rate of 50.2 % (range 26.3–74.2 %, $I^2 = 80.93$, p heterogeneity = 0.001, $p < 0.001$, Fig. 3a).

Partial remission was inconsistently reported and finally for 25 out of 55 patients, for an overall rate of 38.8 % (range 13.1–64.6 %, $I^2 = 52.82$, p heterogeneity = 0.145, $p = 0.003$, Fig. 3b).

Uncontrolled disease was encountered in 36 out of 108 patients, for an overall rate of 32.7 % (range 24–41.4 %, $I^2 = 0$, p heterogeneity = 0.758, $p < 0.001$, Fig. 3c).

3.7. Factors involved in biological control

The factors involved in biological control were pretreatment IGF-1i (p = 0.02) and retreatment IGF-1 (p = 0.03) as illustrated by Ehret et al. [42], smaller tumor size (p = 0.02) and higher BED (172 Gy_3 versus 94 Gy_3, p < 0.01) as illustrated by Roberts et al. [43], higher BED (163 +/-47 Gy_4 versus 111+/-43 Gy_4) (p = 0.01) as illustrated by Sala et al. [44], 14 months between surgery and CK (p = 0.02) as illustrated by Moore et al. [45] or patients with lower preoperative UFC as illustrated by Apaydin et al. [49]. For details, please see Table 3.

3.8. Time to biochemical remission

Studies reported a mean time of biochemical remission for

Table 3
Predictors of biological control.

Factors predicting biochemical remission if p < 0.05	
Acromegaly	
Ehret et al. [42]	Pretreatment IGF-1i (p = 0.02)Pretreatment IGF-1 (p = 0.03)
Roberts et al. [43]	Smaller tumor size (p = 0.02)Higher BED (172 Gy_3 versus 94 Gy_3, p < 0.01)
Sala et al. [44]	Higher BED (163 +/-47 Gy_4 versus 111+/-43 Gy_4) (p = 0.01)
Cushing	
Moore et al. [45]	<14 months between surgery and CK (p = 0.02)
Apaydin et al. [49]	Higher in patients with lower preoperative UFC

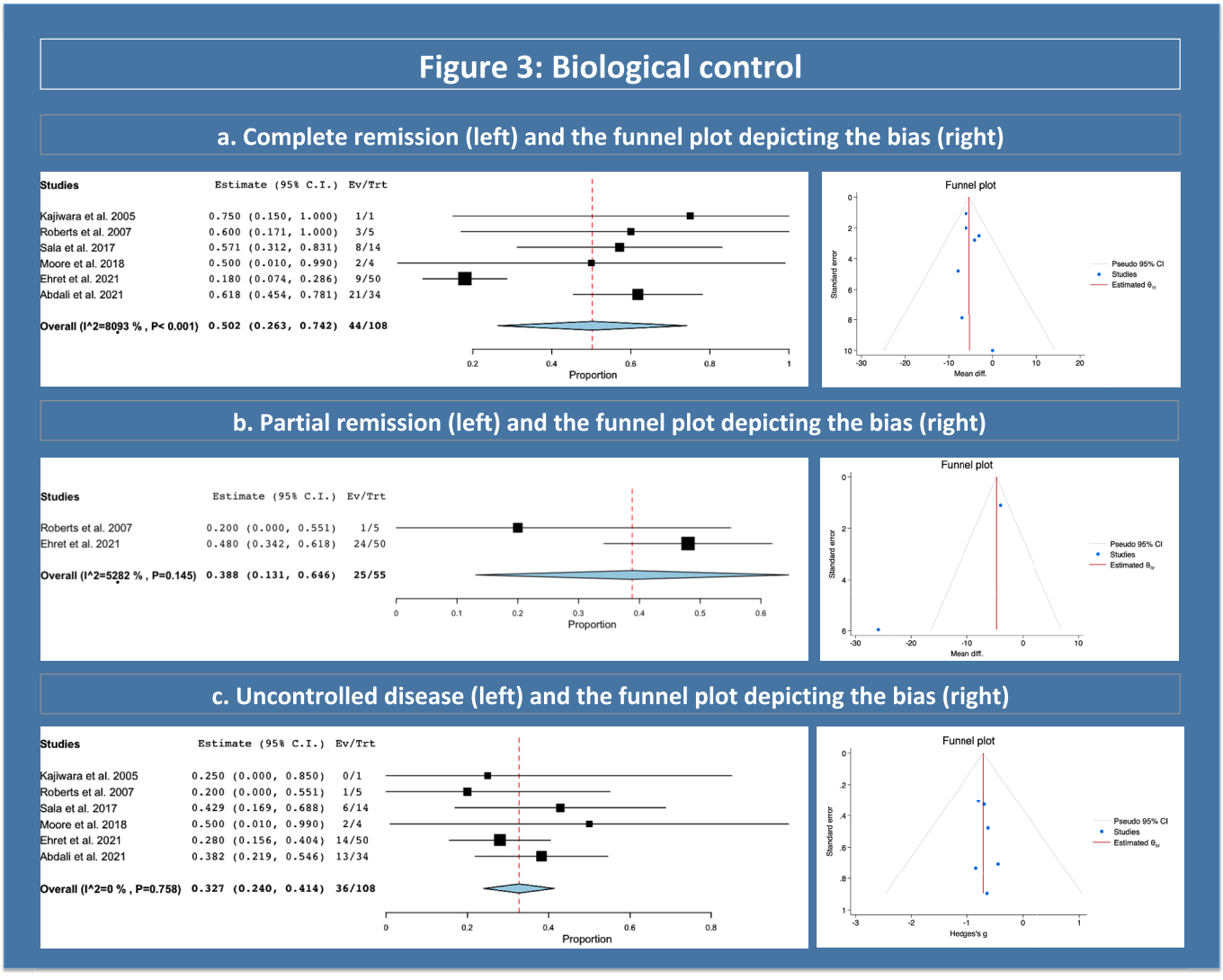

Fig. 3. Biological control: a- complete remission, b- partial remission, c- uncontrolled disease and the corresponding funnel plots with the effect size and standard error.

acromegaly that ranged between 12 (3–19) months [43] to 30.3 months [44], while for CD a median of 12.5 months [45] to 14 months [48].

3.9. Outcome: Time to hypopituitarism and hypopituitarism rates

One study reported hypopituitarism at 31.6 months after CK, similar to biochemical cure mean of 30.3 months in the same study [44].

The exact details of the hypopituitarism can be found in Table 2. The largest series of single fraction CK SRS were reported by Ehret et al. [42], with 19/50 patients and Abdali et al. [48] with 19/34 patients experiencing hypopituitarism. The most commonly found was GH deficiency, followed by hypogonadism and hypothyroidism.

No composite hypopituitarism rate for all studies is included as it is not uniformly reported.

3.10. Outcome: Other endpoints

One study reported a worsening in visual acuity in 2/26 cases visual (see Table 2). However, this study did not provide data on the doses received by the optic apparatus.

There was no reported carotid stenosis, radionecrosis, stroke or radiation induced neoplasia in the reported series.

4. Discussion

Our data suggest that the vast majority of patients treated with CK radiosurgery for secreting PA undergo single fraction CK RS. Here, the overall rates of total remission were 50.2 %, while partial remission rates were 38.8 %. Uncontrolled disease was observed in 32.7 %. Although tumor control was not reported separately for secreting and non-secreting PA, overall high rates were achieved.

Previous literrature on the treatment of secreting PA exists, with data available for both by GK (with the largest amount of data) and CK (although with a lower amount of data, as it appeared more recently). A recent international multicentric retrospective cohort by Ding et al. [39] included 371 patients (mean endocrine follow-up 79 months). The actuarial rates of reported initial and durable endocrine remission at 10 years were 69 % for GK and 59 %, respectively. Adverse radiation effects included the development of grade $\geq$ 1 new endocrinopathy was reported in 26 % and $\geq$ 1 cranial neuropathy in 4 % of the cases [39]. Temporary cessation of IGF-1 lowering Somatostatin analogues around the time of GK was found to be an independent variable of both initial and durable remission [39], being associated with better outcomes. Another study compared single fraction SRS with conventional fractionated radiotherapy suggested that GH normalization was quicker in the first group as compared with the second one (1.4 years versus 7.1 years) [52].

The treatment of recurrent CD is considered a challenge for both endocrinologists and neurosurgeons, especially as repeated microsurgical resection is complicated in most cases by high rates of hypopituitarism (even by pan-hypopituitarism), persistent diabetes insipidus and postoperative CSF leaks [48]. A recent international multicentric study by Mehta et al. [41] included a large number of cases (n = 278) with a mean follow-up of 5.6 years. Cumulative initial control of hypercortisolism was 80 % at 10 years (mean time to normalization 14.5 months). Recurrence occurred in approximately 18 % of cases [41]. The authors advocated that GK could result in quicker response times than conventional radiotherapy in this indication [41]. Other studies further reported that CD cases achieved earlier and far better biological remission as compared with acromegaly [53]. New paradigms have been recently developed, including whole-sellae irradiation, suggested to provide high rates of endocrine remission and similar complications rates as compared to the classical series describing targeting only clearly visualized tumor [54,55]. The most common complication in these series was hypopituitarism [54,55]. The use of SRS by GK for CD has been detailed in several studies reporting a tumor control as high as 100 %, a wide range of rates of biochemical control, between 17–87 % [35,56–64], with a hypopituitarism rate of 0–66 %[35,56–64], visual field loss 0–5.5 %[58,60].

Several CK studies reported a mean time of biochemical remission for acromegaly ranging between 12 (3–19) months [43] to 30.3 months [44], while for Cushing a median of 12.5 months [45] to 14 months [48], favorably comparing to what has been previously reported in GK studies, as by Sheehan et al. [65] with a median of 18.5 months. An important factor is that the mean time to remission after conventional RT is much longer (after GK was 1.5 years compared to 7.5 years) [52].

In the SRS treatment for secreting PA, typically higher doses of irradiation are recommended, as high as 30–35 Gy [38]. A concept that was recently explored was the BED. Such was not reported in all CK studies, but rather seldom. Higher BED (172 Gy_3 versus 94 Gy_3, $p < 0.01$), usually more than 150 Gy_3, was evocative for higher rates of biochemical remission, as suggested by Roberts [43]. In other studies [45] BED was quite low as referenced for single fraction, with a mean of 171.5 Gy (median 181; 143–181). Several retrospective GK studies suggested a relevance of the BED in endocrine remission [19,66].

The most at-risk structure is the optic pathway, as it is the most radiosensitive intracranial structure, and as the risk increases in cases of previous radiation treatments. A security space is compulsory to ensure optimal GK planning. In some centers, this is achieved by the use of peroperative spacer (chiasmopexy with interposition of fat or muscle tissue) and is of valuable help to avoid such type of complications [67]. Recent studies have additionally shown the importance of the dose received by the pituitary stalk (cut-off at 4.1 Gy) [68] and by the pituitary gland (cut-off at 15 Gy) [69] as predictors of pituitary insufficiency. Recent studies suggested that the optic apparatus might receive doses up to 12 Gy without major risks for optic neuropathy [70].

Our *meta*-analysis has several limitations. The first is related to the retrospective nature of the included studies. A second limitation is driven by different fractionation schemes prescribed by different authors, in the absence of a full discussion on the BED or equivalent dose. A third limitation is given by the different tumor volumes which have been irradiated. A fourth is the definition of tumor control, varying among series. A fifth limitation is the invasion of the cavernous sinus, which is a limiting factor for complete surgical resection; moreover, such invasion will imply the need of a refined neuroimaging protocol, to be able to clearly identify tumor boundaries, which is sometimes difficult, particularly after microsurgery (with or without chiasmopexy). A sixth limitation is due to the study attrition rates. A seventh limitation is the variation in surgical indications and approaches (transsphenoidal versus transcranial etc). A eighth factor is the different follow-up periods, which might also influence the results. The level of uncertainty in the findings of this systematic review is influenced by several factors, including moderate to high heterogeneity, suggesting variability in the effect size accros studies. Additionally, some studies might have increased the potential for random error, due to their limited sample sizes. Moreover, wide confidence intervals for some pooled estimates suggest potential imprecision in the data, further contributing to uncertainty. Several studies did not report enough information for full risk of bias assessement or data analysis. All these limitations could affect the comprehensiveness of our conclusions.

5. Conclusion

Single fraction CK radiosurgery was a common practice for secreting PA among CK series. Our *meta*-analysis suggests high rates of both total and partial remission (as high as 89 % taken both together), with a complete remission rate of 50.2 %. These results encourage the use of single fraction CK radiosurgery for secreting PA. To attain high rates of biochemical control, high doses of irradiation should be used (as high as 30–35 Gy). However, the present study has the limitations already acknowledged, including different fractionnation schemes, variability of tumor control definition, invasion of particular anatomical areas such as

the cavernous sinus, the attrition rates of the variations in surgical indications and approaches.

CRediT authorship contribution statement

Camil Bourhila: Writing – original draft, Methodology. **Cristian Cotrutz:** Validation, Methodology, Formal analysis. **Alfredo Conti:** Writing – review & editing, Visualization, Validation, Resources, Conceptualization. **Luis Schiappacasse:** Writing – review & editing. **Marc Levivier:** Writing – review & editing. **Constantin Tuleasca:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Ethics approval

NA (systematic review).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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