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Systematic Analysis of Clinical Outcomes Following Stereotactic Radiosurgery for Central Neurocytoma

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Central neurocytoma (CN) typically presents as an intraventricular mass causing obstructive hydrocephalus. The first line of treatment is surgical resection with adjuvant conventional radiotherapy. Stereotactic radiosurgery (SRS) was proposed as an alternative therapy for CN because of its lower risk profile. The objective of this systematic analysis is to assess the efficacy of SRS for CN. A systematic analysis for CN treated with SRS was conducted in PubMed. Baseline patient characteristics and outcomes data were extracted. Heterogeneity and publication bias were also assessed. Univariate and multivariate linear regressions were used to test for correlations to the primary outcome: local control (LC). The estimated cumulative rate of LC was 92.2% (95% confidence interval: 86.5−95.7%, $p<0.001$). Mean follow-up time was 62.4 months (range 3−149 months). Heterogeneity and publication bias were insignificant. The univariate linear regression models for both mean tumor volume and mean dose were significantly correlated with improved LC ($p<0.001$). Our data suggests that SRS may be an effective and safe therapy for CN. However, the rarity of CN still limits the efficacy of a quantitative analysis. Future multi-institutional, randomized trials of CN patients should be considered to further elucidate this therapy.

Key Words Brain tumors; Neurocytoma, central; Gamma Knife radiosurgery; Linear accelerators; Stereotactic radiosurgery.

INTRODUCTION

Central neurocytoma (CN) is an extremely rare neuroepithelial tumor that accounts for 0.1−0.5% of all adult primary brain tumors [1-5]. CN is classified by the World Health Organization as a grade II (benign) neoplasm [3,6]. By definition, CN is located in the ventricular system. As such, patients often present with headaches, nausea, or vomiting consistent with an obstructive pattern of hydrocephalus [3,4,7-17]. Computed tomography images demonstrate a heterogeneously hyperdense, enhancing mass. CN is typically isointense, isohyperintense and moderately hyperintense on T1-, T2-, and contrast enhanced magnetic resonance imaging, respectively [4,8,11,15,17-21].

Management of CN involves surgical resection and/or adjuvant treatment consisting of radiotherapy or chemotherapy. Gross total resection (GTR) is often curative, with a 99% 5-year survival rate [4,12,22-25]. However, due to its central location, GTR is rarely achieved (30% to 50% of cases) [26,27]. Thus, subtotal resection (STR) with adjuvant treatment is often necessary [4,12,26,28]. Adjuvant therapy for CN traditionally consisted of conventional radiotherapy, but was limited by associated cognitive deficits and other neurotoxicities [22,27,29-33]. Recently, stereotactic radiosurgery (SRS) is increasingly utilized as an alternative modality because of fewer fractions and associated toxicities [5,22,27,31,34-48]. Several studies have demonstrated equivalent tumor control and fewer complications with adjuvant SRS when compared with conventional radiotherapy [12,49].

A quantitative systematic review by Park and Steven [22] in 2012 (62 patients) demonstrated the efficacy of SRS for CN.

The current systematic analysis updates the findings of Park and includes several additional case series published since then for a total of 150 patients [50-53]. To our knowledge, this study represents the largest and most current review of CN patients treated with SRS.

MATERIALS AND METHODS

Search strategy

Adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (http://www.prisma-statement.org) was maintained throughout this study. The PubMed database was searched by two independent authors using terms "CN" and "radiosurgery." Abstracts were reviewed and screened against inclusion and exclusion criteria. Inclusion criteria were: 1) original data, 2) sufficient data on SRS outcomes for treatment of CN, and 3) more than one patient. Exclusion criteria were: 1) non-English text, 2) review articles, and 3) studies from the institutions/utilizing the same patient pool already included in analysis. Our screening process is summarized in Fig. 1.

Statistical analysis

Statistical analysis was performed using Comprehensive Meta-Analysis software (version 3.0; Biostat, Englewood, NJ, USA). The Q Statistic of the χ^2 value test and inconsistency index was used to estimate heterogeneity of included studies. A random-effect model was chosen to better account for heterogeneity between included studies. A funnel plot, Begg's rank correlation test, and Egger's linear regression method were used to graphically and quantitatively assess publication bias. The summary of local control (LC) rate and 95% confidence interval (CI) were calculated from reported pooled data. Sensitivity analysis was done to see if any individual study significantly affected our results.

Additional univariate and multivariate analyses were completed using the Statistical Analysis System (SAS, version 9.3; SAS Institute Inc., Cary, NC, USA). Linear regression of the overall data was used to test if various predictive variables were correlated with patient outcomes. Independent variables analyzed included mean tumor volume and dose. Data collated from individual articles was also analyzed using N-1 Pearson chi-squared tests to compare proportions [54,55]. Statistical significance was set at a p-value less than 0.05.

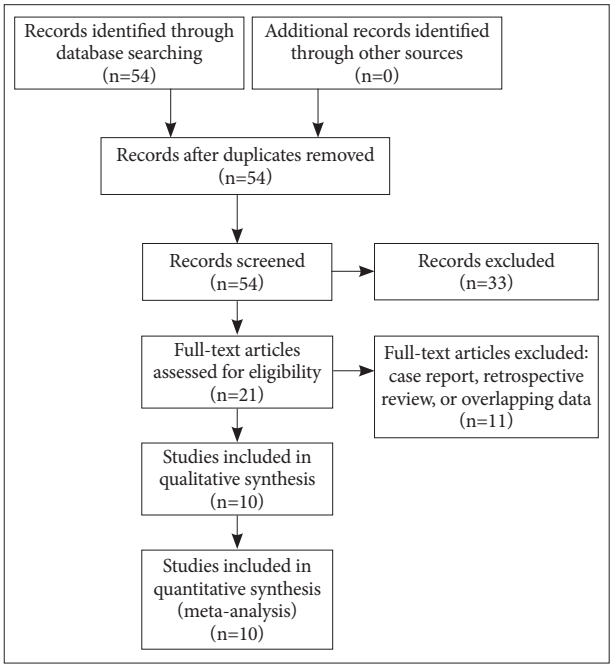

Fig. 1. Flow chart of systematic search process.

RESULTS

A total of 10 studies (all case series) comprising 150 patients were included in our quantitative synthesis. These patients were treated with either Gamma Knife radiosurgery (GKRS; n=146, 97%) or linear accelerator radiosurgery (n=4, 3%) (Table 1). Resection (STR or GTR) was previously performed in 125 patients (83.3%), while 25 patients (16.7%) were treated with primary SRS. Mean marginal dose was 14.7 Gy (range 9–25 Gy). Mean tumor volume was 9.3 mL (range 0.4–36.4 mL). Complications included intracerebral (tumoral) hemorrhage (n=3), cerebral edema (n=3), and radiation injury (n=2). Overall survival was 98% at a mean follow-up of 62.4 months (range 3–149 months).

Test of heterogeneity was non-significant (p=0.98). The Q-value was 2.53 (df=9) and I^2=0. Publication bias was assessed graphically via funnel plot, which displays no significant asymmetry (Fig. 2). Begg's rank correlation test and Egger's linear regression method were both insignificant, with 2-tailed p-values of 0.09 and 0.93, respectively. Fig. 3 displays the control rates of all included studies. Overall LC was 92.2% (95% CI 86.5–95.7%) (p<0.001).

Univariate linear regression models for both mean tumor volume and mean dose were significantly correlated with improved LC. Smaller tumor volumes were associated with better overall LC (p<0.001). Likewise, greater radiation doses correlated with better overall LC (p<0.001).

DISCUSSION

The optimal management of CN remains controversial [56]. Schild et al. [12] first reported the use of SRS for CN in 1997. Since then, multiple case series and systematic reviews have reaffirmed its efficacy [5,22,27,31,34-49]. The aforemen-

Table 1. Literature review of SRS for central neurocytoma

Author and year [ref]	n	Mean age	Modality	MTV (mL)	Mean dose (Gy)	F/U (mos)	RR (%)	LC (%)	DC (%)	OS (%)	Complications
Yamanaka et al., 2016 [53]	36	35.0	GKRS	4.9*	15.0*	54.5*	88	94	92	97	Tumor hemorrhage×2, radiation injury×1
Monaco et al., 2015 [52]	8	29.0	GKRS	5.5	14.6	63.3	88	100	88	100	−
Kim et al., 2013 [29]	20	32.0	GKRS	11.0	15.4	103	70	85	85	100	Edema×1
Karlsson et al., 2012 [50]	42	32.0	GKRS	12.0	13.0	73	91	95	95	100	Edema×1
Genc et al., 2011 [56]	22	30.2	GKRS	13.4	16.4	36	95	95	100	100	−
Yen et al., 2007 [46]	7	26.7	GKRS	6.0	16.0	60	100	100	100	86	Tumor hemorrhage×1
Martín et al., 2003 [41]	4	26.3	LINAC	3.2	16.5	33	100	100	100	100	Alopecia, edema, necrosis×1
Anderson et al., 2001 [27]	4	28.3	GKRS	7.0	17.0	17	100	100	100	100	−
Bertalanffy et al., 2001 [34]	3	22.3	GKRS	3.9	12.8	60	100	100	100	67	−
Cobery et al., 2001 [35]	4	27.5	GKRS	14.8	10.5	44	100	100	100	100	−
Total	150										
Mean		31.5		9.3	14.7	62.4	89	94	94	98	

*Median. GKRS, Gamma Knife radiosurgery; LINAC, linear accelerator; MTV, mean tumor volume; Gy, Gray; F/U, follow-up; RR, recurrence rate; LC, local control; DC, distant control; OS, overall survival; SRS, stereotactic radiosurgery

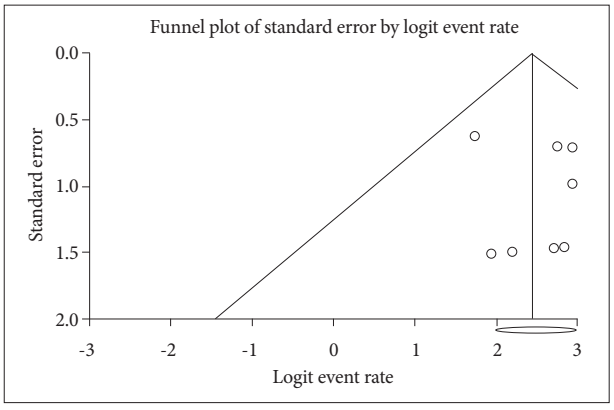

Fig. 2. Funnel plot of included studies showing asymmetry.

tioned study by Park and Steven [22] represents the first quantitative systematic review of SRS for treatment of CN. That study analyzed 5 retrospective case series (64 CNs in 62 patients). Of the 62 patients, only 4 displayed tumor growth after undergoing SRS (6.3%). We have analyzed 10 retrospective case series with a total of 150 patients, making this the largest review to date. Park and Steven [22] initially reported a LC rate of 91.1% with 2 local failures at a mean follow-up of 59.3 months. The expanded patient pool used in our study allowed us to calculate a similar LC rate (92.2%) reflecting 9 local failures at a mean follow-up of 62.4 months. Our data supports the conclusion that SRS is a viable treatment for CN.

The two LC failures in Park and Steven's [22] initial review were associated with unknown etiology and inadequate dosing. In our analysis, individual data was available for 4 of the 9 LC failures. Mean marginal dose for local recurrences was 12.8 Gy compared to 15.6 Gy in 62 reported patients achieving tumor control. In addition, we found that mean dose was significantly correlated with LC. Despite the small sample size, this provides evidence that radiation dose could contribute to LC. Matsunaga et al. [5] reported improved LC with relatively low marginal doses of 13 to 18 Gy and therefore recommend a marginal dose of at least 13 Gy for effective tumor control. Our findings corroborate the recommendation of Matsunaga et al. [5] to maintain a dose high enough to achieve tumor control but not so high as to cause toxicity. This is largely consistent with the studies we reviewed, which have an overall mean dose of 14.7 Gy (range 10.5−17.0 Gy) (Table 1).

MIB-1 (Ki-67) labeling index has been demonstrated to be the most important marker of potentially malignant behavior in CN [4,56-64]. CN is considered atypical if the MIB-1 (Ki-67) labeling index is greater than or equal to 2% [4,57,58]. Interestingly, Genc et al. [56] reported that MIB-1 (Ki-67) indices had no significant effect on tumor response to SRS. However, the authors acknowledge that interpretation of their findings may be limited by a short follow-up duration (mean 36 months), particularly of atypical CNs. Data on MIB-1 (Ki-67) labeling index was not available for most studies, which prevented further analyses with regard to index and LC.

SRS has been demonstrated to be effective in primary management of CN, particularly in cases less amenable to surgical resection [29,31,50]. In our study, 25 patients (16.7%) were treated with GKRS alone. Individual patient data was available for 18 patients. We found similar LC between primary SRS and our overall cohort (88.9% vs. 92.2%, p=0.63). Kim et al. [29] report a 20% LC failure rate for patients treated with primary SRS vs. 40% LC failure in patients treated with adjuvant SRS. Similarly, Karlsson et al. [50] found primary SRS to be efficacious in control of incidental, asymptomatic CN. The report of effective primary control is consistent with our findings that mean tumor volume is directly correlated with LC failure, since smaller tumor volumes are less likely to need surgical decom-

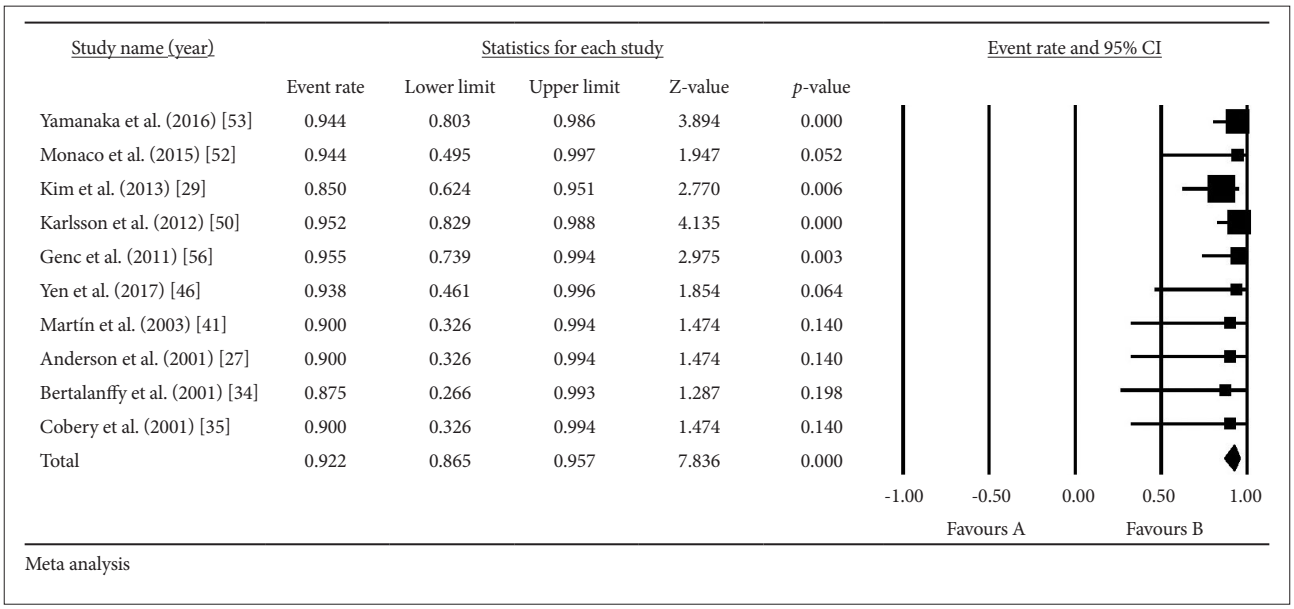

Fig. 3. Forest plot quantitative analysis of included studies.CI, confidence interval.

pression or be symptomatic. Moreover, our data suggests that smaller tumor volume is significantly correlated with better LC.

Radiation associated adverse events (AREs), defined as hyperintensity surrounding the treated lesion on imaging, are rare after SRS for CN (Table 1) [52]. There are only 3 reported AREs (all cases of cerebral edema) in the literature with only one becoming symptomatic (Table 1) [29,41,50]. Only 2% of the patients reviewed experienced AREs. Interestingly, Karlsson et al. [50] also reported that 45% (19/42) of their patients developed ventricular enlargement with 33% (1/3) requiring surgical management. This has not been reported elsewhere in the literature. Long term outcomes and toxicities of SRS for CN are not known. There have been two reported cases of increased MIB-1 (Ki-67) index, angiogenesis and glial differentiation in recurrent tumor that may have been attributable to SRS [5,65]. Given the low complication rate and favorable tumor control, current dosages reported are considered both safe and effective, respectively.

Limitations to this study were ever-present despite an increase in sample size (>two-fold) as compared to the prior quantitative systematic review. The rarity of CN makes available data sporadic, consisting of only case series. Mean follow-up for the included studies is another limitation, as a limited window can blind our results to potential failures occurring after end-of-study (Table 1).

CONCLUSION

Our data suggests that SRS may be an effective and safe therapy for CN. The rarity of CN limits the efficacy of a quantitative analysis. Future prospective, randomized studies with extended follow-up should be conducted to elucidate long-term efficacy of SRS in treatment of typical and atypical CN.

Conflicts of Interest

The authors have no financial conflicts of interest.

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