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TOPIC REVIEW

Stereotactic radiosurgery for acromegaly: an international systematic review and meta-analysis of clinical outcomes

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Abstract

Introduction We performed a systematic review and meta-analysis of clinical outcomes for patients with acromegaly treated with stereotactic radiosurgery (SRS).

Methods Primary outcomes were 5- and 10-year endocrine remission (ER) and endocrine control (EC). Secondary outcomes were 10-year radiographic local control (LC), visual toxicity, and hypopituitarism rates. Weighted random effects meta-analyses using the DerSimonian and Laird methods were conducted to characterize and compare effect sizes. Mixed effects regression models were used to examine correlations between potential prognostic factors and primary and secondary outcomes.

Results In total, 1533 patients across 20 published studies with acromegaly treated with SRS were included. At 5-years, estimated ER and EC rates were 43.2% (95% CI 31.7–54.6%) and 55.0% (95% CI 27.6–82.4%), respectively. At 10-years, estimated ER and EC rates were 56.9% (95% CI 47.5–66.4%) and 69.7% (95% CI 47.7–91.8%), respectively. The estimated 10-year LC rate was 92.8% (95% CI 83.0–100%). Visual toxicity and hypopituitarism following SRS were estimated to be 2.7% (95% CI 1.3–4.2%) and 26.8% (95% CI 16.9–36.7%), respectively. Every 1 Gy increase in margin prescription dose beyond 17 Gy was estimated to result in a 0.41% increased risk of visual toxicity ($p = 0.03$). No prognostic factors were associated with EC, ER, LC, or hypopituitarism.

Conclusions SRS was well-tolerated in the management of pituitary acromegaly resulting in gradually improving ER and EC rates over time that approached 60% and 70%. SRS-related visual loss is an uncommon treatment-related side effect, and patient-specific clinical decision making remains critical.

Keywords Stereotactic radiosurgery · SRS · Acromegaly · Biochemical control · Local control · Toxicity · Meta-analysis

Introduction

Pituitary adenomas comprise close to 20% of brain tumors in adults in the United States with roughly 12,000 cases diagnosed each year [1]. Functioning pituitary adenomas comprise roughly 70–75% of these, and of these growth-hormone secreting pituitary adenomas account for approximately 10% of all functioning pituitary adenomas [2]. Growth-hormone secreting pituitary adenomas left untreated may result in acromegaly with subsequent symptoms such as macrognathia, forehead furrowing, enlarging nose and ears, and, in pediatric patients, gigantism with an associated two- to three- fold increase in mortality compared to age- and gender-adjusted controls [3, 4]. Also, both functioning and non-functioning pituitary adenomas may cause local mass effect on adjacent structures such as the optic nerve as well

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as optic chiasm and result in potential visual field deficits as well as hypopituitarism [5].

Generally, first-line management for growth-hormone secreting pituitary adenomas includes surgical resection typically via a trans-sphenoidal approach with or without somatostatin analogues such as octreotide or lanreotide [6, 7]. Options for management should the former interventions not be successful include radiotherapy in the form of fractionated stereotactic radiotherapy (RT) or stereotactic radiosurgery (SRS), which delivers an ablative dose of radiation typically in 1–5 fractions with submillimeter accuracy with some studies suggesting less toxicity and more rapid endocrine remission with SRS as compared to fractionated stereotactic radiotherapy (RT) [8, 9]. Prior single institution and multi-institutional studies as well as meta-analyses have noted encouraging local control (LC) and biochemical control following SRS. However, earlier manuscripts have had short and non-uniform follow-ups and subsequent studies have reported improved biochemical outcomes with longer term follow-up [9–11]. As such, we aimed to provide an updated systematic review and meta-analysis of biochemical control, LC, and subsequent toxicity rates following SRS for the management of growth-hormone secreting pituitary adenomas. We also examine any potential prognostic factors that were associated with biochemical control, LC, or toxicity rates.

Materials and methods

Literature selection

A literature search was performed using PubMed, EMBASE, and the Cochrane Library through March 1st, 2020. Inclusion criteria for selection was defined using the Population, Intervention, Control, Outcomes, Study Design (PICOS) method (Supplementary Table 1) [12–14]. Additionally, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) selection algorithm (Supplementary Fig. 1) was designed [13]. Guidelines from the PRISMA checklist [15] (Supplementary Fig. 2) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [16] (Supplementary Fig. 3) were followed.

The following combination of keywords were searched: radiosurgery, SRS, radiation therapy, acromegaly, pituitary, fractionation, endocrine control, endocrine remission, local control, toxicity, GammaKnife, CyberKnife, LINAC, protons, and side-effects. Related articles as well as reference lists were reviewed of manuscripts that were initially found with additional relevant publications included. A total of 20 published studies were chosen for inclusion in both the qualitative and quantitative portions of the meta-analysis.

The inclusion criteria for the quantitative meta-analysis included studies with information on: (1) patients clinically or pathologically diagnosed with acromegaly secondary to a functioning pituitary adenoma; (2) either endocrine control (EC), endocrine remission (ER), local control (LC), or pituitary or visual toxicity rates; (3) dose and fractionation (4) patients treated with SRS either definitively or post-operatively (with SRS defined as being delivered in hypofractionated courses of 1–5 fractions). Definitions for each of these endpoints were based upon the individual studies themselves. Exclusion criteria included: (1) studies without information on ER, EC, LC, visual toxicity, or hypopituitarism rates; (2) studies that included patients without outcomes specific to those with functioning pituitary adenomas resulting in acromegaly; (3) studies without a minimum follow-up of at least 2 years and at least 15 patients (4) works involving patients included in more than one study; (5) works involving non-human subjects; (6) works not published in English; (7) unfinished manuscripts.

Data extraction

Independent authors (R.S., P.D., E.L.) conducted and reviewed extraction of relevant data. Information obtained included the primary and secondary outcomes, as well as patient, study, and treatment characteristics. Authors of relevant studies were contacted for missing data if such studies met inclusion criteria.

Outcome measures

The primary outcome of the study was 5- and 10-year ER and EC rates, with secondary outcomes of 10-year radiographic LC and both new visual toxicity rates secondary to cranial nerve (CN) II neuropathy or hypopituitarism secondary to SRS. The definition of ER across studies varied but generally was defined as a post-SRS GH < 1–2 ng/mL and/or normal IGF-1 levels for patient sex and age without the use of pharmacologic management/suppressive medications. The definition of EC was defined similarly to ER but with the use of pharmacologic management/suppressive medications.

Statistical analysis

Statistical analyses were conducted using R Studio Version 1.1.383 (Boston, MA) [17]. The Meta-Analysis for R (metafor) package version 2.0-0 was used to conduct the meta-analyses, meta-regressions, tests for heterogeneity, analysis of publication bias, and Wald-type tests [18]. The DerSimonian and Laird method was used to calculate between study variances [19]. Proportions were calculated for each of the outcome measures, where the denominator was the

total number of patients in each study or arm. Weighted random effects models were used to determine an overall summary estimate for each of the outcome measures [20, 21]. Summary estimates for each of the outcome measures were depicted on forest diagrams with their associated 95% confidence interval.

Heterogeneity was assessed using both the I^2 statistic [22] and Cochran Q-Test [23]**.** Significant heterogeneity was considered to be present if $I^2 > 50\%$ and the p value of the Q-Test was < 0.10. An assessment of publication bias was performed using the Egger test [46]. Publication bias was considered to be present if the p-value of the Egger Test was < 0.05.

Meta-regression and the Wald-type test were used to compare summary effect sizes on each of the forest diagrams for ER, EC, LC, visual toxicity and hypopituitarism rates, where treatment category was used as a categorical covariate. The null-hypothesis was rejected for $p < 0.05$.

For dose response analyses, mixed effects meta-regression models utilizing an ordinary least squares (OLS) approach were used to estimate weighted linear relationships between ER, EC, and LC rates and median post-operative growth hormone (GH) and insulin-like growth factor-1 (IGF-1), gross tumor volume (GTV), and median margin prescription dose as well as between visual toxicity and new hypopituitarism rates and GTV and median margin prescription dose. The weight applied to a given study's published effect estimate was the ratio of the number of patients analyzed in that study divided by the total number of patients over all studies used for the meta-estimate of that effect [20]. Results were summarized by slopes representing expected changes in independent variables based on per unit changes in independent variables.

Results

Characteristics of studies included for quantitative analysis

Among 20 published studies, 1533 pituitary patients with acromegaly treated with definitive, adjuvant, or salvage SRS were identified that met inclusion criteria [10, 11, 24–41]. Studies were published from 2001 to 2020 with patients from the United States, Italy, France, Turkey, Germany, Japan, Czech Republic, Taiwan, Hong Kong, China, Norway, the United Kingdom, Australia, and South Korea. Data on both the primary and secondary outcomes are listed for each study in Table 1. Other information regarding patient age, radiation technique, prescription dose and prescription isodose, GTV or planning target volume (PTV), EC, ER, LC, visual and pituitary toxicity rates, whether patients had received prior radiation therapy or had prior surgery, and other relevant information can also be found in Table 1. Among studies examining SRS, the majority of patients had received adjuvant SRS with a few patients in some studies having received definitive SRS. Median pre-SRS GH and IGF-1 levels were 10.53 ng/mL (range: 0–442) and 665.5 ng/mL (range: 18.5–2915), respectively. The median GTV was 2.0 cc (range: 0.1–49.5), and the median margin prescription dose was 24 Gy (range: 8.8–42 Gy). In nineteen of twenty studies, single fraction SRS was utilized with one experience reporting on fractionated SRS in 3 or 5 fractions [40].

Endocrine remission, endocrine control, and local control

With respect to ER, 17 studies with 1,298 patients had information on 5-year ER [10, 11, 24, 26, 28–37, 39–41], and 10 studies with 1,023 patients had information on 10-year ER [10, 11, 31, 34–37, 39, 41]. At 5-years, the estimated ER rate was 43.2% (95% CI 31.7–54.6%; Fig. 1), and at 10-years the estimated ER rate was 56.9% (95% CI 47.5–66.4%; Fig. 1). On meta-regression for evaluation of potential prognostic factors, median GH ($p = 0.90$), IGF-1 ($p = 0.57$), GTV ($p = 0.55$), and margin prescription dose ($p = 0.43$) were not found to be correlated with 5-year ER. Similarly, median GH ($p = 0.78$), IGF-1 ($p = 0.90$), GTV ($p = 0.78$), and margin prescription dose ($p = 0.66$) were not found to be correlated with 10-year ER. Egger's test assessing publication bias for 5-year ($p = 0.77$) and 10-year ER ($p = 0.28$) were non-significant.

Upon examination of EC, 4 studies with 317 patients on 5-year EC [11, 30, 36, 39] and these same 4 studies with 317 patients had information on 10-year EC [11, 34, 36, 39]. At 5-years, the estimated EC rate was 55.0% (95% CI 27.6–82.4%; Fig. 2), and at 10-years, the estimated EC rate was 69.7% (95% CI 47.7–91.8%; Fig. 2), respectively. On meta-regression for evaluation of potential prognostic factors, median GH ($p = 0.26$) and margin prescription dose ($p = 0.22$) were not found to be correlated with 10-year EC. The potential correlation between median IGF-1 levels and GTV and 10-year EC were not able to be examined due to a lack of enough information on both of these variables. Egger's test assessing publication bias for 5-year ($p = 0.90$) and 10-year EC ($p = 0.73$) were non-significant.

Five studies with 360 patients in total had information on 10-year LC [29, 31, 37]. The estimated 10-year LC rate was 92.8% (95% CI 83.0–100%; Fig. 3). On meta-regression for evaluation of potential prognostic factors, neither GTV ($p = 0.35$) nor margin prescription dose ($p = 0.45$) were found to be correlated with 10-year LC. Egger's test assessing publication bias for 10-year LC was non-significant ($p = 0.10$).

Table 1 Studies examining clinical outcomes following SRS for the management of acromegaly

Study	*n* (Patients)	Median age (years) (range)	Median follow-up (range)	Pre-SRS GH/IGF-1 levels (ng/mL) (range)	Median GTV/PTV (cc) (range)	Treatment planning (range)	Hormonal control (GH and IGF-1)	LC (95% CI)	Toxicities	Additional notes/comments
Attanasio et al. (2003) [24]	30 Prior RT at least 10 years prior to SRS: 4 Prior surgery: 27 Adjuvant pharmacologic management after SRS: 5	46 (23-68)	46 months (9–96 months)	Mean GH: 10 (6.4–15)	Mean PTV: 1.43 (0.2–3.7)	All single fraction GK-SRS Median marginal dose: 20 Gy (15–35) 50% isodose: 27 patients	1-year pathologic hormonal levels: 93% 3-year: 75% 5-year: 70%	Tumor shrinkage: Decrease of at least 25% of initial volume 1-year tumor shrinkage: 28% 4-year tumor shrinkage: 79%	Acute: 1/30 patients with severe headache/nausea Chronic: 12/30 with hypo-adrenalism New anterior pituitary failure in 2 patients (6.67%) No visual toxicities changed from baseline	Limited dose to optic structure to < 8 Gy
Castinetti et al. (2005) [25][6]	82 Prior transsphenoidal surgery: 63 Previous RT: 2 Pharmacologic management with SRS: 42	Mean: In remission: 50.5 (32–76) Uncured: 53.5 (21–74)	Mean: 49.5 months (6–108)	Adjuvant SRS: Mean GH: 24 (4–240) Mean IGF–1: 640 (305–2200) Definitive SRS: Mean GH: 15 (2.3–49) Mean IGF-1: 695 (390–1600) 40 patients off medications prior to SRS	N/A 3/82 with suprasellar extension	All single fraction GK-SRS Mean marginal dose: Primary treatment: 30 Gy (20–35 Gy) Adjuvant treatment: 25 Gy (12–40 Gy)	3-year remission rate (both GH and IGF-1): 17% 3-year GH: 20.7% 3-year IGF-1: 25.6%	N/A	New pituitary deficiency in 14 patients (17.1%) One case of trigeminal neuralgia "Few patients" with transient headaches and vomiting No chronic visual deficits	Lower pre-SRS GH and IGF-1 levels associated with higher remission rates Primary treatment if microadenoma or small (10–15 mm) enclosed macroadenoma with laterosellar extension

Table 1 (continued)

Study	*n* (Patients)	Median age (years) (range)	Median follow-up (range)	Pre-SRS GH/IGF-1 levels (ng/mL) (range)	Median GTV/PTV (cc) (range)	Treatment planning (range)	Hormonal control (GH and IGF-1)	LC (95% CI)	Toxicities	Additional notes/comments
Ding et al. (2019) [10]	371 (326 with residual tumor, 19 with recurrent tumor) Prior resection: 93% Pharmacologic management prior to SRS: 35.6% Prior RT: 5.4%	Mean: 46 (13.6-92)	Mean endocrinologic follow-up: 79 months Mean radiographic follow-up: 64.5 months (3–229)	Mean GH: 12.6 (0–173) Mean IGF-1: 699 (65.3–2915) 56.1% with medication held prior to SRS	Median PTV: 3.0 (0.1–22.9) 47.7% and 10.8% with cavernous sinus and suprasellar components targeted, resepctively	All single fraction GK-SRS Mean marginal dose: 24.2 Gy (8.8–40 Gy) Mean isodose: 51.2% (25–90%)	Initial endocrine remission: 54% Durable endocrine remission: 45% 5-year: 43% 10-year: 59% 15-year: 64% Crude durable remission rate (off of medications): 39%	65% with radiologic tumor regression at last follow-up	New pituitary dysfunction: 26% New cranial neuropathy: 4% 3.5% with visual deficits following SRS attributable to CN II	Temporary cessation of IGF-1 lower medications prior to SRS associated with higher remission rates SRS targeting of whole sella associated with endocrinopathy
Erdur et al. (2011) [26]	22 All with prior surgery Prior RT: 4	N/A	Median: 60 months (IQR: 24–60 months)	Median GH: 5.65 (IQR: 3.85–7.2) Median IGF-1: 582.5 (IQR: 515–655)	N/A	All single fraction GK-SRS Mean marginal dose: 23.8 Gy (SD: 3 Gy) Mean isodose: 50% (range: 40–60%)	GH: 1-year: 31.5% 2-year: 42.8% 3-year: 58.3% 4-year: 66.6% 5-year: 63.6% IGF-1: 1-year: 21% 2-year: 42.8% 3-year: 50% 4-year: 50% 5-year: 81.8% 54.5% in remission at end follow-up	1-year LC: 95.2%	6/21 (28.5%) with new-onset pituitary dysfunction No worsening visual deficits noted	
Gutt et al. (2004) [27]	44 Prior surgery: 43 Concomitant pharmacologic management: 40 Prior RT: 5	43 (20–71)	1.9 years (range: 0.5–4.3)	Median IGF-1: 1.9× upper limit of normal) (0.5–8.9)	Median GTV: 1.5 cc (0.1–6.9)	All single fraction GK-SRS Median marginal dose: 18 Gy (12–23 Gy) Majority with 50% isodose line	Only IGF-1 levels available, not GH levels 47.7% with normal age-adjusted IGF-1 levels at last follow-up	Decrease in median tumor size to 0.3 cc	No adverse visual or endocrine toxicities reported	

Table 1 (continued)

Study	*n* (Patients)	Median age (years) (range)	Median follow-up (range)	Pre-SRS GH/IGF-1 levels (ng/mL) (range)	Median GTV/PTV (cc) (range)	Treatment planning (range)	Hormonal control (GH and IGF-1)	LC (95% CI)	Toxicities	Additional notes/comments
Ikeda et al. (2001) [28]	18 All with prior transsphenoidal surgery and received adjuvant GK SRS if persistent biochemical dysfunction or residual tumor	47 (11–75)	3.8 years (range: not provided)	Mean pre-operative GH: 51.2 (3.1–456)	Mean GTV: 2.3 cm (0.5–5.8 cm)	All single fraction GK-SRS Marginal dose: 20–40 Gy (median not listed)	Endocrine remission rates: 2-, 3-, and 4-year: 82% IGF-1: normalized 2 years after GK SRS and stabilized 4 years after GK SRS GH: stabilized 4 years after GK SRS	4-year LC: 100% (all with > 50% tumor volume reduction)	No cases of pituitary dysfunction or visual toxicities following treatment	Limited dose to optic apparatus to < 10 Gy
Jezkova et al. (2006) [29]	96 Prior surgery: 72 Prior RT: 11	Mean: 48.8 (16–76)	53.7 months (12–120)	Mean GH: 20.4 (SD: 26.5) Mean IGF-1: 944.1 (SD: 341.7) All patients off of medications 2 months prior to SRS	Mean GTV: 1.35 cm (0.933–12.7 cm)	All single fraction GK-SRS Median marginal dose: 35 Gy (10–42 Gy)	GH: 1-year 14.6% 3-year: 28.6% 5-year: 44.2% 8-year: 57.1% IGF-1: 1-year: 20.8% 3-year: 41.4% 5-year: 55.8% 8-year: 71.4%	10-year LC: 100% (no growth recorded in any patients) Tumor reduction: 2-year: 46.9% 5-year: 61.1%	26/96 (27.1%) with pituitary/endocrine dysfunction following GK SRS No visual toxicities	Pituitary toxicities only noted with marginal doses of 15 Gy or greater Limited dose to edge of optic chiasm to < 8 Gy
Knappe et al. (2020) [11]	119 treated with SRS	Median: 39.4 (SD = 11.6)	9.1 years (SD: 5.1 years)	Mean GH: 3.5 (1.8–6.9) 9% of patients documented as being on suppressive medication prior to SRS	N/A	GK-SRS: 75 patients LINAC-based SRS: 44 patients Information on median marginal dose N/A	Endocrine remission rate: 3-year: 38.0% 5-year: 50.9% 10-year: 52% Endocrine control rate: 3-year: 57% 5-year: 76.1% 10-year: 78.1%	N/A	56/89 (63%) with at least one pituitary insufficiency at last follow-up Visual or other toxicities were not able to be reported from registry	Remission: normal or low IGF-1 levels without pharmacologic intervention Controlled: normal or low IGF-1 levels with pharmacologic medication:

Table 1 (continued)

Study	*n* (Patients)	Median age (years) (range)	Median follow-up (range)	Pre-SRS GH/IGF-1 levels (ng/mL) (range)	Median GTV/PTV (cc) (range)	Treatment planning (range)	Hormonal control (GH and IGF-1)	LC (95% CI)	Toxicities	Additional notes/comments
Liu et al. (2012) [30]	40 Prior surgery: 34	45 (16–81)	Median endocrine follow-up: 72 months (24–145 months)	N/A 13 patients (32.5%) on suppressive medication at time of SRS	Median GTV: 2.0 cc (0.2–16.1) 30% and 35% with cavernous sinus invasion and suprasellar extension, respectively	All single fraction GK-SRS Median marginal dose: 21 Gy (12–30 Gy)	Endocrine remission: 3-years: 18.6% 5-years: 44.5% 7-years: 67.6% Endocrine control: 5-year: 57.5%	LC achieved in 97.5% of patients 27/40 with tumor regression	40% with new pituitary dysfunction No visual toxicities	
Pai et al. (2018) [31]	76 Prior surgery: 97.4% of patients Prior RT: 7.9%	42 (16–76)	Median endocrine: 72.8 months (6.1–235) Median radiographic follow-up: 65.8 months (4.8–228.9)	Median GH: 11.05 (5.02–25.1) Median IGF-1: 891 (629–1038) 6 patients on suppressive medications during SRS	Median PTV: 2.8 cc (0.1–49.5 cc) 51.3% and 13.2% of patients with cavernous sinus invasion and suprasellar extension, respectively	All single fraction GK-SRS Median marginal dose: 15.8 Gy (11.9–22 Gy) Median isodose line: 57.5% (50–80%)	Endocrine remission rates: 2-year: 8.4% 3-year:13.6% 4-year: 20.3% 5-year: 28.9% 6-year: 39.9% 7-year: 45.1% 8-year: 49.9% 10-year: 67.5% 12-year: 76.3%	LC: 6-year: 100% 8-year: 93.8% 10-year: 93.8% 12-year: 93.8% Tumor regression: 76.3% of patients at last radiographic follow-up	11.8% of patients with new pituitary dysfunction No visual toxicities	Only treated with “low dose” GK SRS (< 25 Gy) Limited optic apparatus to < 10 Gy
Pollock et al. (2007) [32]	46 Previous surgery: 43 Prior RT: 6	45 (12–75)	63 months (22–168)	Median GH: 8.4 (0.4–82) Median IGF-1: 2.25× upper limit of normal (1.05–7.0) 41% of patients on suppressive medications during SRS	Median GTV: 3.3 cc (0.5–18.0 cc)	All single fraction GK-SRS Median marginal dose: 20 Gy (14.4–30 Gy)	Endocrine remission rates: 2-year: 11% 3-year: 30.4% 4-year: 55.7% 5-year: 60% 7-year: 63.8% 8-year: 63.8%	LC: No tumor growth in any patient at last follow-up 30% with no change in tumor size, 70% with tumor regression	33% of patients with new pituitary dysfunction at 5-year follow-up No visual toxicities	IGF-1 < 2.25× upper limit of normal associated with higher remission rates 36 patients received > 8 Gy to optic apparatus

Table 1 (continued)

Study	*n* (Patients)	Median age (years) (range)	Median follow-up (range)	Pre-SRS GH/IGF-1 levels (ng/mL) (range)	Median GTV/PTV (cc) (range)	Treatment planning (range)	Hormonal control (GH and IGF-1)	LC (95% CI)	Toxicities	Additional notes/comments
Poon et al. (2010) [33]	40 Prior surgery: 37	Mean: 64 (19–73)	73.8 months (12–132)	N/A for entire cohort	N/A	All single fraction GK-SRS Peripheral dose range: 20–35 Gy (median not provided)	Endocrine remission rate: 75% SRS once: 69.2% SRS twice: 81.8%	62% of patients with tumor regressions of 76–100%	11.4% of patients with pituitary dysfunction following SRS once; 27.3% if SRS twice No visual toxicities	Dose to optic apparatus limited to < 9 Gy
Ronchi, et al. (2009) [34]	35 Prior surgery: 32 Prior RT: 4	Mean: 45 SD: 12	114 months (24–158)	Mean GH (off medication): 12.9 (SD: 14.3) Mean IGF-1: 97.9 nmol/L (SD: 36.9) (748.74 ngmL)	Median PTV: 0.9 cc (0.2–3.7)	All single fraction GK-SRS Median marginal dose: 20 Gy (15–35 Gy) Median isodose: 50% (45–60%)	Endocrine remission rate: 3-year: 6% 5-year: 9.03% 7-year: 25% 10-year: 46% Endocrine control rate: 10-year: 50%	Tumor shrinkage > 25%: 2-year: 7.8% 3-year: 16.5% 5-year: 25.8% 6-year: 29.2% 8-year: 40% 10-year: 40%	70% of patients with new pituitary dysfunction following SRS No visual toxicities	Optic chiasm limited to < 8 Gy
Vik Mo et al. (2007) [35]	61 Prior surgery: 56	Mean: 47 (18–81)	Mean: 5.5 years	Mean GH: 28.1 (0.6–442) Mean IGF-1: 69.2 nmol/L (18.5–184) (528.5 ng/mL)	Median GTV: 1.23 (0.01–6.6)	All single fraction GK-SRS Mean marginal dose: 26.5 Gy (12–35 Gy) Median isodose: 49.5% (30–70%)	IGF-1 control rate: 3-year: 45% 5-year: 58% 10-year: 86% GH control rate: 3-year: 42% 5-year: 51% 10-year: 56%	Tumor growth stopped in all patients treated 22 patients with tumor shrinkage > 50%	14/61 (23%) with new pituitary dysfunction following SRS 2/61 (3.3%) with visual toxicities (minor visual field deficits)	Dose to optic chiasm ranged from 0.3 Gy to 16.2 Gy

Table 1 (continued)

Study	*n* (Patients)	Median age (years) (range)	Median follow-up (range)	Pre-SRS GH/IGF-1 levels (ng/mL) (range)	Median GTV/PTV (cc) (range)	Treatment planning (range)	Hormonal control (GH and IGF-1)	LC (95% CI)	Toxicities	Additional notes/comments
Sims-Williams et al. (2018) [36]	20 All treated with upfront SRS	54.5 years (N/A)	166.5 months (N/A)	Median GH: 9.0 Median IGF-1: 2.0× upper limit of normal	N/A	All single fraction GK-SRS Median marginal dose: 27.5 Gy	Endocrine remission rate: 3-year: 23.1% 5-year: 23.1% 7-year: 22.5% 8-year: 48.4% 10-year: 48.4% 20-year: 74.4% Endocrine control rate: 3-year: 50% 5-year: 50% 7-year: 50% 8-year: 66.7% 10-year: 83.4% 20-year: 83.4%	No cases of tumor expansion compromising vision or prompting surgery	53% (9/17 patients) with new pituitary dysfunction 1/20 (5%) of patients with visual toxicities (CT-guided treatment)	Dose limited to optic nerves < 8 Gy
Lee et al. (2014) [37]	136 Prior surgery: 134 Prior RT: 10	44 (14–93)	Median endocrine follow-up: 61.5 months (12–191) Median imaging follow-up: 43.5 months (12–191)	Median GH: 4.3 (0.6–108) Median IGF-1: 528.5 (181–1800) 15 patients (17.4%) on suppressive medication prior to SRS	Median GTV: 2.3 cc (0.3–16.0) Median PTV: 3.0 cc (0.3–16.0) 41.2% and 8.8% with cavernous sinus invasion and suprasellar extension, respectively	All single fraction GK-SRS Median marginal dose: 25 Gy (8.8–30 Gy) Median isodose: 50% (25–70%)	Endocrine remission rates: 2-year: 31.7% 3-year: 49.2% 4-year: 64.5% 5-year: 69.3% 6-year: 73.4% 7-year: 78.4% 8-year: 82.6% 10-year: 82.6%	LC rates: 2-year: 100% 4-year: 98.1% 6-year: 98.1% 8-year: 97.5% 47% and 51.5% of patients with decrease in tumor size or stable size at last follow-up, respectively	31.6% of patients with new pituitary dysfunction 4/136 (2.9%) with visual deficits following SRS	Lower initial IGF-1 levels associated with favorable endocrine responses; initial GH levels were not

Table 1 (continued)

Study	*n* (Patients)	Median age (years) (range)	Median follow-up (range)	Pre-SRS GH/IGF-1 levels (ng/mL) (range)	Median GTV/PTV (cc) (range)	Treatment planning (range)	Hormonal control (GH and IGF-1)	LC (95% CI)	Toxicities	Additional notes/comments
Wilson et al. (2013) [38]	86	48.5 (21–78)	5.5 years (0–15.5)	N/A	Median GTV: 2.0 cc (0.17–44)	LINAC-based SRS Median marginal dose: 20 Gy (14–25 Gy)	GH: 19.8% of patients had GH < 5 ng/mL following SRS IGF-1: 16/86 patients reached normal age-adjusted IGF-1 levels	3/86 (4%) with documented increase in tumor size following SRS	19.8% of patients with new pituitary dysfunction 1/86 (1.16%) with visual toxicities	
Konget al. (2018) [39]	138	43.2 (19–74)	85.2 months (12–304)	Median GH: 9.4 (0.4–176) Median IGF-1: 691 (108–1870) 33.3% of patients on suppressive medication prior to SRS	Median GTV: 0.9 cc (0.1–10.3) 50% and 23% of patients with cavernous sinus invasion and suprasellar extension, respectively	All single fraction GK-SRS Median marginal dose: 25 Gy (12–35 Gy) Median isodose: 50% (33–70%)	Endocrine remission rates: 3-years: 15% 5-years: 20.3% 7-years: 25.6% 8-years: 32.3% 10-years: 44.9% 20-years: 67.6% Endocrine control rates: 3-years: 27.3% 5-years: 35.9% 7-years: 42.3% 8-years: 50.2% 10-years: 65.3% 20-years: 91.6%	N/A	8.6% of patients with new pituitary dysfunction	Dose to optic chiasm limited to < 8 Gy Mean margin dose of 27.5 Gy associated with higher rates of pituitary dysfunction vs. 25 Gy

Table 1 (continued)

Study	*n* (Patients)	Median age (years) (range)	Median follow-up (range)	Pre-SRS GH/IGF-1 levels (ng/mL) (range)	Median GTV/PTV (cc) (range)	Treatment planning (range)	Hormonal control (GH and IGF-1)	LC (95% CI)	Toxicities	Additional notes/comments
Iwata et al. (2016) [40]	52 Prior surgery: 51	35 (14–67)	60 months (27–137)	Mean GH: 5.0 (1.9–161) Mean IGF-1: 457 (119–1400)	Median GTV: 4.4 cc (0.2–19.8)	All LINAC-based hypo-fractionated SRS Marginal dose: 3 fractions: 17.4–26.8 Gy 5 fractions: 20–32 Gy	Endocrine remission rate: 5-year: 17.3%	5-year LC: 100% 10-year LC: 82.5%	1.9% of patients with new pituitary dysfunction No visual toxicities	
Bostrom et al. (2015) [41]	21 Mean: 45 (30-75)		8 years (2–13 years)	N/A Nearly all patients on suppressive medication prior to SRS	Mean CTV: 1.18 cc (0.11–4.8)	All LINAC-based SRS Median marginal dose: 20 Gy (15–36 Gy)	Endocrine remission rate: 5-year: 23.8% 10-year: 37.6%	5-year LC: 90.5% 10-year LC: 90.5%	13 patients treated with either SRS or RT) with new pituitary dysfunction 1 patient with visual dysfunction following either SRS or RT	

GK Gamma Knife, *RT* radiation therapy, *LC* local control, *SRS* stereotactic radiosurgery, *GH* growth hormone, *IGF-1* insulin-like growth factor 1 (*IQR* interquartile range, *SD* standard deviation, *LINAC* linear accelerator, *GTV* gross tumor volume, *PTV* planning target volume, *CN* cranial nerve

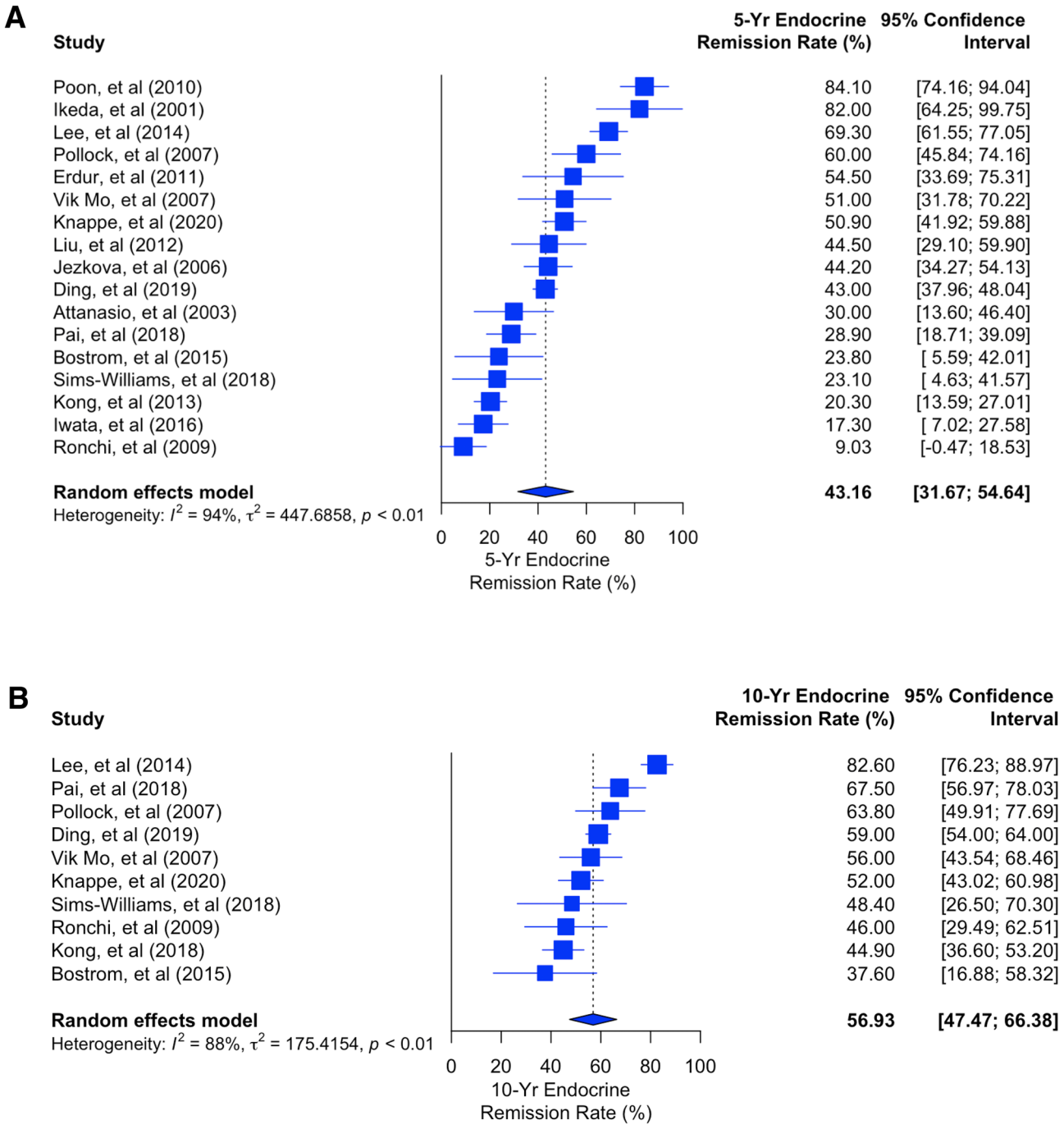


Fig. 1 Forest plots examining 5- (**a**) and 10-year (**b**) endocrine remission (ER) rates following SRS

Visual toxicities and hypopituitarism

Across 17 studies, 1255 patients were identified has having information on visual toxicity rates following SRS secondary to CN II neuropathy [10, 24–38, 40]. The estimated rate of visual toxicity secondary to CN II neuropathy following SRS was 2.7% (95% CI 1.3–4.2%; Fig. 4). On meta-regression for evaluation of potential prognostic factors, margin prescription dose was found to be correlated with visual toxicity incidence with the model estimating a 0.41% increased risk of visual toxicity for every 1 Gy increase in margin prescription dose beyond approximately 17 Gy (Supplementary Fig. 4; $p = 0.03$). GTV at the time of SRS was not found to be associated with visual toxicity incidence ($p = 0.40$). Egger's test assessing publication bias for visual toxicity was non-significant ($p = 0.73$).

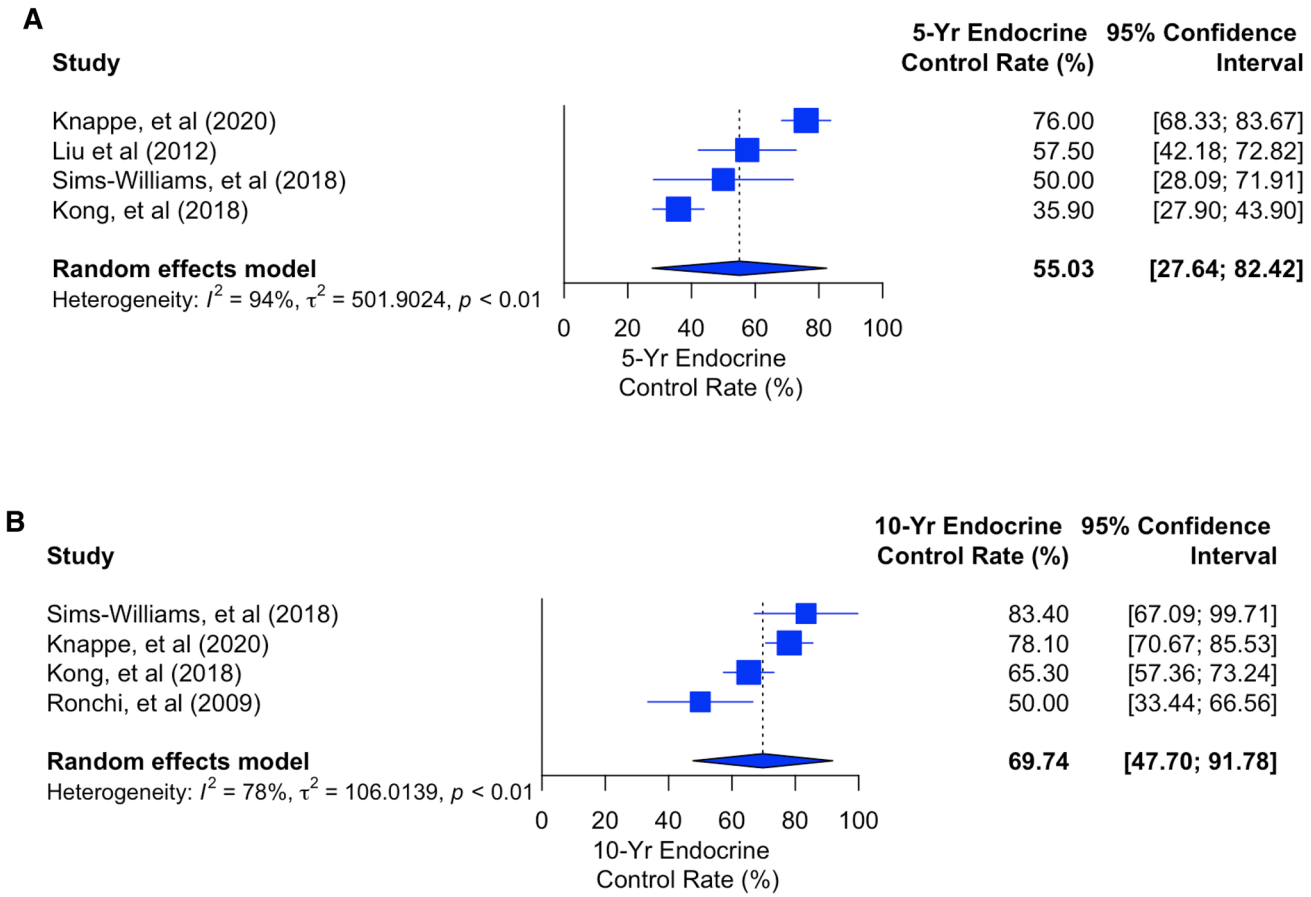


Fig. 2 Forest plots examining 5- (**a**) and 10-year (**b**) endocrine control (EC) rates following SRS

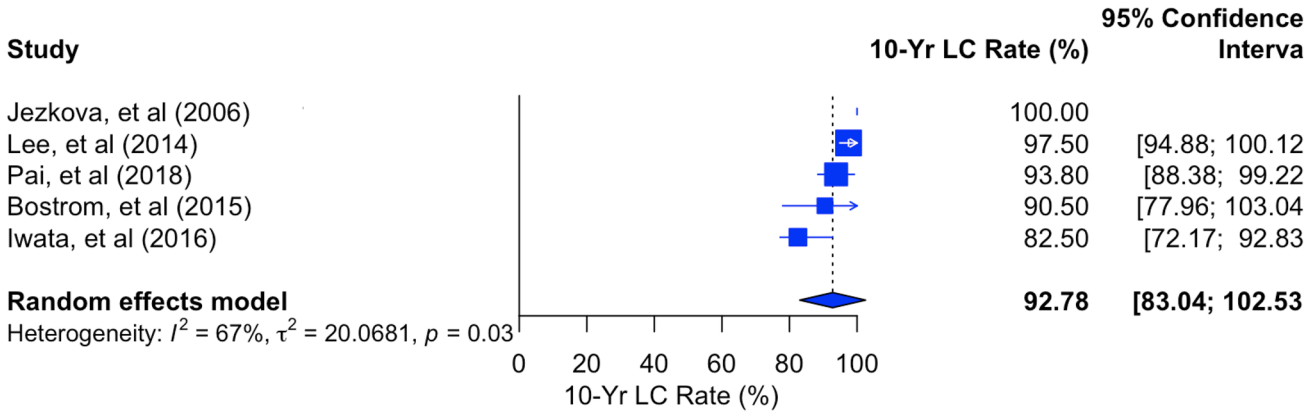
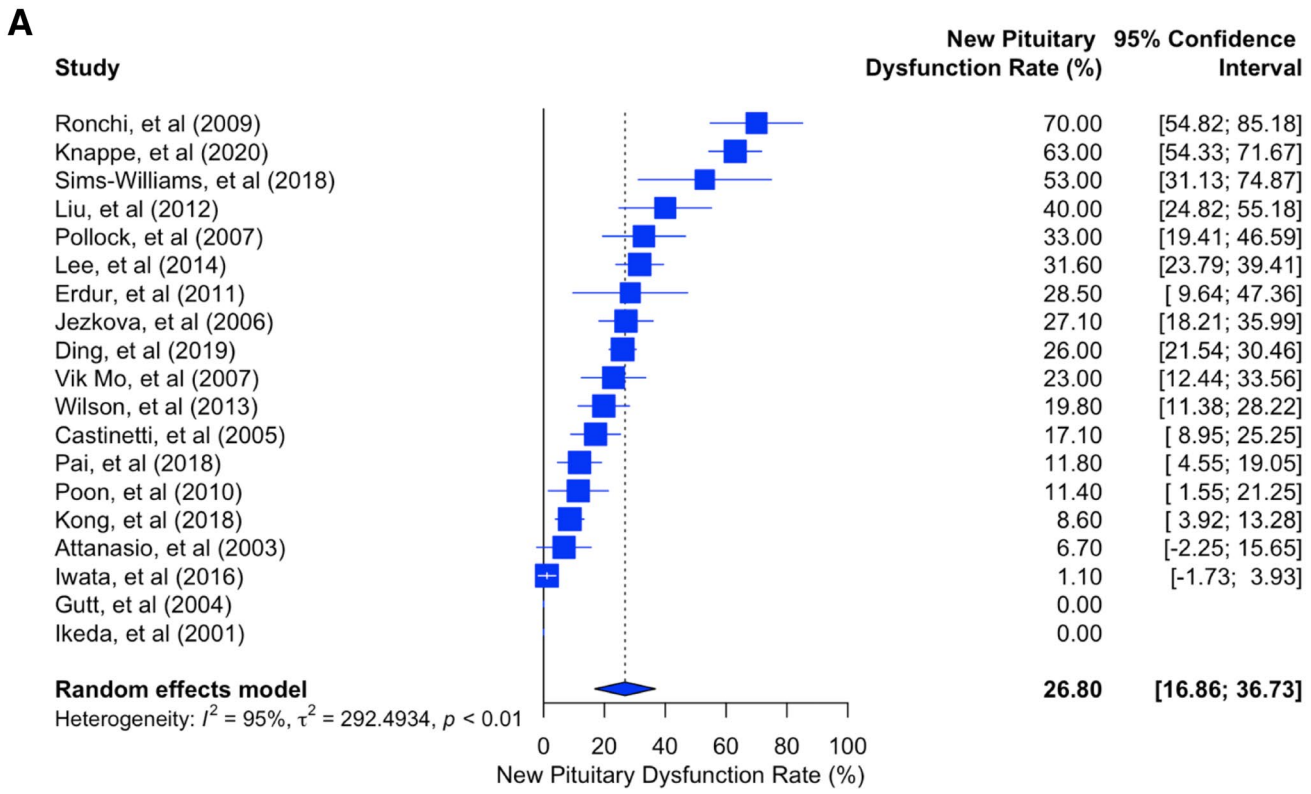


Fig. 3 Forest plot examining 10-year local control (LC) following SRS

With regards to rates of hypopituitarism, 19 studies with 1,512 patients had information on this outcome [10, 11, 24–40]. The estimated rate of hypopituitarism following SRS was estimated to be 26.8% (95% CI 16.9–36.7%; Fig. 4). On meta-regression for evaluation of potential prognostic factors, neither GTV ($p = 0.29$) nor margin prescription dose ($p = 0.95$) were found to be correlated with incidence of hypopituitarism. Egger's test assessing publication bias for hypopituitarism rates were significant ($p = 0.003$).



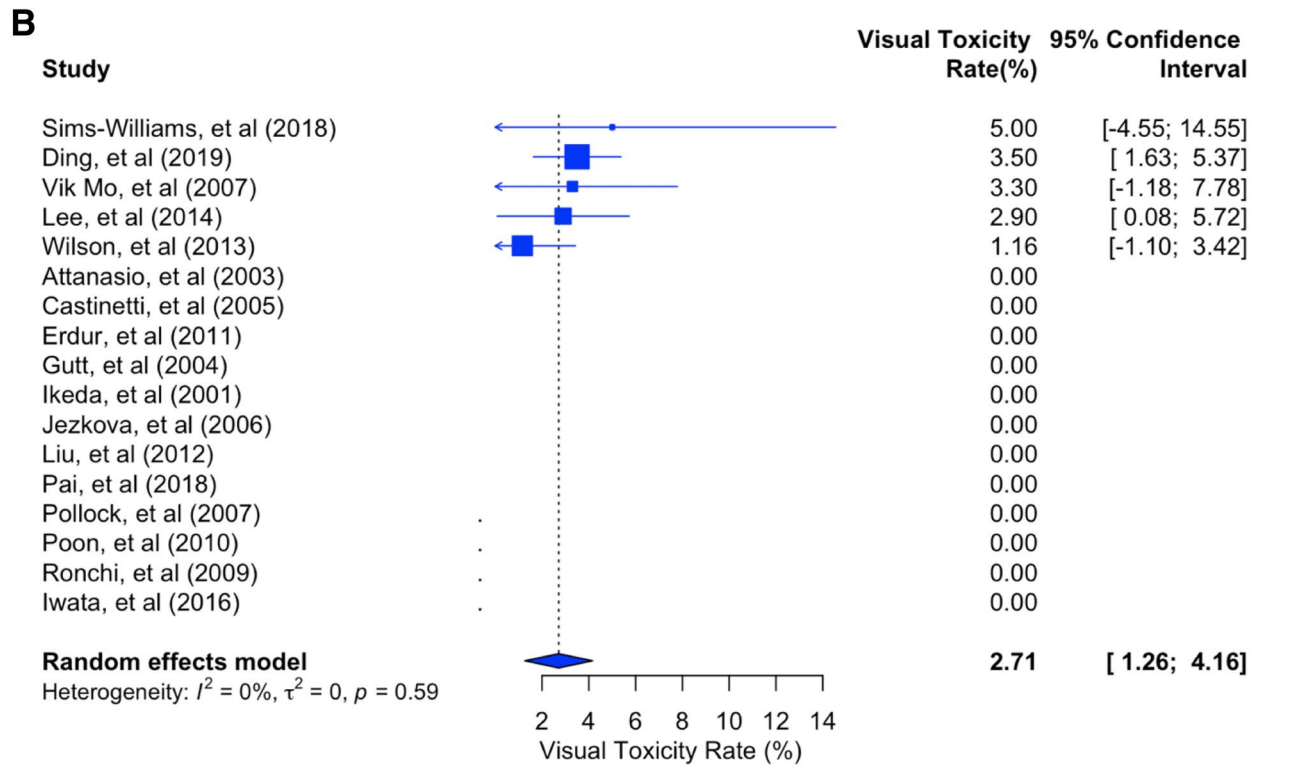


Fig. 4 Forest plots examining incidences of visual toxicity (**a**) and hypopituitarism (**b**) following SRS

Discussion

SRS is increasingly being utilized in both adjuvant and salvage settings for the management of acromegaly, and also provides an attractive option as definitive management for patients who are not surgical candidates and/or have poor biochemical control or symptoms secondary to mass effect should the adenoma be refractory to pharmacologic management. Multiple single and multi-institutional trials have reported on biochemical control, LC, and toxicity outcomes following SRS with variable follow-up. This study thus aimed to characterize ER, EC, LC, and visual and pituitary toxicities at time-specific to characterize both long-term efficacy and toxicity following SRS. Ten-year ER and EC was estimated to be approximately 56% and 70%, respectively, with 10-year LC exceeding 90% with visual and pituitary toxicities following SRS estimated to be < 3% and 30%, respectively. Visual toxicity was found to be associated with increasing margin prescription dose, with incidence rates with margin prescription doses of 20, 25, 30, and 35 Gy estimated to be approximately 1.2%, 3.3%, 5.3%, and 7.4%, respectively.

As noted above, improving biochemical control rates were noted over time, with 5- and 10-year estimated ER rates of 43.2% and 56.9% and 5- and 10 year EC rates of 55.0% and 69.7%. This temporal rise in both ER and EC was seen across all studies and may be indicative of a gradual benefit over time in biochemical control that requires follow-up over time to confirm. Of note, this finding is not limited to SRS, as a prior study by Minniti, et al., have also noted improving IGF-1 normalization rates over time of 23%, 42%, and 61% at 5-, 10-, and 15-years following conventionally fractionated radiation therapy to 45–50 Gy in 25–28 fractions for patients with persistent or recurrent acromegaly [42]. Moreover, the benefits of EC in acromegalic patients can translate to improvements in medical management, downstream effects on organ systems affected by acromegaly, and overall quality of life.

A prior meta-analysis by Abu Darbh, et al., aimed to compare outcomes following SRS for patients with acromegaly as compared to RT [9]. At last follow-up, the estimated ER rate was 52% with SRS as compared to 36% with RT, though this difference was not found to be significantly different ($p = 0.14$). These results are similar to the estimated 10-year ER rate of 56.9% (95% CI 47.5–66.4%) from our study. Interestingly, when looking at post-treatment IGF-1 levels, however, SRS was found to result in a statistically significantly higher reduction in IGF-1 levels (− 409.72 ng/mL) as compared to with RT (− 102 ng/mL) ($p = 0.002$). With regards to toxicity rates, lower rates of hypopituitarism were noted following SRS (32%) as compared to RT (51%), though did not meet statistical significance ($p = 0.05$). With respect to hypopituitarism rates, we noted a similar incidence of 26.8% (95% CI 16.9–36.7%) following SRS in studies included in our analysis. However, the authors discussed the possibility of selection bias in comparing outcomes with SRS as compared to RT as RT may be selected for larger or bilateral tumor remnants following resection with SRS most often utilized as a treatment modality for smaller tumors (often times < 2.5 cm) with adequate distance from the optic apparatus (generally 2–3 mm) [43]. A prior study examining whole sella SRS as compared to targeted SRS have noted higher rates of hypopituitarism (40.6% vs. 29.7%), albeit not achieving significance [44].

Prior studies have assessed whether certain clinical features may be prognostic with respect to biochemical control. Castinetti, et al., found that median pre-SRS GH ($p = 0.01$) and IGF-1 levels ($p = 0.047$) off of somatostatin analogous were significantly lower in patients that achieved biochemical remission (7.1 ng/mL and 495 ng/mL) as compared to patients that remained uncured (25.3 ng/mL and 673 ng/mL) [25]. Pre-SRS GH values have also been noted to be associated with ER by Ronchi, et al. [34]. A multi-institutional cohort study by Ding, et al., noted that cessation of IGF-1-suppressive medications was an independent predictor of durable ER (HR 2.49 (95% CI 1.21–5.11); $p = 0.01$) with factors found to be associated with recurrence after initial remission being prior resection (HR 0.21 (95% CI 0.06–0.74); $p = 0.01$) and maximum dose (HR 0.95 (95% CI 0.87–0.99); $p = 0.01$) [10]. Pollock, et al., have also found that cessation of IGF-1 and GH suppressive medications prior to SRS in addition to lower IGF-1 levels (< 2.25 × the upper normal limit adjusted for sex and age) were associated with improved rates of ER [32]. Another study by Pai, et al., previously noted that the absence of cavernous sinus invasion ($p = 0.041$) and lower baseline IGF-1 levels ($p = 0.019$) were significantly correlated with durable ER [30]. However, when examining the impact of pre-SRS IGF-1 levels or GH levels, we did not find that either were associated with durable ER. We were unable to assess the potential impact of the cessation of IGF-1/GH lower medications or cavernous sinus invasion as few studies reported these proportion of patients.

With regards to toxicities, Ding, et al., noted that targeting of the whole sella was associated with a higher risk of hypopituitarism following SRS ($p = 0.01$) and tumors treated with suprasellar extension were associated with an increased risk of optic apparatus injury ($p = 0.02$) [10]. Jezkova, et al., have also noted in their cohort of patients that no thyroid or sex hormone deficiencies were noted if the mean pituitary dose was less than 15 Gy and no cortisol deficiencies with mean pituitary doses less than 18 Gy [29]. Other studies have noted that new hypopituitarism may be associated with margin doses exceeding 25 Gy or GTVs greater than 2.5 cc [37]. In comparing SRS

to RT, Knappe, et al., have noted lower rates of either thyreotropic of adenocorticotropic hypopituitarism following SRS as compared to RT (HR 0.54 (95% CI 0.3–1.00); $p = 0.049$), consistent with the findings of the meta-analysis by Abu Darbh, et al. [9, 11].

Of note, experiences thus far reporting on hypofractionated SRS for the management of acromegaly are quite limited [40]. Iwata, et al., have reported the largest study thus far on the use of hypofractionated SRS in 3 or 5 fractions for 52 patients with acromegaly [40]. The 5-year ER rate was noted to be 17.3%, somewhat lower than other series have reported following single fraction SRS, with 5- and 10-year LC of 100% and 82.5%. With regards to toxicities, only 1/52 patients (1.9%) noted SRS-induced hypopituitarism following treatment with no visual toxicities reported. However, further studies are required to better characterize both the efficacy and safety of hypofractionated SRS as compared to single fraction SRS. Other promising avenues potentially include the utilization of proton therapy, particularly with respect to improving the therapeutic ratio with respect to visual or pituitary toxicities, though results following proton therapy with large patient cohorts with robust follow-up are pending [45].

Study limitations

Our analysis has limitations that merit discussion. The studies included in this meta-analysis were conducted at many institutions with differing treatment guidelines resulting in heterogeneity with respect to patient selection criteria and patient-level data that could be not accounted for, such as pre-SRS GH and IGF-1 levels, duration of biochemical control or LC prior to SRS, whether patients had ceased using somatostatin analogues prior to SRS, extent of initial resection (either gross total or subtotal resection), receipt of either prior surgery or radiation therapy, age, performance status, prescription dose, GTV, and extent of disease that was treated (cavernous sinus invasion, optic apparatus contact, and/or suprasellar extension). There also was heterogeneity noted in the estimates of both primary and secondary outcomes. As only one study examined hypofractionated SRS, we were unable to compare clinical outcomes between single fraction and hypofractionated SRS. The definitions for LC, ER, and EC varied to some degree depending upon the era of the study and clinical team that published the work. Similarly, with respect to hypopituitarism, studies varied in defining general hypopituitarism or specific hormonal deficiencies, and as such were not able to provide estimates of hormone specific toxicities. Our analysis also included retrospective experiences of SRS, which also raises the possibility of bias in our effect estimates [46].

Conclusions

SRS resulted in gradually improving ER and EC rates over time that approached 60% and 70%, respectively, 10 years following SRS. Higher margin prescription doses were found to be associated with increased incidences of SRS-related visual toxicity. Further studies are warranted examining the use of SRS for the management of acromegaly patients either after failed resection or as a primary treatment, particularly given encouraging and improving ER and EC rates over time following SRS with longer follow-up.

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Compliance with ethical standards

Ethical approval The procedures followed for the purposes of this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Helsinki Declaration (1964, amended in 1975, 1983, 1989, 1996 and 2000) of the World Medical Association.

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