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Review Article

Stereotactic Radiosurgery for Craniopharyngioma Management: A Comprehensive Review of Treatment Outcomes, Dose Optimization, and Future Directions

Yi Lin, Ning Luo, Wenhao An, Han Lin and Zhixiong Lin*

Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, China

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Abstract

Craniopharyngioma (CP), although histologically benign, is a surgically challenging sellar-region tumor for which stereotactic irradiation is increasingly used as an alternative or adjuvant strategy. This review summarizes the role of stereotactic radiosurgery (SRS) in managing CP, with a focus on treatment outcomes, technical advances, and emerging strategies to support evidence-based clinical practice. Literature reports indicate that Gamma Knife radiosurgery achieves variable tumor control rates (36–100%), with optimal outcomes (79.6–91.4%) when marginal doses ≥12 Gy are delivered and patients receive adequate follow-up. Smaller tumors (<5 cm^3) and those with higher solid components show particularly favorable outcomes. SRS demonstrates a favorable safety profile, with visual impairment occurring in approximately 4% of cases and endocrine dysfunction in 6%. Compared to conventional radiotherapy, SRS significantly reduces the risk of hypothalamic obesity in pediatric patients. The identification of *BRAF* mutations in papillary CPs has created novel opportunities for combining targeted therapies with SRS. Collectively, these advances underscore the role of SRS as an essential component of multidisciplinary CP management, particularly in the treatment of residual or recurrent lesions. It offers a more favorable toxicity profile and may improve quality of life outcomes compared to conventional radiotherapy. Further studies are needed to optimize patient selection, dosing strategies, and integration with novel systemic therapies.

Introduction

Craniopharyngioma (CP) is a benign epithelial tumor that arises from remnants of the craniopharyngeal ducts during embryonic development. Recent epidemiological data indicate that CP accounts for 2–5% of all primary brain tumors and 5–10% of pediatric brain tumors.[1–5] Despite being histologically classified as a benign tumor, CP presents a formidable challenge in neurosurgery and radiation oncology due to its unique anatomical location and invasive growth characteristics.[6,7] Located in the sellar region, CPs are closely associated with critical structures, including the hypothalamus, pituitary gland, optic chiasm, and third ventricle. The therapeutic challenge lies not only in achieving effective tumor control but also in preserving neuroendocrine function and maintaining quality of life.[6,8]

Gross total resection (GTR) offers effective tumor control but is associated with a 20% to 50% incidence of severe postoperative complications, including permanent visual impairment, pituitary insufficiency, and hypothalamic dysfunction.[9] Currently, adjuvant radiotherapy after subtotal resection (STR) can achieve tumor control rates comparable to those of GTR while reducing related complications.[10–12] However, conventional fractionated radiotherapy, although effective in controlling tumors, is associated with long-term risks, including radiation-induced brain necrosis, progressive endocrine dysfunction, and cognitive decline.[13]

Stereotactic radiosurgery (SRS) represents a paradigm shift in CP management.[13] This high-precision radiation technique employs stereotactic localization to achieve submillimeter targeting accuracy, delivering focused radiation beams that generate steep dose gradients between tumor and adjacent normal tissues.[14] Current SRS platforms include Gamma Knife, CyberKnife, and linear accelerator (LINAC) systems. For larger CPs, fractionated stereotactic radiotherapy (FSRT) employs a fractionated dosing approach to ensure treatment efficacy while further minimizing the risk of injury to surrounding normal tissues.[15]

Keywords: Craniopharyngioma; Stereotactic radiosurgery; Gamma Knife; Hypothalamic preservation; Pediatric outcomes; Dose optimization; Tumor control rate; Fractionated radiotherapy.

***Correspondence to:** Zhixiong Lin, Department of Neurosurgery, Sanbo Brain Hospital of Capital Medical University, Beijing 100093, China. ORCID: https://orcid.org/0000-0002-0522-4201. Tel: +86-10-62856913, Fax: +86-10-62856913, E-mail: linzx@ccmu.edu.cn

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Recent advances in neuroimaging, treatment planning systems, and clinical experience have refined SRS applications in CP management. For recurrent or progressive CPs, whether predominantly solid or cystic, additional therapeutic interventions are frequently required. Multiple clinical studies have demonstrated that SRS/FSRT achieves favorable tumor control rates with relatively low complication profiles, particularly offering advantages in minimizing severe surgery-related morbidity.[16,17] However, optimal treatment indications, dose-fractionation schemes, outcome assessment criteria, and long-term safety continue to be active areas of investigation.

SRS employs precise stereotactic localization to deliver highly conformal radiation to defined targets through non-invasive techniques. Its underlying physical principle involves multiple convergent radiation beams (gamma rays or high-energy X-rays) to achieve focal dose escalation within tumor volumes while achieving rapid dose fall-off in surrounding normal tissues.[18] This "high-dose center-low-dose edge" gradient characteristic is particularly suitable for CP with complex anatomical structures adjacent to the optic chiasm, hypothalamus, and pituitary stalk.[19] In the treatment of CP, SRS technology fully leverages its clear imaging characteristics and relatively radiation-sensitive biological properties. The high precision of SRS technology makes it a valuable therapeutic option for CPs, particularly for patients with residual or recurrent disease or those who are unsuitable for surgery.[20,21]

Currently, the primary devices used for SRS include three categories: Gamma Knife, which employs multiple cobalt-60 radiation sources for fixed irradiation, combined with a precise collimator system to focus radiation on intracranial targets. Tumor control rates for Gamma Knife treatment of CPs range from 79.6 to 91.4%.[22,23] While effective marginal doses of 12–16 Gy are typically maintained, maximum point doses exceeding 35 Gy may increase the risk of delayed neurological complications[13] Cyber Knife system combines a linear accelerator with robotic technology, and uses a robotic arm to deliver X-ray beams in a non-coplanar manner. It incorporates real-time image guidance and can deliver 1–5 fractionated treatments, making it particularly suitable for large or irregularly shaped CPs.[24,25] It has certain advantages in treating CPs with a high cystic component, as the treatment plan can be adjusted according to changes in cyst size.[26] LINAC can perform either SRS or fractionated SRT, particularly suitable for large-volume CPs requiring fractionated treatment, thereby maintaining tumor control while minimizing acute radiation-induced complications.[27]

The selection criteria for SRS and fractionated SRT are primarily based on tumor volume, anatomical location, and distance from adjacent critical structures. SRS is primarily used for smaller tumors (<3 cm^3) located at a safe distance from the optic chiasm, such as solid tumors or postoperative residual lesions. In contrast, SRT is suitable for larger tumors in close proximity to or compressing optic nerve structures. SRT may offer superior functional preservation, particularly for large-volume or location-sensitive tumors.[28] Therefore, in the treatment of CP, the choice between SRS and SRT requires a comprehensive consideration of tumor type, residual location, patient age, and intended neurological functional preservation goal. A tailored treatment plan should be developed accordingly.

This review synthesizes current evidence regarding the outcomes, technical considerations, and evolving practices in SRS for CP, with the aim of providing evidence-based guidance for clinical decision-making and highlighting future research directions. A comprehensive literature search was conducted in PubMed and Web of Science databases up to August 2025 using the following terms: (craniopharyngioma OR craniopharyngiomas) AND (stereotactic radiosurgery OR stereotactic radiotherapy OR gamma knife OR cyberknife OR LINAC OR SRS OR FSRT). Studies were limited to English-language studies involving human subjects. The initial search yielded 586 records. Following title and abstract screening, 92 full-text articles were assessed for eligibility, 34 of which met our inclusion criteria. As a comprehensive rather than a formal systematic review, we used a PRISMA-style flowchart (Fig. 1) to illustrate the search and screening process for transparency.[29]

SRS vs. conventional radiotherapy

Radiotherapy has been widely used as an adjuvant therapy for CP, particularly following STR. A recent meta-analysis found no clear superiority between radiosurgery and conventional fractionated radiotherapy in long-term progression-free survival (PFS), and reported comparable endocrine outcomes between the two modalities.[30,31] Due to the relative radiosensitivity of CP, effective local control typically requires a total radiation dose of 54–60 Gy, with a treatment duration of 5–6 weeks. However, this dose results in a significant radiation burden on surrounding critical structures (e.g., optic chiasm, hypothalamus, and pituitary gland), thereby increasing the risk of long-term radiation-induced damage, particularly in pediatric patients.[32] A cross-sectional cohort study further demonstrated that the incidence of stroke in pediatric patients receiving radiotherapy was significantly higher than that in the general population. This risk was particularly pronounced in patients with lower low-density lipoprotein cholesterol levels and longer follow-up periods after radiotherapy.[33] Additionally, two pediatric cases of Moyamoya disease after postoperative radiotherapy have been reported.[34] Moreover, seven patients, five of whom were children, developed secondary glioblastoma multiforme within several years after radiotherapy.[35,36] Four pediatric patients who developed radiation-induced meningioma, with a long latency period and presented with either solitary or multiple lesions have also been reported.[37] These long-term complications significantly impair quality of life and may lead to disability or death, particularly in pediatric or adolescent populations, thereby creating a long-term follow-up burden. Although SRS generally reduces the risk of hypothalamic obesity compared to conventional radiotherapy,[38] treatment outcomes vary among specific patient groups depending on tumor characteristics and the precision of SRS irradiation.[39,40] Therefore, personalized treatment strategies should be developed based on individual anatomical and functional characteristics.

Effects of SRS treatment

Gamma Knife

Gamma Knife, currently the most widely used SRS technique, has been evaluated in numerous retrospective studies on Gamma Knife radiosurgery for the treatment of CP (Table 1).[13,14,17,19,22,23,41–62] Multiple studies have confirmed a significant dose-response relationship between gamma knife marginal dose and local control rate. Ulfarsso *et al*.[41] suggested that a marginal dose ≥6 Gy is the minimum threshold for achieving effective control. Xu *et al*.[42] and Kobayashi *et al*.[43] reported that marginal doses >14.5 Gy and ≥11.7 Gy, respectively, were associated with longer PFS after CP surgery. In a large retrospective study (137 cases/162 Gamma Knife Surgery sessions), Lee *et al*.[20] found that when the margin dose reached 12–14 Gy, the 5-year control rate reached approximately 70–73%.[19] Ogino *et al*.[44] demonstrated that even in high-risk cases where the tumor was less than 3 mm from the optic nerve system, delivering a dose of ≥12 Gy to at least 85% of the tumor volume

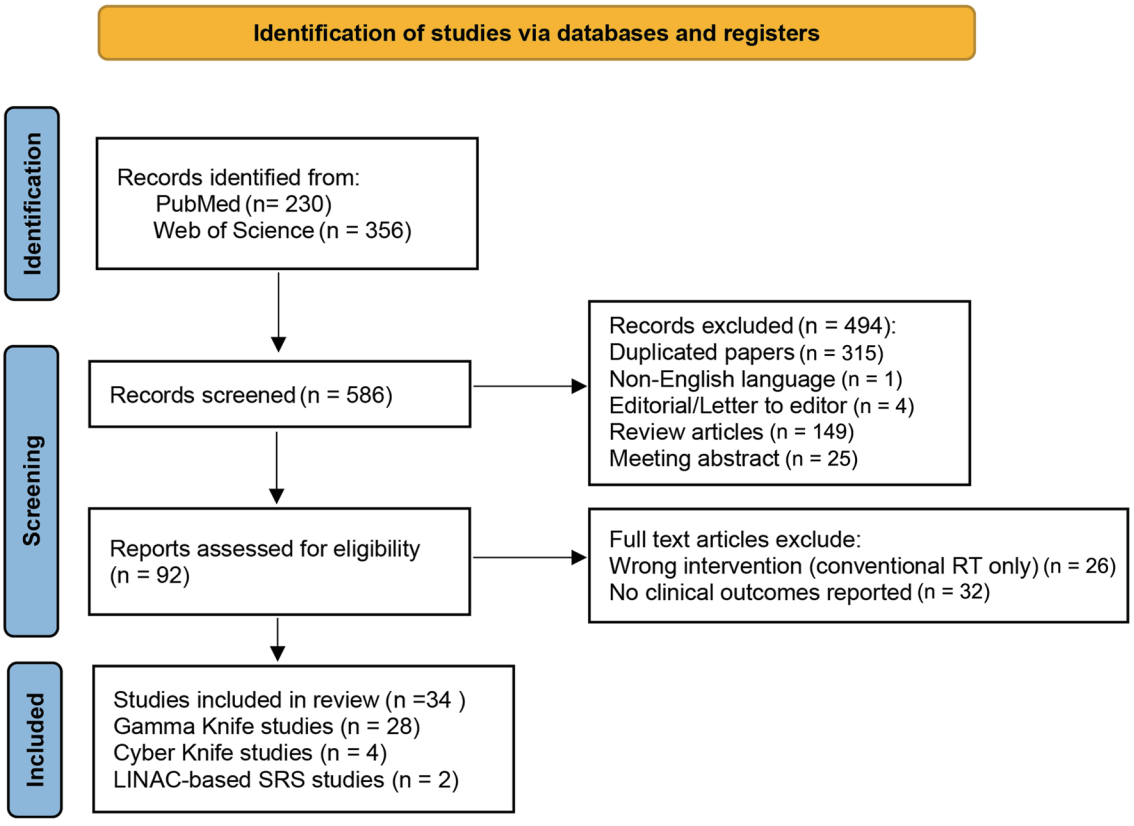

Fig. 1. Flowchart of the literature screening process.

could effectively improve tumor control rates after SRS treatment for recurrent or residual CPs.[44] However, excessively high radiation doses may increase the risk of complications, necessitating a careful balance between efficacy and safety.

Multiple studies have shown a significant correlation between tumor volume and treatment outcomes. Smaller tumors (<5 cm^3) typically exhibit higher control rates. In an analysis of 23 patients, Mokry noted that initial tumor volume and target volume are significant prognostic factors, with smaller tumors and target volumes being more likely to shrink.[45] Similarly, Xu *et al*.[41] found that tumor volume ≤ 1.6 cm^3 was associated with longer PFS after CP surgery.[42] Kobayashi *et al*.,[23] using receiver operating characteristic analysis, identified that a tumor diameter <19 mm serves as a good prognostic factor for gamma knife radiosurgery treatment of CPs.[23] Smaller tumors are more suitable for SRS treatment, possibly because of their more uniform dose distribution and better protection of critical structures.

The ratio of solid to cystic components also influences the efficacy of SRS. Solid tumors are generally more sensitive to radiation therapy than cystic tumors. In a study of 98 cases, Kobayashi *et al*.[45] reported that cystic or mixed tumors were statistically unfavorable prognostic factors, whereas those with a higher proportion of solid components achieved better tumor control rates.[63] Long-term follow-up data show that the PFS rate after gamma knife treatment decreases slightly over time. However, repeated gamma knife treatment or adjuvant therapy can prolong the control time, suggesting that extended follow-up is needed to assess the long-term efficacy of SRS accurately. Additionally, gamma knife combined with radioactive isotope therapy for recurrent mixed cystic-solid tumors has also achieved promising efficacy.[46,64]

Other SRS treatments

CyberKnife, as an emerging SRS technology, has also demonstrated unique advantages in the treatment of CPs. Although long-term follow-up data remain limited, preliminary evidence supports its efficacy (Table 2).[15,25,28,65] Compared with RT, fractionated SRT using CK reduces the volume of irradiated tissue without significantly affecting local control.[28] Low-fractionated SRT may contribute to the preservation and protection of the optic nerve and neuroendocrine function, particularly for tumors located near the optic nerve pathway, those with a high cystic component, or larger tumor volumes.[15] CyberKnife achieves high tumor response rates for both residual and recurrent CPs.[26] The fractionated treatment capability of CyberKnife enables optimized dose fractionation schemes that enhance treatment safety, particularly suitable for tumors near the visual pathway.

The main advantages of frameless technology include improved patient comfort, the ability to perform fractionated treatment, and suitability for tumors with complex shapes.[24,47] The optimal choice should be individualized based on tumor location, tumor volume, and patient compliance.

Safety

The safety profile of SRS for CP is a critical consideration for clinical decision-making. Based on data from multiple large-scale studies, the incidence of complications associated with SRS treatment is relatively low; however, systematic assessment and pre-

Table 1. Gamma Knife for craniopharyngioma in current studies

Author &Year	No. of patients	Mean margin dose (Gy)	Mean volume (cm^3)	Mean follow-up time (m)	Tumor control Rate %
Kobayashi *et al*, 1994[52]	10	14.2	6.14	13.9	100
Prasad *et al*, 1995[53]	9	12.9	11.07	24	77.7
Chung *et al*, 1998[54]	21	12.21	9	18.4	90.4
Mokry, 1999[45]	23	10.8±8.7	7.0±8.3	24	74
Chung *et al*, 2000[55]	31	9.5–16	9	36	87
Yu *et al*, 2000[46]	46	8–18	13.5	12	89
Chiou *et al*, 2001[49]	10	16.4[a]	1.35	72[a]	58
Ulfarsson *et al*, 2002[41]	21	3–25	7.8	90	36
Amendola *et al*, 2003[56]	14	14	7.2	36	86
Albright *et al*, 2005[57]	5	14.65	6.5	24	80
Hasegawa *et al*, 2010[14]	100	11.4[a]	3.3[a]	6[a]	60
Yomo *et al*, 2009[58]	18	11.6	1.8	24	94
Niranjan *et al*, 2010[59]	46	13[a]	1[a]	62.2	68
Xu *et al*, 2010[42]	37	14.5[a]	1.6[a]	50[a]	68
Jeon *et al*, 2011[51]	50	11[a]	2[a]	71.2	62
Kobayashi *et al*, 2012[23]	98	12	3.1	65.5	79.6
Saleem *et al*, 2013[60]	35	12	12	22	89
Lee *et al*, 2014[19]	137	12[a]	5.5[a]	45.7[a]	69
Kobayashi *et al*, 2015[43]	30	12	2.64	79.9	87.9
Dho *et al*, 2018[50]	35	15[a]	1.45	71.9	60
Losa *et al*, 2018[61]	50	14.3±0.3	2.15±0.3	74.6±8.4	86
Tsugawa *et al*, 2020[17]	242	11.4	3.1	61.4[a]	69
Pikis *et al*, 2021[13]	38	13.26	5.15	48	58
Lee *et al*, 2021[48]	22	15.8	0.05–15.28	85.8	70
Ogino *et al*, 2021[44]	53	12[a]	0.63[a]	86[a]	53.4
Samanci *et al*, 2023[47]	24	20[a]	2.4	23.5[a]	61
Gupta *et al*, 2024[22]	44	12	3.25	62.01	91.4
Buwaider *et al*, 2025[62]	44	10[a]	2[a]	5.75	40

[a]Presented in median.

vention of potential risks remain necessary.

Dose constraints & target precision

In SRS treatment for CPs, minimizing radiation exposure to surrounding critical structures is a key principle of treatment planning, particularly for lesions adjacent to the optic nerve and optic chiasm. Radiation-induced optic neuropathy (RION) remains a major concern, especially in patients who have previously received

Table 2. CyberKnife for craniopharyngioma in current studies

Author &Year	No. of patients	Mean per fraction (Gy)	Mean follow-up time (m)	Tumor Control Rate %
Mohamad *et al*, 2020[28]	16	1.8–2.0	44.4	93.75
Ohhashi *et al*, 2020[25]	33	13.66	61–129	74.8
Iwata *et al*, 2011[15]	43	5.3	40[a]	69.8
Lee *et al*, 2021[65]	16	5.43	15.4	90.9

[a]Presented as the median.

conventional radiotherapy, as the risk of RION after single-fraction SRS or hypo-fractionated SRS (2–5 fractions) is approximately tenfold higher compared with those without prior irradiation.[66] Therefore, strict control of the maximum point dose to the optic apparatus and careful patient selection are essential to minimize visual complications.

The standard edge dose used in SRS is 12–16 Gy. Studies have shown that when ≥85% of the tumor volume receives at least 12 Gy, a high local control rate can be achieved, with 10-year PSF rates ranging from 53.4% to 93.3%.[44] In pediatric patients, if D98% (the minimum dose covering 98% of the tumor volume) exceeds 11.5 Gy, the risk of recurrence can be significantly reduced.[48] Data from multicenter studies in the United States and Italy indicate that the application of SRS in pediatric patients, by reducing radiation doses to the hypothalamus, helps maintain long-term quality of life. Therefore, dose restrictions for the hypothalamus and adjacent structures are more stringent in the pediatric population.[67]

Complications

The overall incidence of complications following SRS treatment for CPs is relatively low, with the majority being mild and reversible. Visual deficits account for approximately 4% of cases, with the primary risk factors including tumor adhesion or compression of the optic nerve structures and a maximum optic nerve dose exceeding 10 Gy.[14,17,30,47] The incidence of hormonal deficits is approximately 6%, and is more frequently observed in patients with pre-existing pituitary insufficiency.[30] Compared to fractionated radiotherapy, SRS reduces the risk of hypothalamic obesity associated with radiation-induced hypothalamic damage in pediatric patients.[38]

Other rare complications include radionecrosis and cognitive impairment, although the incidence is low. However, evidence suggests that the maximum dose exceeding 35 Gy may be associated with delayed neurological deficits.[13] Therefore, precise dose control and individualized plan optimization are crucial for reducing long-term adverse outcomes.

General synthesis and future directions

SRS has emerged as a critical therapeutic option in CP management, despite considerable heterogeneity in outcomes. The observed tumor control rates ranging from 36% to 100% reflect not only variations in patient cohorts but also the evolution of treatment techniques over the past three decades. This wide variability can be largely attributed to three key factors: dose optimization, patient selection criteria, and follow-up duration.

The dose-response relationship stands out as the most critical determinant of treatment efficacy. Studies employing marginal doses less than 10 Gy have consistently reported inferior outcomes (36–60% control rates).[13,14,41,44,49,50] Selected studies using optimized protocols have achieved control rates as high as 79.6–91.4%,[22,23] although the median control rate across all studies remains approximately 70%. This well-defined dose threshold aligns with radiobiological principles and emphasizes that sufficient dose delivery, while respecting normal tissue tolerance, is non-negotiable for achieving successful outcomes. When contemporary standards are met—marginal doses ≥12 Gy, follow-up periods exceeding 24 months, and adequate sample sizes—the convergence of control rates within the range of 79.6–91.4% strongly validates SRS efficacy.

Despite these encouraging results, several inherent limitations constrain SRS application in CP management. The anatomical proximity to critical structures presents the primary challenge. The low radiation tolerance (8–10 Gy in a single fraction) of the optic chiasm often necessitates dose compromise for tumors in close proximity, potentially affecting treatment efficacy.[14] This limitation has motivated the development of fractionated approaches, allowing for a more favorable therapeutic ratio while maintaining acceptable toxicity profiles.[15,51,68] Tumor characteristics further influence treatment feasibility. Cystic CPs pose particular challenges due to their relative radioresistance and the potential for cyst expansion during treatment, which can affect dose distribution uniformity.[23] Similarly, larger tumors (>3 cm diameter) often exceed the size limits for safe single-fraction treatment, requiring either fractionation or multimodal approaches.[68] These limitations underscore that patient selection is equally as crucial as technical execution in achieving optimal treatment outcomes.

Recent discoveries of *BRAF* gene mutations in papillary CPs have opened up a promising avenue for targeted therapy.[69,70] This mutation is present in nearly all papillary CPs, supporting a new treatment paradigm involving the combination of targeted therapy with SRS. In particular, the neoadjuvant therapy with molecular targeted drugs, which are first used to reduce tumor volume, followed by precise SRS treatment, may further enhance treatment efficacy and minimize damage to surrounding critical structures. Given the rarity and diversity of this tumor, future studies should utilize multicenter prospective databases to increase sample size and enable comparisons among different treatment regimens.

Moving forward, several research priorities are evident. Prospective multicenter trials with standardized treatment protocols and consistent outcome measures are essential to provide higher-level evidence for optimizing therapeutic algorithms.[40] Furthermore, long-term quality of life assessments, incorporating neurocognitive function, endocrine outcomes, and psychosocial measures, will be crucial for accurately evaluating the comparative benefits of SRS versus alternative approaches.[6] The optimal integration of molecular targeted therapies with SRS requires systematic evaluation through well-designed clinical trials. Recent studies combining stereotactic approaches with phosphorus-32 brachytherapy have shown promising outcomes.[64] Given the rarity and heterogeneity of CPs, international collaboration through prospective registries will be necessary to accumulate sufficient data for meaningful subgroup analyses.[12] Such efforts should prioritize developing consensus guidelines for patient selection, dose prescription, and outcome reporting to facilitate meaningful comparisons across institutions and treatment modalities.

Conclusions

SRS has proven to be a crucial component in the multidisciplinary management of CPs, particularly for patients with residual or recurrent disease. While conventional radiotherapy remains integral for certain cases, SRS offers the advantages of reduced treatment-related toxicity and improved quality of life. As therapeutic strategies continue to evolve, the incorporation of advanced imaging techniques, dosimetric planning, and molecularly targeted therapies provides a pathway toward optimizing outcomes for patients with these challenging tumors. Continued research is essential to refine treatment protocols and understand the long-term implications of these therapies for patient health and quality of life.

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Conflict of interest

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Author contributions

Conceptualization, supervision, and project management (ZXL), methodology, formal analysis, data curation, visualization, writing – original draft, review and editing (YL), validation, review and editing (NL), literature search and article revision (HWA, HL). All authors contributed to the article and approved the final version of the manuscript.

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