

Single-session versus hypofractionated stereotactic radiosurgery for residual or recurrent craniopharyngiomas: a systematic review and meta-analysis

Bao Nguyen

University of Virginia Medical Center

Rodolfo Cortez

Beth Israel Deaconess Medical Center

Allen Lasoff

Beth Israel Deaconess Medical Center

Bardia Hajikarimloo

University of Virginia Medical Center

Onam Verma

University of Virginia Medical Center

Jason Sheehan

JPS2F@uvahealth.org

University of Virginia Medical Center

Research Article

Keywords: Craniopharyngioma, Stereotactic radiosurgery, hypofractionated stereotactic radiosurgery, single-session stereotactic radiosurgery, tumor control, progression-free survival

Posted Date: August 6th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10552930/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Purpose

Stereotactic radiosurgery (SRS), delivered as either single-session (SSRS) or hypofractionated (HSRS) regimen, is used to treat residual or recurrent craniopharyngioma. However, the comparative efficacy and safety of SSRS and HSRS remain unclear. This study aimed to systematically evaluate outcomes following SRS for residual or recurrent craniopharyngioma and compare outcomes between SSRS and HSRS.

Methods

PubMed, Embase, Scopus, and Cochrane were searched through April 2026. Eligible studies included ≥ 3 craniopharyngioma patients treated with SRS in ≤ 5 fractions with > 6 months of follow-up, and reported on outcomes. Target endpoints were pooled using random-effects models, and meta-regression was performed to identify outcome moderators.

Results

Seventeen studies (782 patients) met inclusion criteria. 655 patients (83.8%) received SSRS and 63 (8.1%) HSRS. Overall tumor control was 74.7% ($p = 0.002$). Among modality-attributable studies ($k = 12$ SSRS, $k = 3$ HSRS), pooled tumor control was 72.6% for SSRS versus 75.2% for HSRS ($p = 0.97$). Five-year progression-free survival was higher for HSRS (76.1% vs. 69.0%, $p = 0.76$). Visual deficit (9.7% SSRS vs. 10.3% HSRS, $p = 0.78$), endocrine/hypothalamic dysfunction (8.4% SSRS vs. 4.2% HSRS, $p = 0.33$) and cyst enlargement (7.9% SSRS vs. 13.3% HSRS, $p = 0.28$) did not differ significantly by modality. Higher biologically effective dose was associated with endocrine/hypothalamic dysfunction.

Conclusion

SRS provides favorable tumor control for craniopharyngioma, and HSRS achieves short- and mid-term outcomes comparable to SSRS despite being reserved for anatomically higher-risk tumors. Nevertheless, limited comparative data and shorter HSRS follow-up warrant prospective, multicenter investigations with patient-level data.

Introduction

Craniopharyngiomas are rare, slow-growing tumors arising from epithelial remnants of the Rathke pouch, typically within the sellar or parasellar regions [1]. Although histologically benign, they can cause substantial morbidity through compression of the optic apparatus, hypothalamus, and pituitary stalk,

resulting in visual and endocrinologic dysfunction [1]. They account for 2% to 5% of primary intracranial neoplasms and up to 15% of pediatric brain tumors [2].

The optimal management of craniopharyngioma remains controversial. Surgery provides tissue diagnosis and rapid decompression, with treatment strategies including gross total resection (GTR) or subtotal resection (STR) followed by radiotherapy [1]. Although some retrospective studies suggest superior local control after GTR [3, 4], complete resection is often limited by tumor adherence to critical neural and vascular structures [5] and may still be followed by recurrence [6]. Consequently, adjuvant radiotherapy is frequently used to improve long-term control after incomplete resection.

For residual or recurrent craniopharyngioma, stereotactic radiosurgery (SRS) is an established treatment associated with favorable tumor control and clinical outcomes [7]. SRS may be delivered in a single session (SSRS) or in two to five fractions as hypofractionated SRS (HSRS) [8]. Although SSRS may increase toxicity risk for larger lesions or tumors near the optic apparatus, HSRS may permit delivery of an effective dose while reducing exposure to adjacent normal tissue [8].

Evidence for SRS in craniopharyngioma is derived predominantly from small, single-center retrospective series, and direct comparisons between SSRS and HSRS are uncommon. It therefore remains unclear whether fractionation independently affects tumor control and toxicity or whether observed differences reflect patient selection, tumor characteristics, and treatment parameters. Fathollahi et al. pooled outcomes from 32 studies comprising 926 patients and identified moderators including tumor volume, solid tumor composition, and prior surgery, but did not stratify outcomes by fractionation schedule [9]. To our knowledge, no previous meta-analysis has directly compared SSRS and HSRS for residual or recurrent craniopharyngioma.

We therefore performed a systematic review and meta-analysis to: (1) estimate pooled tumor control, progression-free survival, and treatment-related toxicity after SRS; (2) compare the efficacy and safety of SSRS and HSRS; and (3) explore potential outcome moderators through meta-regression, with particular emphasis on biologically effective dose (BED), a fractionation-adjusted dose metric not previously evaluated as a moderator of craniopharyngioma SRS outcomes.

Methods

Literature search strategy

This study was performed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. We searched PubMed, Embase, Scopus, and Cochrane Clinical Trials database from inception to April 11, 2026, for articles reporting the outcomes in patients undergoing single-fraction stereotactic radiosurgery or hypofractionated stereotactic radiation therapy for residual or recurrent craniopharyngioma. The search terms utilized for this meta-analysis were:

(Craniopharyngioma) AND ("stereotactic radiosurgery" OR SRS OR "Gamma Knife" OR GKRS OR LINAC OR "linear accelerator" OR CyberKnife) AND (single OR hypofractionated OR fractionated OR

fractionation). Reference lists of the relevant articles were also reviewed manually to identify any additional eligible studies.

The primary endpoint of this study was long-term tumor control at the last available follow-up, defined as the absence of radiographic disease progression. Secondary endpoints included progression-free survival, overall survival, and treatment-related toxicity including visual deficit, endocrine or hypothalamic dysfunction, and cyst enlargement requiring intervention. Progression-free survival was defined as the actuarial proportion of patients alive without radiographic disease progression, with death from any cause treated as an event equivalent to progression. Overall survival was defined as the proportion of patients alive regardless of tumor status. Visual toxicity was defined as any new or worsening visual impairment after radiotherapy. Endocrine or hypothalamic toxicity included new or progressive hypopituitarism, diabetes insipidus, or other hypothalamic dysfunctions. Cyst enlargement was defined as an increase in cystic component volume or diameter on follow-up imaging requiring intervention beyond observation.

Study selection

Two reviewers (B.L.N and R.M.C) independently screened the identified articles according to pre-defined eligibility criteria, with disagreements resolved through discussion. Studies were included if they: (1) were published in English; (2) included patients of any age treated with single-session or hypofractionated stereotactic radiosurgery for residual or recurrent craniopharyngioma; (3) used SRS as a primary, adjuvant, or salvage therapy; and (4) reported adequate tumor-control and clinical-outcome-data.

Studies were excluded if they: (1) were non-original investigations including reviews and commentaries; (2) published in a language other than English; (3) included fewer than five participants; (4) lacked tumor size or volume data; (5) lacked sufficient outcome data by treatment modality; (6) documented concurrent secondary interventions during follow-up. Given the rarity of craniopharyngioma, however, all otherwise eligible studies with more than six months of follow-up were included regardless of sample size. According to the American Society for Radiation Oncology and the American College of Radiology guidelines, SRS was defined as radiation therapy delivered to a predefined target volume with curative intent, in five or fewer fractions, at approximately 1 mm targeting accuracy [11]. Studies using more than five fractions were excluded. No restrictions were placed on the specific radiosurgery platform or device. For overlapping or duplicate cohorts, only the most recent report was retained, when it substantially the same patient population.

Data extraction

The following variables were extracted from each included study: patient characteristics, including the number of patients and lesions, age, sex, histologic subtype, extent of prior resection, and residual

versus recurrent disease; tumor characteristics, including volume, composition, suprasellar location, and proximity to the optic apparatus; treatment characteristics, including treatment modality and platform, marginal dose, prescription isodose line, number of fractions for HSRS, dose per fraction, BED, and the role of SRS; and clinical outcomes, including overall tumor control, solid-component control, and cyst control. Follow-up variables included 5-year progression-free survival, 5-year survival, overall survival, and follow-up duration. Treatment-related toxicities included new or worsened visual deficits, new endocrine or hypothalamic dysfunction, and cyst enlargement requiring intervention.

Quality assessment

A modified version of the Joanna Briggs Institute (JBI) Critical Appraisal tool was adopted from Fathollahi et al. [9] and used to evaluate the quality of the included studies (see Supplementary Table 1 for the full item-by-item rationale). Two reviewers (B.L.N and R.M.C) independently performed quality assessment, resolving any discrepancies through discussion.

Statistical analysis

Meta-analyses were performed in R version 4.6.1 using the metafor package. Raw proportions were logit-transformed before pooling, and back-transformed pooled rates with 95% CIs were reported. Random-effects models using the restricted maximum likelihood estimator served as the primary pooling method, with a continuity correction of 0.5 applied to studies reporting zero events. Heterogeneity was quantified using I^2 and τ^2 , and its statistical significance was assessed using Cochran's Q test. Publication bias was assessed via Egger's test and funnel plots, with trim-and-fill used to generate bias-adjusted estimates where indicated.

The SSRS-versus-HSRS comparison excluded two mixed-cohort studies and was restricted to studies reporting modality-specific events ($k = 12$ for SSRS; $k = 3$ for HSRS). Subgroup difference evaluated via logit-based mixed-effects meta-regression.

Exploratory meta-regression to evaluate BED as a continuous moderator of tumor control and relevant clinical outcomes. BED was calculated using the linear-quadratic model ($BED = nd[1 + d/(\alpha/\beta)]$) at α/β values of 2 (BED2) and 10 (BED10). An α/β of 10 was used for early-responding tumor tissue, whereas an $\alpha/\beta = 2$ characterizes late-responding tissue, including the optic apparatus and adjacent CNS structures [11]. This analysis included 15 single-arm SSRS or HSRS studies with a calculable BED value. Two mixed-cohort studies [15, 16] were excluded because their pooled tumor-control outcomes could not be assigned to a single BED value. The findings are presented as a weighted scatterplot with unadjusted regression lines and should not be interpreted as definitive dose-response relationships.

Results

Study characteristics

The database search identified 1,196 articles. After duplicate removal, 796 papers underwent title and abstract screening, of which 56 were assessed in full text. Thirty-nine studies were excluded because they did not report the outcomes of interest ($n = 22$), lacked follow-up duration data ($n = 12$), included three or fewer patients ($n = 3$), and contained potentially overlapping cohorts (2 studies). Ultimately, 17 studies met the inclusion criteria and were included in the systematic review and meta-analysis [12–28]. The study selection process is depicted in the PRISMA flow diagram (Fig. 1), and study characteristics are presented in Table 1.

Quality assessment

All 17 included studies met the core JBI criteria for diagnostic confirmation, consistent case definition, and appropriate statistical analysis, supporting reliability of the pooled tumor-control and toxicity estimates. Reporting was less consistent for secondary domains, particularly participant demographic and clinical-history, and tumor composition. Histologic composition was incompletely reported in 7 studies. In contrast, the primary pooled analyses of tumor control, progression-free survival, and toxicity incorporated the full or near-full study set and were less affected by these reporting limitations. Item-level JBI scores for each study are provided in Supplementary Table 1.

Patient characteristics

The 17 comprised 782 patients (Table 1). Twelve studies [17–28] reported the use of SSRS, three [12–14] reported HSRS, and two [15, 16] included mixed SSRS- and HSRS cohorts without treatment specific outcomes. Overall, 655 patients (83.8%) underwent SSRS and 63 (8.1%) underwent HSRS. The remaining patients came from the mixed-cohort studies and were included only in the overall pooled analyses. The mean age of the study population was 35.0 years, and 404 patients (52.1%) were males (Table 2).

Overall tumor control

Seventeen studies with 782 patients reported overall tumor control [12–28]. The pooled tumor control rate was 74.7% (95% CI, 67.6–80.6%), with moderate heterogeneity ($\tau^2 = 0.2849$, $I^2 = 68.8\%$, $Q_{16} = 36.96$, $p = 0.002$). Among 15 studies with modality-attributable outcomes, pooled tumor control was 72.6% (95% CI, 64.9–79.1%) for SSRS ($k = 12$) and 75.2% (95% CI, 46.3–91.4%) for HSRS ($k = 3$), with no significant difference by mixed-effects moderator test ($p = 0.97$). Egger's test suggested publication bias ($p = 0.015$). Sensitivity analysis identified no outlying studies. Meta-regression did not identify tumor volume, solid composition, or BED (BED2, BED10) as significant predictors of overall tumor control ($p = 0.52$, $p = 0.068$, $p = 0.57$, $p = 0.45$, respectively).

3-year tumor control

Four studies with 259 patients [15, 18, 23, 24] reported 3-year tumor control (Supplementary Fig. 1). The pooled rate was 78.8% (95% CI, 72.8–83.8%) with low heterogeneity ($\tau^2 = 0.0132$, $I^2 = 10.2\%$, $Q_3 = 2.60$, p

= 0.46). Egger's test was not significant ($p = 0.22$). "Lee, 2014" was identified as an influential. Its removal increased the pooled estimate to 82.3% (95%CI, 74.7–87.9%, $I^2 = 0\%$), compared with the original estimate of 78.8% (95% CI, 72.8–83.8%). Meta-regression showed no significant association between 3-year tumor control and tumor volume ($p = 0.20$) or solid composition ($p = 0.33$).

5-year tumor control

Five studies with 279 patients [15, 18, 22, 23, 24] reported tumor control at 5 years, with a pooled proportion of 69.5% (95% CI, 63.8–74.6%) and no significant heterogeneity ($\tau^2 = 0$, $I^2 = 0\%$, $Q_4 = 0.83$, $p = 0.93$). Egger's test for publication bias was not significant ($p = 0.39$). Sensitivity analysis identified no outlying studies. Meta-regression found no significant association between tumor volume and 5-year tumor control ($p = 0.89$) or between percent solid composition and 5-year tumor control ($p = 0.93$).

Overall survival

Fifteen studies with 737 patients reported overall survival at last follow-up [12–24, 27, 28]. The pooled overall survival rate was 87.7% (95% CI = 81.2–92.2%), with substantial heterogeneity ($\tau^2 = 0.51$, $I^2 = 70.6\%$, $Q_{14} = 47.6$, $p < 0.001$). Egger's test did not show significant publication bias for the studies ($p = 0.24$). "Buwaider, 2025" was identified as an outlier. Its removal resulted in an overall survival rate of 88.8% (95% CI = 85.1–91.6%) and reduced heterogeneity to $I^2 = 26.1\%$. In a post-hoc moderator analysis, pooled overall survival was 85.3% (95% CI 77.5–90.7%) for SSRS ($k = 10$) versus 97.7% (95% CI 87.9–99.6%) for HSRS ($k = 3$), with a significant subgroup difference ($p = 0.034$). Meta-regression analysis revealed no significant association between overall survival and tumor volume ($p = 0.80$), marginal dosage ($p = 0.57$), solid tumor composition ($p = 0.45$), cystic tumor composition ($p = 0.81$), or prior radiotherapy ($p = 0.23$).

3-year progression-free survival

Five studies comprising 358 patients [14, 15, 20, 21, 24] reported 3-year progression-free survival. The pooled rate was 79.5% (95% CI, 66.5–88.3%) with moderate heterogeneity ($\tau^2 = 0.3496$, $I^2 = 68.9\%$, $Q_4 = 10.26$, $p = 0.04$). Egger's test was not significant ($p = 0.27$), although its power was limited by the small number of studies. "Gupta, 2024" was identified as an influential study and its removal reduced the pooled 3-year progression-free survival of 73.7% (95% CI, 68.5–78.3%, $I^2 = 0\%$), compared with the original 79.5% (95% CI, 66.5–88.3%). Meta-regression found no significant association between 3-year progression-free survival and tumor volume ($p = 0.92$), marginal dose ($p = 0.18$), cystic composition ($p = 0.29$), or solid composition ($p = 0.92$).

5-year progression-free survival

Nine single-arm studies reported 5-year progression-free survival [12, 14, 17, 19, 20, 21, 22, 23, 24]. Among 7 SSRS, the pooled 5-year progression-free survival was 69.0% (95% CI, 56.3–79.5%), with high heterogeneity ($I^2 = 83.4\%$). Among the two HSRS studies [12, 14], the pooled rate was 76.1% (95% CI, 30.5–95.8%), also with high heterogeneity ($I^2 = 81.1\%$). Mixed-effects moderator test showed no

statistically significant difference between modalities ($p = 0.76$), with substantial residual heterogeneity ($I^2 = 86.2\%$, $Q_7 = 25.68$, $p < 0.001$). Although HSRS trended toward a higher 5-year progression-free survival than SSRS (76.1% vs. 69.0%), the wide confidence interval around the HSRS estimate precluded meaningful conclusion about a modality-driven difference.

Visual deficit

Seventeen studies with 782 patients [12–28] reported new or worsened visual deficit. The pooled rate was 9.0% (95% CI 5.3–14.9%), with substantial heterogeneity ($\tau^2 = 0.8153$, $I^2 = 72.3\%$, $Q_{16} = 52.19$, $p < 0.001$). Among the 15 studies with modality-attributable outcomes, pooled visual deficit rates were 9.7% (95% CI, 5.3–17.0%) for SSRS ($k = 12$) versus 10.3% (95% CI, 1.9–40.4%) for HSRS ($k = 3$) with no significant difference as per mixed-effects moderator test ($p = 0.78$). Egger's test suggested publication bias ($p = 0.006$). Sensitivity analysis identified "Tsugawa, 2020" as an outlier. Its removal increased the pooled rate to 11.5% (95% CI, 7.3–17.5%, $I^2 = 58.3\%$), compared with the original 9.0% (95% CI, 5.3–14.9%). Meta-regression found no significant association between visual deficit and tumor volume ($p = 0.89$), marginal dose ($p = 0.14$), percent cystic composition ($p = 0.43$), or percent solid composition ($p = 0.79$).

Endocrine or hypothalamic dysfunction

Sixteen studies [12, 13, 15–28] with 753 patients reported new endocrine or hypothalamic dysfunction. The pooled proportion under the random-effects model was 7.1% (95% CI, 4.4–11.1%), with moderate heterogeneity ($\tau^2 = 0.368$, $I^2 = 46.2\%$, $Q_{15} = 24.47$, $p = 0.058$). Among fourteen studies with modality-attributable outcomes ($k = 11$ SSRS, $k = 3$ HSRS), pooled endocrine/hypothalamic dysfunction was 8.4% (95% CI, 5.0–13.6%) for SSRS versus 4.2% (95% CI, 1.2–13.6%) for HSRS ($p = 0.33$). Egger's test for publication bias was not significant ($p = 0.21$). Sensitivity analysis identified no outlying studies. Meta-regression found no significant association between endocrine/hypothalamic dysfunction and tumor volume ($p = 0.89$), marginal dose ($p = 0.60$), cystic composition ($p = 0.78$), or solid composition ($p = 0.65$). However, higher BED and dose per fraction were positively associated with endocrine or hypothalamic dysfunction: BED2 (slope = 0.038 per Gy, $p = 0.0008$, $R^2 \approx 100\%$), BED10 (slope = 0.117 per Gy, $p = 0.0085$, $R^2 \approx 94\%$), and dose per fraction (slope = 0.227 per Gy, $p = 0.0051$, $R^2 \approx 80\%$). Predicted event rates increased from approximately 3.3% to 18.7% across the observed range of BED2 (61–112 Gy), 4.5% to 15.2% across BED10 (22–34 Gy), and 2.4% to 12.7% across dose per fraction (6–14 Gy/fraction).

Cyst enlargement requiring intervention

Ten studies ($n = 373$) reported cyst enlargement requiring intervention, with 40 events overall [12, 13, 15, 16, 17, 19, 21, 23, 25, 26]. The pooled rate was 10.5% (95% CI, 5.4–19.4%), with substantial heterogeneity ($\tau^2 = 0.8187$, $I^2 = 70.1\%$, $Q_9 = 29.06$, $p = 0.001$). Among eight studies with modality-attributable outcomes ($k = 5$ SSRS, $k = 3$ HSRS), pooled enlargement was 7.9% (95% CI, 5.1–12.1%; $I^2 = 0\%$) for SSRS versus 13.3% (95% CI, 1.8–56.7%; $I^2 = 81.0\%$) for HSRS ($p = 0.28$). Egger's test for publication bias was not significant ($p = 0.24$). Sensitivity analysis identified no outlying studies. Meta-regression showed no significant association between cyst enlargement and tumor volume ($p = 0.69$), cystic composition ($p =$

0.97), or solid composition ($p = 0.56$). Higher marginal dose was associated with nonsignificant trend toward lower cyst enlargement ($p = 0.093$).

Discussion

To our knowledge, this is the first meta-analysis to directly compare SSRS and HSRS for residual or recurrent craniopharyngiomas. Across seventeen studies comprising 782 patients, the overall pooled tumor control rate was 74.7% (95% CI, 67.6–80.6%, $p = 0.002$). Among the fifteen studies with modality-attributable outcomes (12 SSRS and 3 HSRS), pooled tumor control was 72.6% (95% CI, 64.9–79.1%) after SSRS versus 75.2% (95% CI, 46.3–91.4%) after HSRS ($p = 0.97$). Five-year progression-free survival rate was higher in the HSRS group than in the SSRS group (76.1% vs. 69.0%, respectively), though the wide confidence interval around the HSRS estimate (95% CI, 30.5–95.8%, $p = 0.76$) precluded a definitive conclusion. Treatment-related toxicity was broadly comparable between modalities, with overlapping pooled rates of visual deficit, endocrine dysfunction, and cyst enlargement requiring intervention. Notably, our meta-regression analyses suggested that higher BED and dose per fraction were associated with increased risk of post-treatment endocrine/hypothalamic dysfunction.

Residual tumor burden remains an important determinant of long-term disease control. A recent meta-analysis comparing GTR alone with STR followed by adjuvant radiotherapy after endoscopic endonasal surgery reported a significantly lower recurrence rate after GTR (10%) radiotherapy [29]. Nevertheless, complete resection is often limited by adherence to critical structures, underscoring the role of adjuvant radiation in residual or recurrent disease. In the largest published meta-analysis of SRS for craniopharyngioma to date, encompassing 32 studies and 926 patients, the pooled overall tumor control rate was 76.1%, closely mirroring the present findings, though that analysis did not stratify outcomes by fractionation schedule [9]. In the present analysis, tumor control did not differ significantly between SSRS and HSRS ($p = 0.97$). This finding is consistent with prior comparative reports. Losa et al. found that multisession Gamma Knife radiosurgery was not less effective than single-session treatment, despite being preferentially used for tumors considered too close to the optic apparatus for SSRS [12]. These data suggest that HSRS may achieve short- and intermediate-term tumor control comparable to SSRS, even in anatomically higher-risk tumor. However, the small number of HSRS studies and limited arm-level data preclude definitive conclusions. A related but distinct technique not evaluated in the present analysis is stereotactic intracavitary brachytherapy using colloidal phosphorus-32, which delivers radiation directly to the internal cyst wall of predominantly cystic craniopharyngiomas. In a series of 53 patients, this approach achieved actuarial tumor cyst control of 86.0% at 12, 24, and 60 months with a low rate of permanent morbidity [30]. Intracavitary brachytherapy may therefore represent a minimally invasive option for selected cystic tumors, either alongside or instead of conventional SRS.

The numerically higher 5-year progression-free survival observed after HSRS may partly reflect the radiobiologic advantages of fractionation. Compared to single-session treatment, fractionation reduces the toxicity to late-responding normal tissues with low α/β ratios and may also enhance tumor radiosensitivity through cell cycle redistribution and reoxygenation between fractions [31].

Craniopharyngiomas have been characterized as late-responding tissue with a low α/β ratio (approximately 2–3 Gy) [32]. Fractionation may therefore permit delivery of a therapeutically effective dose while limiting exposure to the optic apparatus and other adjacent structures. This principle is consistent with established optic-pathway dose constraints. Milano et al. reported that maximum point doses associated with less than 1% risk of radiation-induced optic neuropathy were approximately 10 Gy in a single fraction, 20 Gy in 3 fractions, and 25 Gy in 5 fractions [8]. Similar dose-response pattern has been observed in other parasellar tumors. In a recent single-institution analysis of parasellar meningioma, a BED threshold greater than 68 Gy was independently associated with improved tumor control [33]. Similarly, Dho et al. likewise identified BED2 greater than 80 Gy as an independent predictor of overall response [14]. These findings support the concept that BED may better characterize treatment intensity than marginal dose or fraction number alone.

Several individual studies included in this analysis point toward a common underlying explanation for the similarity in outcomes between modalities. Dho et al. identified tumor location and distance from the optic nerve as predictors of progression-free survival, with parasellar location and greater optic-nerve distance associated with improved outcomes [14]. Kamogawa et al. reported that proximity to the optic apparatus was the principal determinant of treatment selection between SSRS and HSRS [16], whereas Iwata et al. [15]. Collectively, these findings suggest that proximity to critical structures influences both modality selection and the dose that can be safely delivered. However, this interpretation should remain cautious. Several included studies suggest that anatomy and achievable dose may be more important than fractionation schedule itself. Dho et al. identified tumor location and distance from the optic nerve as significant predictors of progression-free survival, with parasellar location and greater optic nerve distance associated with improved outcomes [14]. Kamogawa et al. reported that proximity to the optic apparatus was the principal determinant of treatment selection between SSRS and HSRS [16], and whereas Iwata et al. identified tumor volume as the primary predictor of treatment failure in a mixed cohort treated with single- and multisession CyberKnife radiosurgery [15]. Collectively, these findings suggest that anatomical proximity to critical structures, and the achievable dose that proximity permits, may be the dominant driver of both treatment selection and outcome in this disease. Accordingly, the comparable outcomes observed between SSRS and HSRS may reflect appropriate selection of fractionation according to anatomic risk rather than an absence of a true fractionation effect. However, this interpretation should remain cautious. All three HSRS studies contributing to this comparison reported zero mortality events, and follow-up duration varied across the comparison, making a survival-duration confound at least as plausible an explanation as a true modality effect. The nominally higher overall survival estimate after HSRS may therefore reflect differences in follow-up and patient selection rather than a true survival benefit.

Treatment-related toxicity was broadly comparable between modalities. The pooled rate of new endocrine or hypothalamic dysfunction was 7.1%, exceeding the rates reported in the largest prior SRS meta-analysis, which analyzed pituitary dysfunction, diabetes insipidus, and hypothalamic dysfunction separately and reported rates of 2.2%, 0.8%, and 0.7%, respectively [10]. This discrepancy likely reflects differences in outcome definition and study population rather than a true divergence in treatment. The

present analysis combined pituitary and hypothalamic endpoints into a single composite outcome, whereas Fathollahi et al. reported them separately and included a partially different study set [9]. Comparisons across studies should therefore account for heterogeneity in endpoint definitions [9]. Rates of new or worsened visual deficit were similar between SSRS and HSRS, although the HSRS estimate was numerically higher and had a wide confidence interval. Visual deterioration after radiosurgery requires close ophthalmologic surveillance. When caused by cyst re-expansion rather than direct radiation injury, management may include cyst aspiration or repeat intervention [34]. Corticosteroids may be used when peritumoral edema contributes to optic-pathway compression [35]. Because the risk of radiation-induced optic neuropathy increases with single-fraction doses exceeding approximately 10 Gy, staged or volume-adaptive strategies have been proposed to limit the dose delivered near the optic apparatus while maintaining treatment intensity within the remainder of the tumor [36–38]. These approaches have not been systematically evaluated in craniopharyngioma and warrant further investigation.

The most notable exploratory finding was the positive association between BED, dose per fraction, and endocrine or hypothalamic dysfunction, whereas tumor control was not associated with these dose metrics. These findings suggest that dose escalation may increase endocrine toxicity without a corresponding improvement in tumor control. This relationship is consistent with evidence from the pituitary adenoma literature identifying the hypothalamic-pituitary axis as dose-sensitive. In 232 patients treated with single-fraction SRS for pituitary adenoma, Xu et al. identified higher margin dose and suprasellar extension as independent predictors of new hypopituitarism [39]. In a subsequent multicenter analysis, Pomeraniec et al. found that pituitary-stalk dose, rather than tumor dose, was a principal determinant of delayed endocrine dysfunction after SRS [40]. Similarly, Vatner et al. reported a continuous increase in endocrine-deficiency risk with increasing hypothalamic-pituitary dose among pediatric and young adult patients receiving fractionated radiotherapy, irrespective of tumor type or location [41]. These studies support the hypothalamic-pituitary axis as a dose-limiting structure across single-session and fractionated treatment. To our knowledge, this relationship has not previously been examined specifically in craniopharyngioma using a fractionation-adjusted dose metric. BED incorporates both total dose and fraction size, whereas marginal dose alone does not account for the distinct biologic effects of delivering the same nominal dose in 1 versus multiple fractions. If confirmed using patient-level data, these findings may support the use of BED-based constraints for the hypothalamic-pituitary axis when selecting between SSRS and HSRS. Nevertheless, the present findings are hypothesis-generating. The analysis was based on study-level data, included relatively few studies, and could not exclude confounding by indication, whereby higher doses may have been used for tumors with greater baseline endocrine risk because of their anatomy or clinical characteristics.

This meta-analysis has several limitations. Most included studies were retrospective, single-center, and English-language, with considerable heterogeneity in dose prescription, fractionation criteria, and tumor-control definitions; tumor-composition data were incomplete in 7 of 17 studies. No study distinguished in-field from out-of-field recurrence, limiting causal interpretation of treatment failure, and the SSRS-versus-HSRS comparison relied on an imbalanced, non-randomized set of studies (12 vs. 3) that

included two mixed-cohort studies inseparable by modality, so the apparent equivalence may reflect confounding by indication rather than a true absence of fractionation effect. Median follow-up was longer for SSRS than HSRS (46.4 vs. 38.3 months; $p = 0.279$), which may have reduced detection of late recurrence or toxicity in the HSRS group. Egger's test suggested publication bias for overall tumor control and visual deficit, and BED analyses relied on study-level rather than patient-level data.

Conclusion

HSRS appears feasible and may provide short- and mid-term tumor control and toxicity outcomes comparable to SSRS, despite being preferentially used for anatomically high-risk tumors near the optic apparatus. However, the limited number of comparative studies, imbalance between treatment groups, and shorter follow-up in HSRS cohorts precludes definitive conclusion. Prospective, multicenter studies using patient-level data are needed to clarify the relative efficacy, safety, and optimal implications of SSRS and HSRS for residual or recurrent craniopharyngioma.

Declarations

Acknowledgments None.

Author contributions BLN conceptualized and designed the study under the supervision of JPS. RMC and AL designed and conducted the literature search in PubMed, Embase, Scopus, and Cochrane Clinical Trials, performed record deduplication, and independently screened titles, abstracts, and full texts according to the eligibility criteria. Data extraction was independently and jointly performed by BLN and RMC. Risk of bias assessment was performed by BLN. JPS supervised the screening, extraction, and quality assessment processes, resolved any discrepancies through discussion, and ensured methodological consistency. BLN, RMC, and AL drafted the manuscript. RMC and AL performed statistical analysis. BH and OV contributed to data interpretation and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability The dataset extracted and analyzed for this meta-analysis is available from the corresponding author on reasonable request.

Ethical approval Waived, since this was a review and meta-analysis.

Consent to participate Not applicable, no patients.

Consent to publish Not applicable, No patients.

Competing Interest The authors declare no competing interests.

References

1. Karavitaki N, Cudlip S, Adams CB, Wass JA, Craniopharyngiomas (2006) *Endocr Rev* 27(4):371–397. <https://doi.org/10.1210/er.2006-0002>
2. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM (1998) The descriptive epidemiology of craniopharyngioma. *J Neurosurg* 89(3):547–551. <https://doi.org/10.3171/jns.1998.89.4.0547>
3. Wang G, Zhang X, Feng M, Guo F (2018) Comparing survival outcomes of gross total resection and subtotal resection with radiotherapy for craniopharyngioma: a meta-analysis. *J Surg Res* 226:131–139. <https://doi.org/10.1016/j.jss.2018.01.029>
4. Akinduro OO, Izzo A, Lu VM et al (2019) Endocrine and visual outcomes following gross total resection and subtotal resection of adult craniopharyngioma: systematic review and meta-analysis. *World Neurosurg* 127:e656–e668. <https://doi.org/10.1016/j.wneu.2019.03.239>
5. Godil SS, Tosi U, Gerges M et al (2022) Long-term tumor control after endoscopic endonasal resection of craniopharyngiomas: comparison of gross-total resection versus subtotal resection with radiation therapy. *J Neurosurg* 136(5):1347–1355. <https://doi.org/10.3171/2021.5.JNS202011>
6. Park HJ, Dho YS, Kim JH, Kim JW, Park CK, Kim YH (2020) Recurrence rate and prognostic factors for adult craniopharyngiomas in long-term follow-up. *World Neurosurg* 133:e211–e217. <https://doi.org/10.1016/j.wneu.2019.08.209>
7. Niranjana A, Kano H, Mathieu D, Kondziolka D, Flickinger JC, Lunsford LD (2010) Radiosurgery for craniopharyngioma. *Int J Radiat Oncol Biol Phys* 78(1):64–71. <https://doi.org/10.1016/j.ijrobp.2009.07.1693>
8. Milano MT, Grimm J, Soltys SG et al (2021) Single- and multi-fraction stereotactic radiosurgery dose tolerances of the optic pathways. *Int J Radiat Oncol Biol Phys* 110(1):87–99. <https://doi.org/10.1016/j.ijrobp.2018.01.053>
9. Fathollahi MA, Soltani Khaboushan A, Iranmehr A, Dabbagh Ohadi MA, Park DJ, Chang SD (2025) Stereotactic radiosurgery for craniopharyngioma: a systematic review and meta-analysis. *Neurosurg Rev* 49(1):2 Published 2025 Nov 15. <https://doi.org/10.1007/s10143-025-03896-1>
10. Seung SK, Larson DA, Galvin JM et al (2013) American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) practice guideline for the performance of stereotactic radiosurgery (SRS). *Am J Clin Oncol* 36(3):310–315. <https://doi.org/10.1097/COC.0b013e31826e053d>
11. Fowler JF (1989) The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 62(740):679–694. <https://doi.org/10.1259/0007-1285-62-740-679>
12. Losa M, Pieri V, Bailo M et al (2018) Single fraction and multisession Gamma Knife radiosurgery for craniopharyngioma. *Pituitary* 21(5):499–506. <https://doi.org/10.1007/s11102-018-0903-5>
13. Samanci Y, Essibayi MA, Askeroglu MO, Budak M, Karaköse F, Peker S (2023) Frameless Hypofractionated Gamma Knife Radiosurgery for Residual or Recurrent Craniopharyngioma.

- Neurosurgery 93(1):102–111. <https://doi.org/10.1227/neu.0000000000002382>
14. Dho YS, Kim YH, Kim JW et al (2018) Optimal strategy of gamma knife radiosurgery for craniopharyngiomas. *J Neurooncol* 140(1):135–143. <https://doi.org/10.1007/s11060-018-2943-0>
 15. Iwata H, Tatewaki K, Inoue M et al (2012) Single and hypofractionated stereotactic radiotherapy with CyberKnife for craniopharyngioma. *J Neurooncol* 106(3):571–577. <https://doi.org/10.1007/s11060-011-0693-3>
 16. Kamogawa M, Shuto T, Matsunaga S (2022) Effects of two different radiotherapies for craniopharyngiomas using stereotactic radiosurgery/ stereotactic radiotherapy or fractionated stereotactic radiotherapy. *Surg Neurol Int* 13:563 Published 2022 Dec 2. https://doi.org/10.25259/SNI_802_2022
 17. Buwaider A, Kananathan M, Tabari S et al (2025) Long-Term Outcomes After Gamma Knife Radiosurgery Treatment of Craniopharyngiomas: A Swedish Nationwide Cohort With a Mean Follow-Up of 21 Years. *Neurosurgery* 97(3):657–670 Published 2025 Mar 5. <https://doi.org/10.1227/neu.0000000000003394>
 18. Ogino A, Niranjana A, Kano H, Flickinger JC, Lunsford LD (2021) Optimizing stereotactic radiosurgery in patients with recurrent or residual craniopharyngiomas. *J Neurooncol* 154(1):113–120. <https://doi.org/10.1007/s11060-021-03806-7>
 19. Pikis S, Mantziaris G, Lavezzo K, Dabhi N, Sheehan J (2021) Stereotactic radiosurgery for craniopharyngiomas. *Acta Neurochir (Wien)* 163(11):3201–3207. <https://doi.org/10.1007/s00701-021-04990-1>
 20. Tsugawa T, Kobayashi T, Hasegawa T et al (2020) Gamma Knife Surgery for Residual or Recurrent Craniopharyngioma After Surgical Resection: A Multi-institutional Retrospective Study in Japan. *Cureus* 12(2):e6973 Published 2020 Feb 12. <https://doi.org/10.7759/cureus.6973>
 21. Gupta S, Agrawal D, Kedia S, Kale SS (2024) Should post-operative stereotactic radiosurgery be the standard of care in Craniopharyngioma patients? *World Neurosurg X* 22:100327 Published 2024 Feb 25. <https://doi.org/10.1016/j.wnsx.2024.100327>
 22. Lee BM, Cho J, Kim DS et al (2025) Differences in Treatment Outcomes Depending on the Adjuvant Treatment Modality in Craniopharyngioma. *Yonsei Med J* 66(3):141–150. <https://doi.org/10.3349/ymj.2023.0566>
 23. Lee C, Yang H, Chen C et al (2014) Gamma Knife surgery for craniopharyngioma: report on a 20-year experience: Clinical article. *J Neurosurg JNS* 121(Suppl2):167–178. <https://doi.org/10.3171/2014.8GKS141411>
 24. Demiral S, Beyzadeoglu M, Sager O et al (2014) Evaluation of linear accelerator (LINAC)-based stereotactic radiosurgery (SRS) for the treatment of craniopharyngiomas. *Int J Hematol Oncol* 24(2):123–129. <https://doi.org/10.4999/uhod.13091>
 25. Barajas MA, Ramírez-Guzmán G, Rodríguez-Vázquez C et al (2002) Multimodal management of craniopharyngiomas: neuroendoscopy, microsurgery, and radiosurgery. *J Neurosurg* 97(5 Suppl):607–609. <https://doi.org/10.3171/jns.2002.97.supplement>

26. Saleem MA, Hashim AS, Rashid A, Ali M (2013) Role of gamma knife radiosurgery in multimodality management of craniopharyngioma. *Acta Neurochir Suppl* 116:55–60. https://doi.org/10.1007/978-3-7091-1376-9_9
27. Amendola BE, Wolf A, Coy SR, Amendola MA (2003) Role of radiosurgery in craniopharyngiomas: a preliminary report. *Med Pediatr Oncol* 41(2):123–127. <https://doi.org/10.1002/mpo.10364>
28. Eder HG, Leber KA, Eustacchio S, Pendl G (2001) The role of gamma knife radiosurgery in children. *Childs Nerv Syst* 17(6):341–347. <https://doi.org/10.1007/s003810000435>
29. Bobeff EJ, Szmyd B, Młynarski W, Jouanneau E, Apra C, Shen M, Patel ZM, Jaskólski DJ, Schwartz TH (2025) Comparative outcomes of gross total resection vs. subtotal resection plus radiotherapy for preventing craniopharyngioma recurrence: a meta-analysis of the endoscopic endonasal approach. *Cancers (Basel)* 17(15):2516. <https://doi.org/10.3390/cancers17152516>
30. Kickingereder P, Maarouf M, Majdoub E (2012) Intracavitary brachytherapy using stereotactically applied phosphorus-32 colloid for treatment of cystic craniopharyngiomas in 53 patients. *J Neurooncol* 109:365–374. <https://doi.org/10.1007/s11060-012-0902-8>
31. Kondziolka D, Shin SM, Brunswick A, Kim I, Silverman JS (2015) The biology of radiosurgery and its clinical applications for brain tumors. *Neuro Oncol* 17(1):29–44. <https://doi.org/10.1093/neuonc/nou284>
32. Speckter H, Santana J, Bido J, Hernandez G, Rivera D, Suazo L et al (2020) Assessment of the alpha/beta ratios of pituitary adenomas and craniopharyngiomas for the quantification of single fraction equivalent dose benefits from hypofractionated radiosurgery. *Int J Radiat Oncol Biol Phys* 108(3):e79. <https://doi.org/10.1016/j.ijrobp.2020.07.087>
33. Shaaban A, Pham D, Tos SM, Mantziaris G, Schlesinger D, Sheehan JP (2024) Biological effective dose as a predictor of local tumor control in stereotactic radiosurgery treated parasellar meningioma patients. *J Neurooncol* 170(1). <https://doi.org/10.1007/s11060-024-04804-1>
34. Steiert C, Grauvogel J, Roelz R et al (2021) Stereotactic cysto-ventricular catheters in craniopharyngiomas: an effective minimally invasive method to improve visual impairment and achieve long-term cyst volume reduction. *Neurosurg Rev* 44(6):3455–3464. <https://doi.org/10.1007/s10143-021-01510-8>
35. Lee EQ, Wen PY (2016) Corticosteroids for peritumoral edema: time to overcome our addiction? *Neuro Oncol* 18(9):1191–1192. <https://doi.org/10.1093/neuonc/now167>
36. Su CF, Liu DW, Lee CC, Chiu TL (2017) Volume-staged Gamma Knife surgery for the treatment of large skull base meningioma surrounding the optical apparatus: a snowman-shape design. *J Chin Med Assoc* 80(11):697–704. <https://doi.org/10.1016/j.jcma.2017.03.011>
37. Haselsberger K, Maier T, Dominikus K et al (2009) Staged Gamma Knife radiosurgery for large critically located benign meningiomas: evaluation of a series comprising 20 patients. *J Neurol Neurosurg Psychiatry* 80(10):1172–1175. <https://doi.org/10.1136/jnnp.2008.156745>
38. Iwai Y, Yamanaka K, Shimohonji W, Ishibashi K (2019) Staged Gamma Knife radiosurgery for large skull base meningiomas. *Cureus* 11(10):e6001. <https://doi.org/10.7759/cureus.6001>

39. Xu Z, Vance ML, Schlesinger D, Sheehan JP (2013) Hypopituitarism after stereotactic radiosurgery for pituitary adenomas. *Neurosurgery* 72(4):630–637. <https://doi.org/10.1227/NEU.0b013e3182846e44>
40. Pomeraniec IJ, Xu Z, Lee CC et al (2021) Dose to neuroanatomical structures surrounding pituitary adenomas and the effect of stereotactic radiosurgery on neuroendocrine function: an international multicenter study. *J Neurosurg* 136(3):813–821. <https://doi.org/10.3171/2021.3.JNS203812>
41. Vatner RE, Niemierko A, Misra M et al (2018) Endocrine deficiency as a function of radiation dose to the hypothalamus and pituitary in pediatric and young adult patients with brain tumors. *J Clin Oncol* 36(28):2854–2862. <https://doi.org/10.1200/JCO.2018.78.1492>

Tables

Table 1 to 3 are available in the Supplementary Files section.

Figures

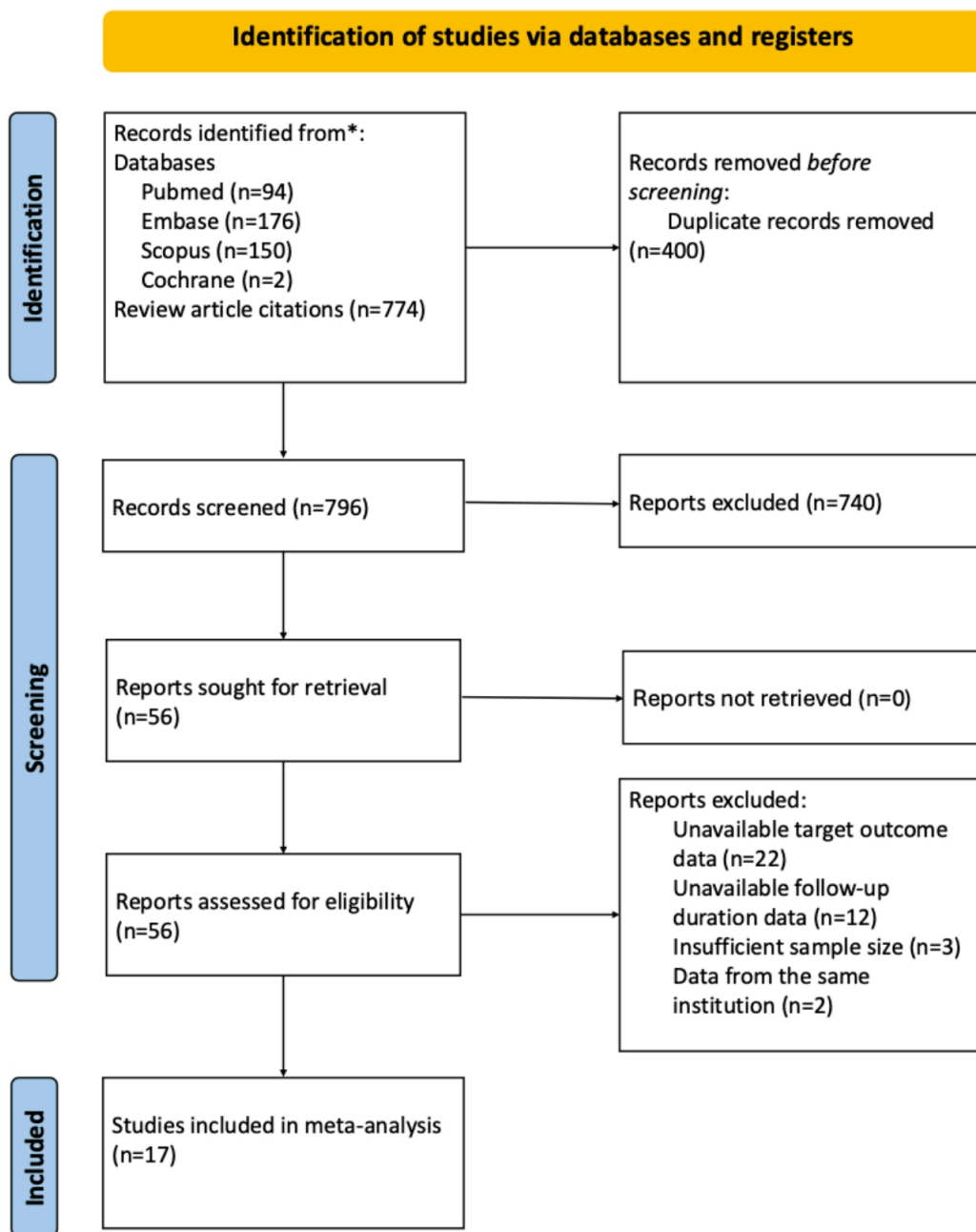
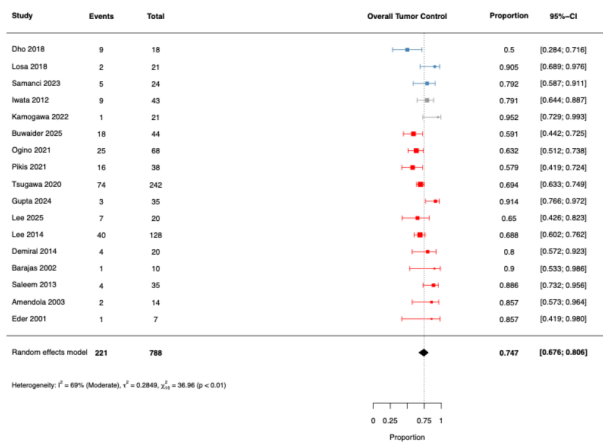
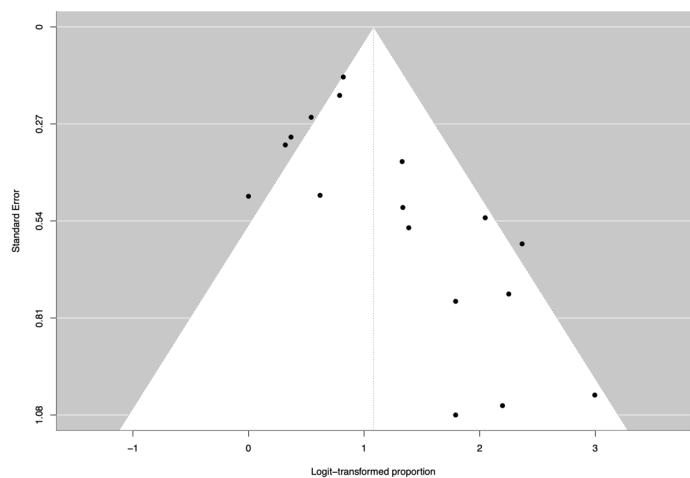


Figure 1

PRISMA flowchart summarizing study identification, screening, and inclusion in the meta-analysis



2a

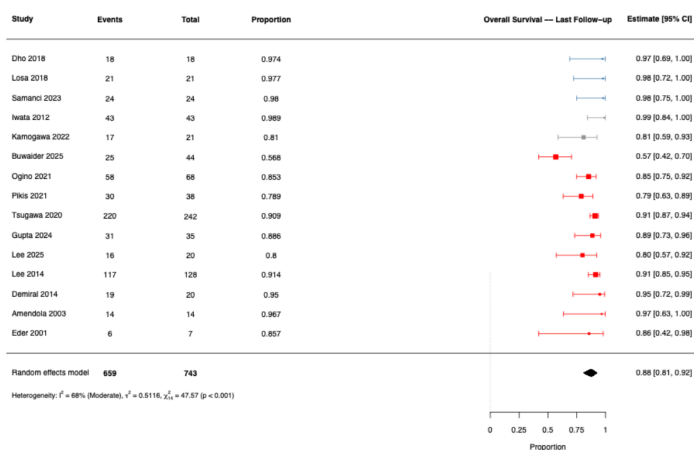


2b

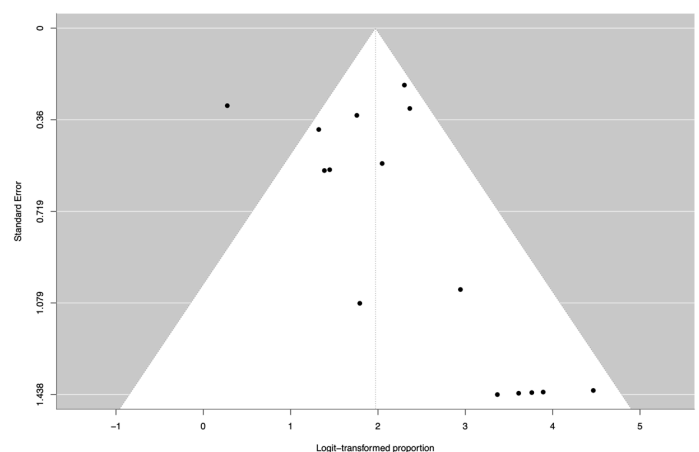
Figure 2

2a Forest plot of pooled tumor control at last follow-up after SRS for residual or recurrent craniopharyngioma. Results include study-level estimates (squares), 95% CIs (horizontal lines), pooled estimates from a random-effects model (diamond), and heterogeneity statistics (I^2 , τ^2 , χ^2 , p-value). Red represents SSRS cohorts. Blue represents HSRS cohort. Gray represents mixed cohorts.

2b Funnel plot for publication bias assessment for pooled overall tumor control



3a



3b

Figure 3

3a Forest plot of pooled overall survival at last follow-up after SRS for residual or recurrent craniopharyngioma. Results include study-level estimates (squares), 95% CIs (horizontal lines), pooled estimates from a random-effects model (diamond), and heterogeneity statistics (I^2 , τ^2 , χ^2 , p-value). Red represents SSRS cohorts. Blue represents HSRS cohort. Gray represents mixed cohorts.

3b Funnel plot for publication bias assessment for pooled overall survival at last follow-up

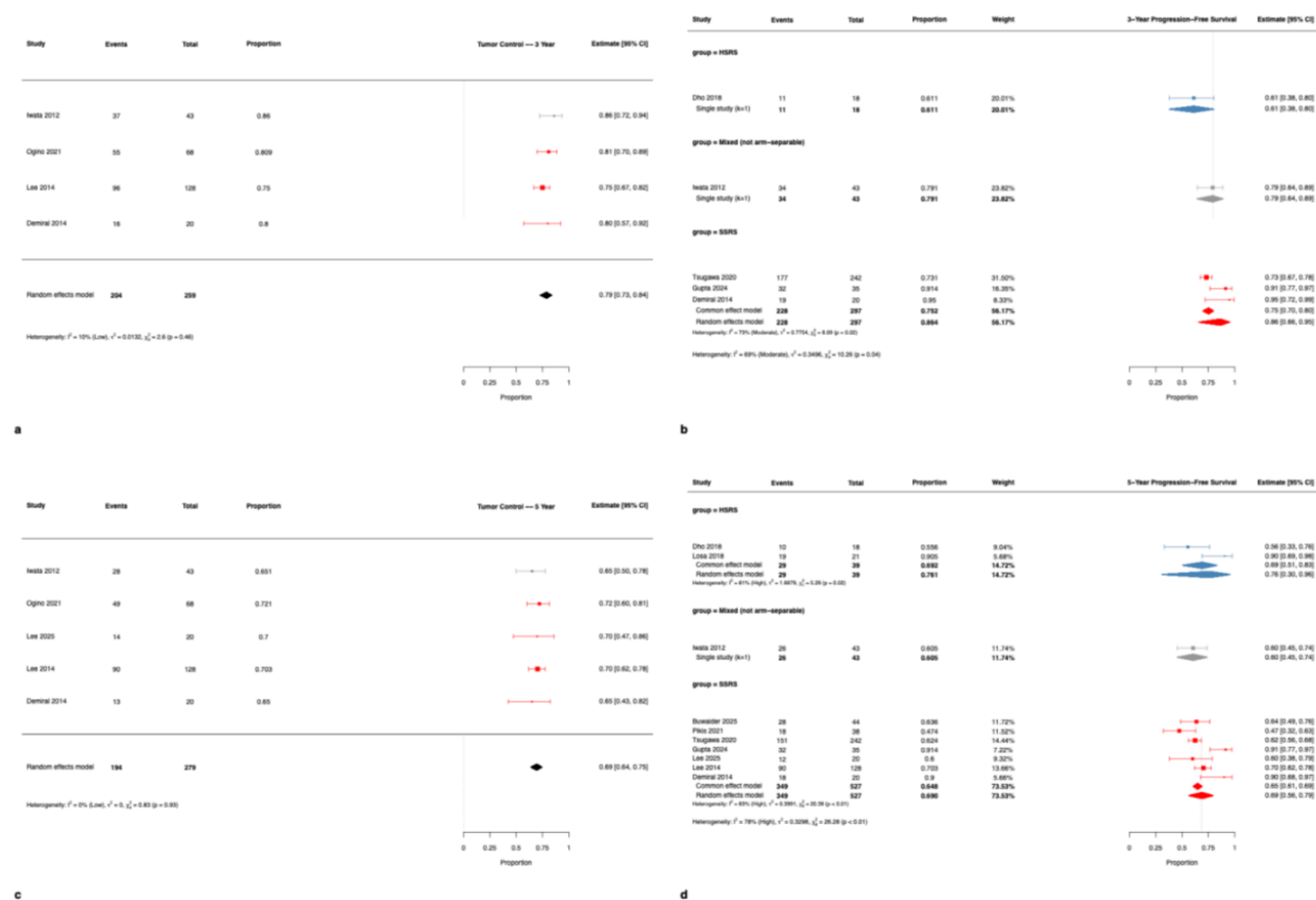


Figure 4

Forest plots showing pooled proportions and 95% CIs for tumor control and progression-free survival after SRS for residual or recurrent craniopharyngioma. (a) 3-year tumor control, (b) 3-year progression-free survival, (c) 5-year tumor control, (d) 5-year progression-free survival

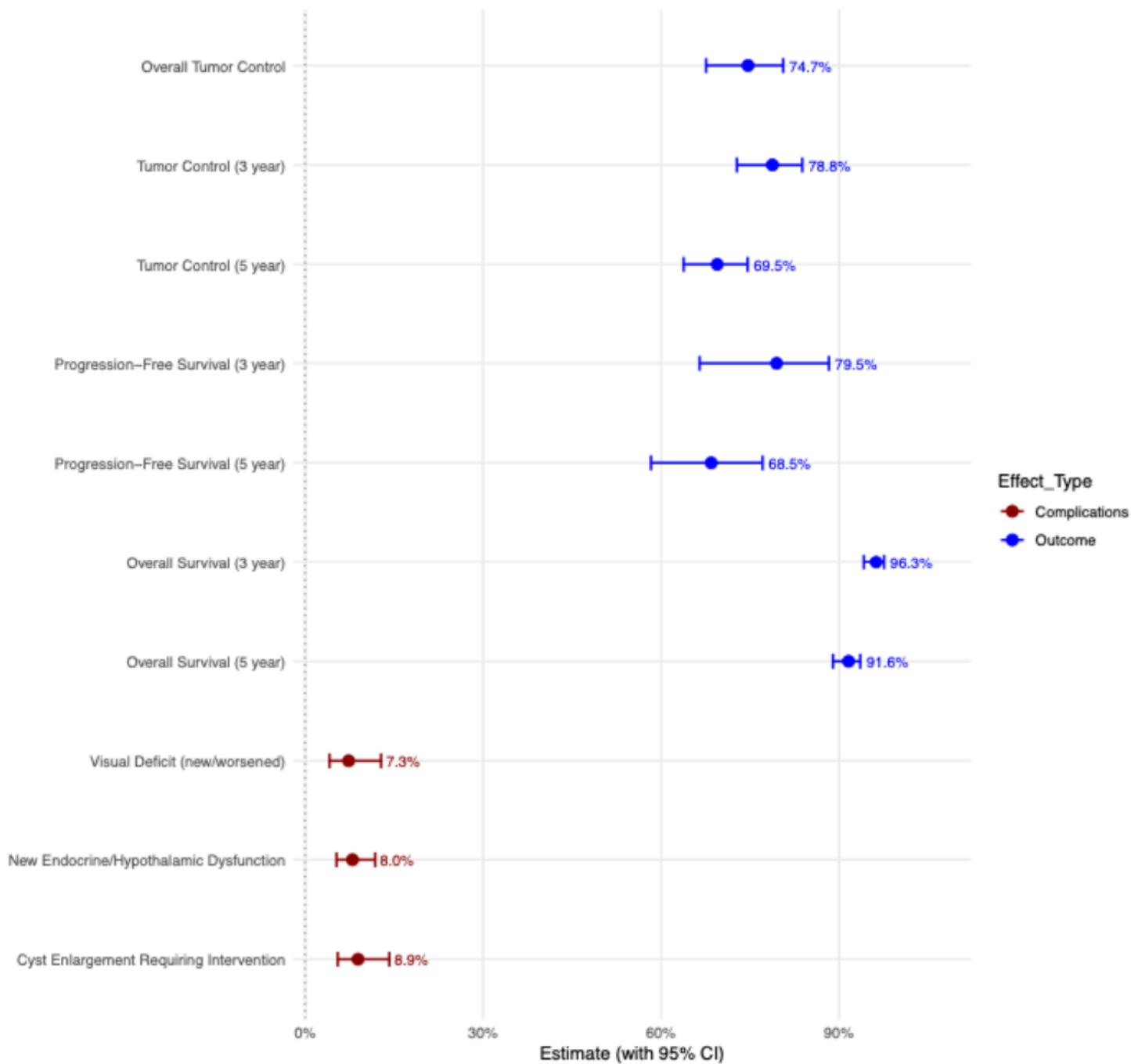


Figure 5

Summary of pooled estimates across key outcomes, including tumor control survival and treatment-related toxicity

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterials.docx](#)
- [Table13.docx](#)