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CLINICAL ARTICLE

Stereotactic radiosurgery for central neurocytomas: an international multicenter retrospective cohort study

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OBJECTIVE Central neurocytomas (CNs) are uncommon intraventricular tumors, and their rarity renders the risk-to-benefit profile of stereotactic radiosurgery (SRS) unknown. The aim of this multicenter, retrospective cohort study was to evaluate the outcomes of SRS for CNs and identify predictive factors.

METHODS The authors retrospectively analyzed a cohort of patients with CNs treated with SRS at 10 centers between 1994 and 2018. Tumor recurrences were classified as local or distant. Adverse radiation effects (AREs) and the need for a CSF shunt were also evaluated.

RESULTS The study cohort comprised 60 patients (median age 30 years), 92% of whom had undergone prior resection or biopsy and 8% received their diagnosis based on imaging alone. The median tumor volume and margin dose were 5.9 cm^3 and 13 Gy, respectively. After a median clinical follow-up of 61 months, post-SRS tumor recurrence occurred in 8 patients (13%). The 5- and 10-year local tumor control rates were 93% and 87%, respectively. The 5- and 10-year progression-free survival rates were 89% and 80%, respectively. AREs were observed in 4 patients (7%), but only 1 was symptomatic (2%). Two patients underwent post-SRS tumor resection (3%). Prior radiotherapy was a predictor of distant tumor recurrence ($p = 0.044$). Larger tumor volume was associated with pre-SRS shunt surgery ($p = 0.022$).

CONCLUSIONS Treatment of appropriately selected CNs with SRS achieves good tumor control rates with a reasonable complication profile. Distant tumor recurrence and dissemination were observed in a small proportion of patients, which underscores the importance of close post-SRS surveillance of CN patients. Patients with larger CNs are more likely to require shunt surgery before SRS.

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KEYWORDS central neurocytoma; Gamma Knife radiosurgery; stereotactic radiosurgery; intracranial neoplasms

ABBREVIATIONS ARE = adverse radiation effect; CN = central neurocytoma; EBRT = external-beam radiation therapy; GTR = gross-total resection; IRRF = International Radiosurgery Research Foundation; PFS = progression-free survival; RANO = Response Assessment in Neuro-Oncology; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery; STR = subtotal resection.

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Central neurocytomas (CNs) are rare central nervous system tumors, representing only 0.1%–0.5% of intracranial neoplasms.[1–3] According to the WHO classification, CNs are categorized as grade II tumors.[4–7] CNs are usually observed near the foramen of Monro in the lateral ventricles. Due to their common intraventricular location, the initial clinical presentation of these lesions is often headaches and obstructive hydrocephalus. CNs primarily occur in young adults, with 70% of cases diagnosed between the 2nd and 4th decades of life.[3] Treatment strategies for CNs include resection, with or without radiation therapy, or biopsy followed by radiation therapy. The 5-year local tumor control rate is approximately 70%–100%.[8–10] Upfront stereotactic radiosurgery (SRS) achieves good tumor control rates for biopsy-proven CNs, even in some cases of large tumors.[11] The tumor control rates are high with both conventional fractionated external-beam radiation therapy (EBRT) and SRS, but the incidence of adverse radiation effects (AREs) may be lower after SRS (3%–20% with SRS vs 60% with EBRT).[4,12–14] However, while SRS ameliorates the risk of AREs with its focused targeting and steep dose falloff, the potential for distant (out-field) recurrence remains with this therapeutic modality.

Tumor recurrence after treatment of CNs is associated with neurological morbidity and mortality.[12,14,15] Because of the rarity of CNs and the limited statistical power of predominantly single-center SRS studies to date, the incidence and risk factors of distant recurrence are not well defined in the literature. Additionally, the risk factors for CSF diversion procedures are not well characterized in CN patients treated with SRS. Therefore, the aims of this multicenter, retrospective cohort study were to 1) determine the rates of local tumor control and progression-free survival (PFS) after SRS for CNs, 2) characterize AREs associated with CNs treated with SRS, and 3) identify risk factors for CSF shunt surgery in SRS-treated CN patients.

Methods

Patient Population

Patients who underwent SRS for CNs between 1994 and 2018 at 10 institutions participating in the International Radiosurgery Research Foundation (IRRF) were included in the study. The contribution from each site was as follows: Beaumont Health System (n = 2), Beijing Tiantan Hospital (n = 8), Cleveland Clinic (n = 4), Na Homolce General Hospital (n = 2), Taipei Veterans General Hospital (n = 32), University of Colorado (n = 1), University of Louisville (n = 2), University of Sherbrooke (n = 4), University of Virginia (n = 7), and New York University (n = 1). Data were collected retrospectively under the institutional review board–approved protocols of each respective institution. As this was a retrospective study, patient consent was not required.

A template database with selected variables was created and sent to all participating centers. De-identified data from each contributing institution were screened for inconsistencies, verified for compliance with current standards of patient privacy and personal information protection, and pooled by an independent third party. The pooled data were transmitted to the first and senior authors for analysis on behalf of the IRRF. Any uncertainties or ambiguities in the data were addressed by the contributing center.

Baseline Data and Variables

The baseline data comprised patient demographics, treatments before SRS, tumor characteristics, and SRS parameters. The patient demographics included age at SRS, sex, and presenting symptoms. Treatments before SRS included the need for CSF shunt surgery, extent of tumor resection (gross-total resection [GTR], subtotal resection [STR], or biopsy), and time interval from tumor surgery to SRS. Tumor characteristics included location and volume. SRS variables included the number of tumors treated, treatment volume, margin dose, maximum dose, and isodose line.

Composition of the Study Cohort

The inclusion criteria for this study were patients with 1) CNs that were treated with single-session SRS, 2) sufficient baseline data to assess demographic information, and 3) ≥ 3 months of radiological and clinical follow-up. After excluding 2 patients who were treated with hypofractionated CyberKnife radiosurgery and 1 with no clinical follow-up, the study cohort comprised 60 eligible patients.

Table 1 details the baseline patient and tumor characteristics of the study cohort. Twenty-nine patients (48%) were male. The median age at the time of SRS was 30 years (range 5–71 years). The most common clinical symptom was headache (n = 45/60, 75%). The most common tumor location was the lateral ventricle (n = 58/60, 97%). The median time from the last tumor surgery to SRS was 6 months (range 1–120 months). Five patients underwent pre-SRS EBRT.

SRS Technique

SRS was performed using either the Gamma Knife (Elekta AB) or the CyberKnife (Accuray Inc.); the specific models used differed by year and availability at each institution. The general protocol for Gamma Knife SRS has been previously described.[16,17] Briefly, with the patient under local or monitored anesthesia, a Leksell model G stereotactic frame (Elekta AB) was affixed to the calvaria. The CyberKnife SRS procedure was frameless and performed without anesthesia. Thin-slice T1- and T2-weighted MRI sequences including gadolinium contrast-enhanced images were obtained for treatment planning.

Treatment parameters and dose plans were dictated, in part, by tumor location and size, distance between the tumor and normal brain, and previous EBRT. Exposure of the bilateral fornices to radiation was minimized when feasible. Dose planning and SRS delivery were performed by a multidisciplinary team of radiation oncologists, medical physicists, and neurosurgeons.

SRS was performed after resection in 50 patients; there were 7 cases of tumor recurrence after GTR (3 tumors were treated with upfront SRS to the resection bed, and 4 tumors were treated due to tumor recurrence) and 43 cases of adjuvant therapy after STR and as an upfront treatment in 10 patients (4 tumors were treated with upfront SRS for residual tumors and the remaining 39 tumors were treated

TABLE 1. Patient characteristics: descriptive statistics (total cases = 60)

Variable	Value
Male sex	29 (48%)
Median age at SRS, yrs (range)	30 (5–71)
Clinical symptoms	
Asymptomatic	8 (13%)
Headache	45 (75%)
Nausea/vomiting	22 (37%)
Memory impairment	12 (20%)
Visual disturbance	7 (12%)
Seizure	11 (18%)
Ataxia	9 (15%)
Location of lesions	
Lateral ventricle	52 (87%)
Lateral & 3rd ventricles	3 (5%)
Lateral & 4th ventricles	2 (3%)
Lateral, 3rd, & 4th ventricles	1 (2%)
Only 3rd ventricle	2 (3%)
Previous shunt	22 (37%)
Tumor <6 cm^3	7/31 (23%)
Tumor >6 cm^3	15/29 (52%)
Diagnosis	
Imaging (no histology)	5 (8%)
Previous op	55 (92%)
Previous op type (n = 55)	
GTR	7/55 (13%)
STR	43/55 (78%)
Biopsy	5/55 (9%)
Median time from op to SRS, mos (range)	6 (1–120)
Previous EBRT	5 (8%)
Reason for SRS	
Regrowth after total removal	7 (12%)
Adjuvant therapy after partial removal	43 (72%)
Upfront treatment w/ or w/o biopsy	10 (17%)
SRS parameter	
No. of treated tumors	
1	53 (88%)
2	4 (7%)
3	3 (5%)
Median treatment vol, cm^3 (range)	5.9 (0.2–48.9)
Median margin dose, Gy (range)	13 (10–30)
Median maximum dose, Gy (range)	23 (15–66)
Median isodose line, % (range)	56 (30–67)
Median clinical follow-up, mos (range)	61 (3–241)
Median imaging follow-up, mos (range)	53 (3–241)

Values presented as number (%) unless otherwise indicated.

because of tumor recurrence). Five cases were biopsy-proven CNs, and the other 5 cases of CNs were diagnosed by neuroimaging alone without histopathological confirmation. The number of tumors treated with SRS was 1, 2, and 3 in 53 (88%), 4 (7%), and 3 (5%) patients, respectively. Patients who had 2 or 3 SRS targets were those with multiple remnants after surgery or new tumors after surgery. For patients with multiple SRS-treated lesions, only the parameters of the largest tumor were selected for analysis. The median treatment volume, margin dose, and maximum dose were 5.9 cm^3 (range 0.2–48.9 cm^3), 13 Gy (range 10–30 Gy), and 23 Gy (range 15–66 Gy), respectively (Table 1).

Clinical and Neuroimaging Follow-Up

Clinical and neuroimaging assessments were generally performed at 6-month intervals for the first 2 years after SRS and then yearly thereafter. When MRI was contraindicated, CT with contrast was performed instead. Additional neuroimaging was performed in patients with neurological changes during the follow-up period. All images were reviewed by the treating clinical team. Whenever possible, clinical follow-up was obtained concurrently with routine neuroimaging follow-up. When in-person follow-up was not feasible, clinical and neuroimaging data from other institutions or physicians were transmitted to the treating institution for review. All follow-up clinical and neuroimaging data were compared with data obtained at the time of SRS.

Outcomes

The radiological tumor outcomes after SRS were evaluated using the criteria proposed by the Response Assessment in Neuro-Oncology (RANO) group.[18] Tumor control was defined by the summation of stable disease, partial response, and complete response. Recurrence was categorized as local versus distant recurrence. Local recurrence was defined as progressive enlargement of the target lesions. Distant recurrence was defined as progression of an existing nontarget lesion or de novo formation of a new lesion. Local tumor control was defined as survival without local recurrence. PFS was defined as survival without local or distant recurrence. AREs and death were recorded. The Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring Schema[19] was used to evaluate the neurotoxicity of SRS.

Statistical Analysis

All statistical analyses were performed using IBM SPSS (version 24.0, IBM Corp.). Descriptive statistics for continuous and categorical variables are reported as median or mean and frequency or percentage, respectively. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to determine risk factors for overall tumor control, survival without local recurrence, and survival without distant recurrence. Hazard ratios and 95% confidence intervals were calculated for each variable.

The Kaplan-Meier method was used to compute PFS, local tumor control, and survival without distant recurrence over time. Comparisons of the aforementioned survival outcomes between patients with versus without pre-SRS EBRT were performed using the log-rank test. The binary logistic regression method was used to identify factors associated with pre-SRS shunt surgery. Odds ratios and 95% confidence intervals were calculated for each variable. Baseline variables in univariate analysis with a p value < 0.15 were entered into a multivariate binary logistic regression model to identify independent predictors

TABLE 2. Outcomes after SRS (in 60 patients)

Variable	No. of Patients (%)
Clinical status	
Improved	9 (15%)
No change	49 (82%)
Deteriorated/new neurological deficit	3 (5%)
Image outcome: RANO criteria*	
Complete response	4 (7%)
Partial response	42 (70%)
Stable disease	10 (17%)
Progressive disease (local recurrence)	4 (7%)
Distant recurrence	4 (7%)
Overall recurrence	8 (13%)
ARE	4 (7%)
Grade I: mild/asymptomatic (n = 4)	4 (100%)
Shunt after SRS	2 (3%)
Death	1 (2%)

* Complete response, disappearance of all CNS target lesions sustained for at least 4 weeks; partial response, at least a 30% decrease in the sum longest diameter of CNS target lesions, using as reference the baseline sum longest diameter sustained for 4 weeks; stable disease, neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study; and progressive disease, at least a 20% increase in the sum longest diameter of CNS target lesions, taking as reference the smallest sum on the study.[18]

of pre-SRS shunt surgery. Statistical significance was defined as $p < 0.05$, and all tests were two-tailed.

Results

Radiological and Clinical Outcomes

Table 2 summarizes the radiological and clinical outcomes of the study cohort, which comprised 60 CN patients treated with SRS. Clinically, 58 patients (97%) showed stability or improvement of their pre-SRS symptoms. With respect to the targeted lesions, the rates of complete response, partial response, stable disease, and progressive disease (i.e., local recurrence) were 7%, (n = 4/60), 70% (n = 42/60), 17% (n = 10/60), and 7% (n = 4/60), respectively. Distant recurrence was observed in an additional 4 patients (7%). In total, tumor recurrence (local or distant) occurred in 8 patients (13%).

The median radiological and clinical follow-up durations after SRS were 53 and 61 months, respectively. The actuarial rates of PFS (i.e., survival without local or distant recurrence) at 2, 5, 8, and 10 years after were 96%, 89%, 85%, and 80%, respectively (Fig. 1A). The actuarial rates of survival without local recurrence (i.e., local tumor control) at 2, 5, 8, and 10 years were 98%, 93%, 93%, and 87%, respectively (Fig. 1B). The actuarial rates of survival without distant recurrence at 2, 5, 8, and 10 years were 98%, 96%, 92%, and 82%, respectively (Fig. 1C).

Post-SRS Treatment of Recurrent Tumors

Additional treatment after SRS was performed in 5 patients (8%) with local or distant recurrence (Table 3). Of the patients with local recurrence (n = 4), tumor resection was performed in 2, both of whom had tumor control at follow-up durations of 28 and 43 months. The remaining 2 patients with local recurrence opted for observation, and their tumors were radiologically stable at the last follow-up (durations of 15 and 38 months). Of the patients with distant recurrence (n = 4), repeat SRS was performed in 3, and 1 patient opted for conservative management. Tumor control was achieved at last follow-up in 3 patients with distant recurrences, including 2 treated with repeat SRS and 1 conservatively managed, at follow-up durations of 24, 28, and 156 months; the tumor in remaining patient

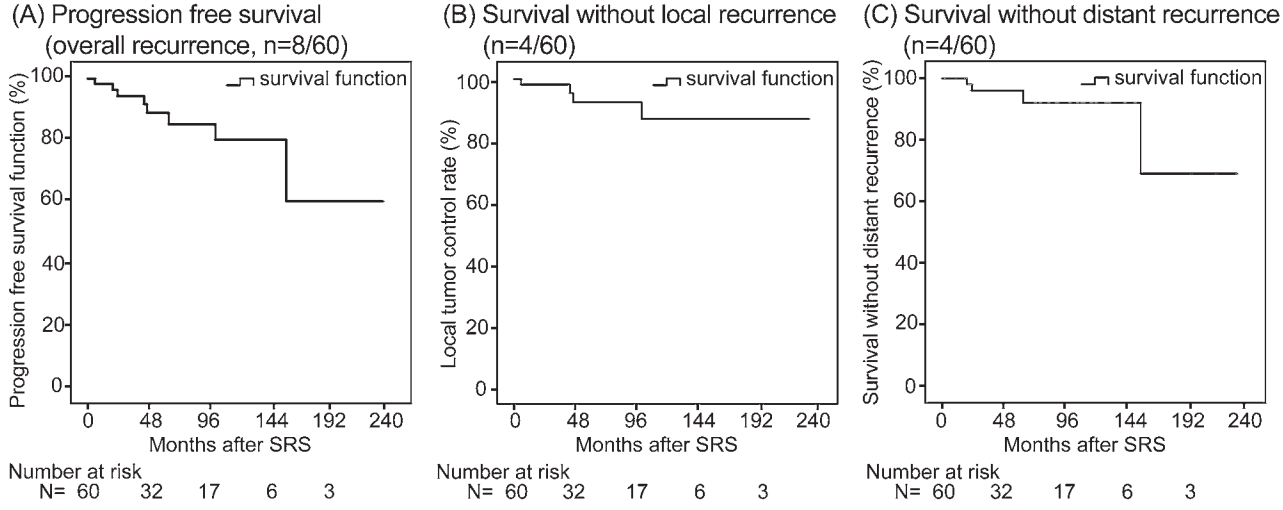

FIG. 1. A: Kaplan-Meier analysis of PFS after SRS. The actuarial rates for this endpoint at 2, 5, 8, and 10 years were 96%, 89%, 85%, and 80%, respectively. **B:** Kaplan-Meier analysis of survival without local recurrence (local tumor control) after SRS. The actuarial rates for this endpoint at 2, 5, 8, and 10 years were 98%, 93%, 93%, and 87%, respectively. **C:** Kaplan-Meier analysis of survival without distant recurrence after SRS. The actuarial rates for this endpoint at 2, 5, 8, and 10 years were 98%, 96%, 92%, and 82%, respectively.

TABLE 3. Treatment of recurrent cases

Case No.	Time to Recurrence (mos)	2nd Treatment	Treatment Vol (cm^3)	Margin Dose (Gy)	Final Tumor Control	PFS (mos)
Local recurrence						
23	46	Surgery			Yes	28
34	104	Surgery			Yes	43
46	48	No			Yes	38
52	6	No			Yes	15
Distant recurrence						
2	66	Repeat SRS	7.3	18	Yes	156
12	20	Repeat SRS	2.1 0.8 0.4 0.03	12 20 23 18	No*	
33	162	No			Yes	28
56	24	Repeat SRS	0.8	15	Yes	24

* Patient died of disseminated disease 21 months after SRS.

who underwent repeat SRS progressed, and the patient died of disseminated disease at 21 months of follow-up.

Risk Factors for Distant Tumor Recurrence

Table 4 details the univariate and multivariate Cox proportional hazards regression models for distant tumor recurrence. Only pre-SRS EBRT was significantly associated with distant recurrence in the univariate analysis ($p = 0.038$). Pre-SRS EBRT remained the only independent predictor of distant recurrence in the multivariate analysis (HR 20.43, 95% CI 1.89–383.00; $p = 0.044$). The actuarial rates of survival without distant recurrence at 1, 2, and 5 years were 100%, 67%, and 67%, respectively, with pre-SRS EBRT versus 100%, 100%, and 98%, respectively, without pre-SRS EBRT. Patients without pre-SRS EBRT had significantly higher rates of survival without distant recurrence ($p = 0.004$; Fig. 2).

Risk Factors for Pre-SRS Shunt Surgery in CN Patients

Table 5 details the univariate and multivariate logistic regression for pre-SRS shunt surgery, which was performed in 22 patients (37%). Only SRS treatment volume was significantly associated with shunt surgery in the univariate analysis ($p = 0.012$). Treatment volume remained

TABLE 4. Risk factors for distant tumor recurrence

Factor	Distant Tumor Recurrence		Univariate Analysis			Multivariate Analysis*		
	No (n = 56)	Yes (n = 4)	HR	95% CI	p Value	HR	95% CI	p Value
Male	28 (50%)	1 (25%)	0.49	0.05–4.85	0.544			
Mean age at SRS, yrs (SD)	32 (14)	34 (15)	1.03	0.96–1.11	0.415			
Pre-SRS shunt	19 (34%)	3 (75%)	4.47	0.46–43.35	0.197			
Pre-SRS tumor op	51 (91%)	4 (100%)	23.60		0.715			
Total tumor removal	7 (12%)	0 (0%)	0.04		0.736			
Tumor biopsy	4 (7%)	1 (25%)	3.65	0.33–40.49	0.292			
Pre-SRS EBRT	3 (5%)	1 (25%)	19.18	1.19–310.21	0.038	20.43	1.89–383.00	**0.044**
Mean time surgery to SRS, mos (SD)	17 (27)	15 (14)	1.00	0.97–1.04	0.956			
Multiple targets at SRS†	7 (12%)	0 (0%)	0.04	0.00–21,821.00	0.627			
Mean treated vol, cm^3 (SD)	9 (9)	16 (22)	1.01	0.94–1.09	0.814			
Mean margin dose, Gy (SD)	14 (3)	15 (2)	1.14	0.92–1.42	0.223			
Mean maximum dose, Gy (SD)	25 (7)	28 (5)	1.04	0.96–1.13	0.336			
Mean isodose line, % (SD)	54 (7)	55 (6)	0.97	0.85–1.11	0.634			
Mean image follow-up, mos (SD)	72 (57)	78 (54)	0.95	0.91–1.00	0.056	0.95	0.89–1.00	0.064

Values presented as number (%) unless otherwise indicated. Boldface type indicates statistical significance ($p < 0.05$). Cox regression, n = 4/60.

* Only factors with $p < 0.15$ in the univariate analysis were listed in the multivariate analysis.

† More than 1 tumor treated during SRS.

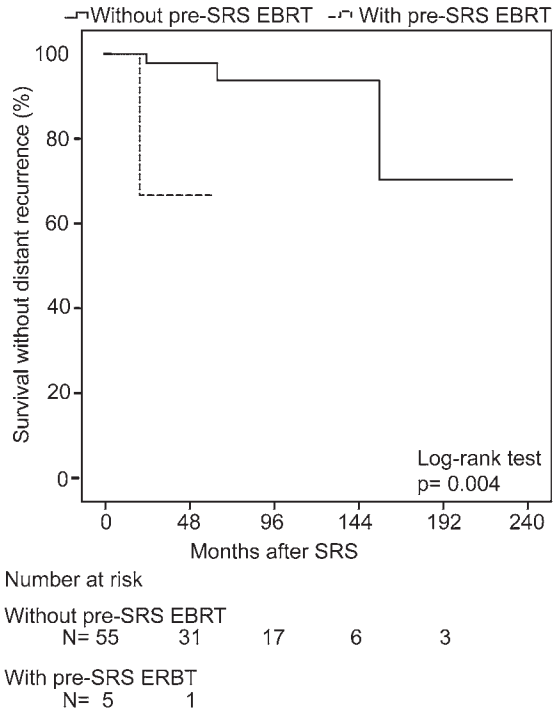

FIG. 2. Kaplan-Meier analysis of survival without distant recurrence comparing CN patients with (100%, 67%, 67% at 1, 2, and 5 years, respectively) versus without (100%, 100%, 98% at 1, 2, and 5 years, respectively) pre-SRS EBRT. The rates of distant recurrence were significantly higher in CNs treated with pre-SRS EBRT (p = 0.004, log-rank test).

the only independent risk factor for pre-SRS shunt surgery in the multivariate analysis (OR 1.08, 95% CI 1.01–1.15; p = 0.022). Two patients with pre-SRS CSF shunts underwent shunt revision surgery after SRS (n = 2/22, 9%).

Complications

AREs occurred in 4 patients (7%), which radiologically manifested as new T2-weighted hyperintensities in the peritumoral brain region. An ARE was only symptomatic in 1 patient (2%), who developed transient diplopia. Overall, 3 patients had worsening symptoms, including the aforementioned patient with a symptomatic ARE. Another patient developed progressive headaches due to multiple distant recurrences. Despite repeat SRS for the recurrent tumors, the patient died at 21 months of progressive disease. The third patient experienced monocular visual deterioration due to retinal vein occlusion without evidence of ARE or tumor recurrence.

Discussion

Surgery and radiation therapy are the typically employed treatments to manage CNs, whereas chemotherapy is reserved for rare cases of recurrent, progressive, or disseminated disease.[15,20,21] Resection of CNs is the first-line treatment, which affords 5-year local tumor control rates of 70%–100%.[8,10,22] However, GTR can be associated with high complication rates due to the surrounding critical neurovascular structures.[4,8,9,23–25] In addition, many CNs are noted to be hypervascular on angiography,[26] which could result in considerable intraoperative or postoperative hemorrhage.[14,17,27]

The supplementation of stereotactic radiotherapy with adjuvant EBRT affords tumor control rates that are comparable with GTR.[8,9] Compared with radiotherapy, SRS reduces the radiation dose to the surrounding normal brain tissue and critical structures.[13,28] In this multicenter, retrospective analysis, we present the largest cohort of CNs treated by SRS to date to evaluate the rates and risk factors for local tumor control, distant tumor recurrence, and pre-SRS CSF shunt surgery.[4,23–25]

Local Tumor Control

Rades and Fehlauer performed a meta-analysis that included patients with CNs treated by surgery with or without EBRT to compare different strategies for achieving tumor control.[8] In this report, STR alone had significantly lower 5-year rates of local tumor control (46%) compared with other single or combination treatment approaches. Supplementing STR with adjuvant EBRT increases the 5-year local tumor control rate (83%), and these outcomes are comparable to GTR with or without adjuvant EBRT.[9] Even for atypical neurocytomas, the additional adjuvant EBRT could still increase the 5-year local tumor control rate from 5%–7% to 65%–70%.[6,9]

CNs are more frequently diagnosed in young adults. Thus, the benefits of a more focused, rather than wide-field, radiotherapy seem appealing.[10] Chen et al. evaluated the long-term outcomes of postoperative EBRT in a cohort of 67 CNs.[12] Thirty-eight patients experienced late neurotoxicity (60%), including 10 with grade 2 or 3 toxicities, as defined by the Common Terminology Criteria for Adverse Events. The most common ARE in that series was short-term memory impairment.

Given the focal and well-demarcated nature of most CNs, SRS has become an important treatment option for these lesions.[28] In the present study, the SRS afforded high rates of local tumor control (93% at 5 years, 87% at 10 years) and PFS (89% at 5 years, 80% at 10 years). SRS also exhibited an excellent safety profile in our cohort. Four patients developed AREs (7%), but only 1 patient was symptomatic (mild diplopia). In other published studies of SRS for residual or recurrent CNs, the 5-year local tumor control rate ranged from 90% to 94%, with neurotoxicity in 3%–20% of patients (Table 6).[14,29–31]

The local tumor control rates of EBRT and SRS were compared in a previous case series (5-year local control rates of 87% and 100%, respectively)[13] and a review (overall local control rate of 88% and 93%, respectively).[28] Unlike SRS for other intracranial neoplasms, the margin dose did not correlate with local tumor control in this study (Table 6).[14,30–32]

Distant Tumor Recurrence and Disseminated Disease

Survival without distant tumor recurrence was observed in 96% and 82% at 5 and 10 years, respectively. This endpoint has not been rigorously assessed in the current literature.[14,17,22,30] One study proposed the use of postoperative EBRT for CNs to prevent distant recurrence.[8] Our Cox pro-

TABLE 5. Predictors for pre-SRS shunt surgery

Factor	Any Shunt Surgery		Univariate Analysis			Multivariate Analysis*		
	No (n = 38)	Yes (n = 22)	OR	95% CI	p Value	OR	95% CI	p Value
Male	18 (47%)	11 (5%)	1.11	0.39–3.18	0.844			
Mean age at treated SRS, yrs (SD)	30 (14)	28 (15)	1.02	0.98–1.06	0.260			
Headache	26 (68%)	19 (86%)	2.92	0.72–11.81	0.132	2.18	0.50–9.02	0.310
Pre-SRS tumor surgery	35 (92%)	20 (91%)	0.86	0.13–5.57	0.872			
Total tumor removal	3 (8%)	4 (18%)	2.67	0.53–13.38	0.233			
Tumor biopsy	2 (5%)	3 (14%)	2.91	0.44–19.13	0.266			
Pre-SRS EBRT	4 (11%)	1 (5%)	0.41	0.04–3.87	0.432			
Mean time surgery to SRS, yrs (SD)	15 (28)	21 (24)	1.01	0.99–1.03	0.437			
Multiple targets at SRS†	4 (11%)	3 (14%)	1.34	0.27–6.64	0.718			
Mean treated volume, cm^3 (SD)	7 (6)	15 (13)	1.09	1.02–1.16	0.012	1.08	1.01–1.15	**0.022**
Mean margin dose, Gy (SD)	14 (3)	14 (2)	0.92	0.74–1.15	0.483			
Mean maximum dose, Gy (SD)	35 (5)	27 (10)	1.03	0.96–1.12	0.397			
Mean isodose line, % (SD)	55 (6)	53 (7)	0.96	0.89–1.04	0.370			
Mean image follow-up, mos (SD)	70 (52)	48 (64)	1.00	0.99–1.01	0.634			

Values presented as number (%) unless otherwise indicated. Boldface type indicates statistical significance ($p < 0.05$). Logistic regression, n = 22/60.

* Only factors with $p < 0.15$ in the univariate analysis were listed in the multivariate analysis.

† More than 1 tumor treated at SRS.

portional hazards regression showed that pre-SRS EBRT was the only predictor of distant recurrence. We hypothesize that CNs previously treated with EBRT may represent a subset of tumors that are more biologically aggressive and/or radioresistant. However, the number of cases of distant recurrence was limited, so our analysis for predictors of this endpoint should be interpreted with caution.

SRS might carry a higher risk for distant recurrence than EBRT due to its relatively smaller treatment field. However, the supposition that EBRT is more effective at preventing CN dissemination is not endorsed by the available literature.[28] Our findings support rigorous, long-term follow-up after SRS for CNs to facilitate early radiological identification of distant recurrence.

Shunt Surgeries in Patients With CNs

The need for CSF diversion is particularly relevant to the management of intraventricular tumors such as CNs. In addition to relieving the symptoms of obstructive hydrocephalus associated with CNs, CSF shunting could also aid in the management of post-SRS complications, such as ventriculomegaly, intraventricular hemorrhage, and peritumoral edema.[17,30,33,34] However, one must also consider the clinical and neurological implications of shunt-related complications, such as malfunction and infection.[4,17,30]

In the present study, 37% of CN patients underwent pre-SRS CSF shunt surgery. Treatment volume was the only risk factor for pre-SRS shunt surgery. This finding is consistent with the greater likelihood of larger intraventricular tumors to impair or obstruct normal CSF flow. Pre-SRS shunt surgery was more frequently performed in patients with a tumor volume ≥ 6 cm^3 at the time of SRS (52% vs 32%, $p = 0.019$). Two of the 22 patients subsequently underwent post-SRS shunt revisions (9%). The tumors in the 2 patients with post-SRS CSF shunt revision were 9 and 12 cm^3 in volume at SRS, and they both showed partial responses to SRS based on RANO criteria (> 30% reduction in tumor diameter). For large CNs, shunt surgery may not be needed after a radical tumor surgery. Nevertheless, this result should be applied according to the uniqueness of each patient.

Limitations

Several limitations of this study should be recognized. Five patients were diagnosed with CNs based on clinical and radiographic evidence alone, without obtaining histopathology. It is possible that the tumors in these patients were pathologies other than CNs. Due to the retrospective design of this study, our findings and conclusions are subject to the inherent selection, treatment, and referral biases of each contributing institution and its physicians, although pooling data across multiple centers may somewhat mitigate the severity of these biases.

Some of the patients included in the present cohort have been previously evaluated in single-center studies from participating IRRF centers.[17,31] However, for the purposes of this study, all patient data were updated as a new data set, which provides sufficient case numbers for statistical analysis. The inclusion of more patients in this multicenter study provides increased statistical power for determining risk factors, compared with prior single-center studies with smaller sample sizes. Since all of the patients in our cohort were treated with SRS, we are unable to compare the SRS outcomes for CNs to those of alternate management options, such as resection (initial or repeat), EBRT (upfront or postoperative), and surveillance.

TABLE 6. Summary of major studies involving EBRT or SRS for central neurocytomas with 5- and 10- year survival and tumor control rates

Authors & Year	Modality, No. of Cases	Surgery, No. of Cases	Median Vol, cm^3 (range)	Median Therapeutic Dose, Gy (range)	Median Follow-Up	PFS	Local Tumor Control Rate	Complication, Neurotoxicity Grade
Rades & Fehlauer, 2002[8]	EBRT, 128	GTR, 30; ITR, 98	NA	NA	>12	5-yr: GTR 95%, STR 90%	3-yr: GTR 96%, STR 89%; 5-yr: GTR 89%, STR 83%	NA
Rades et al., 2004[6] (atypical CN)	EBRT, 53	GTR, 13; ITR, 40	NA	NA	>12	3-yr: GTR 90%, STR 87%; 5-yr: GTR 90%, STR 78%	3-yr: GTR 81%, STR 85%; 5-yr: GTR 53%, STR 70%	NA
Rades & Schild, 2006[9]	EBRT, 177	GTR, 43; ITR, 134	NA	Typical tumor, NA (50–54); atypical tumor, NA (56–60)	44	5-yr: GTR 97%, STR 89%; 10-yr: GTR 97%, STR 89%	5-yr: GTR 87%, STR 83%; 10-yr: GTR 87%, STR 76%	NA
Rades & Schild, 2006[13]	EBRT, 41; SRS, 21	ITR, 62	NA	EBRT, 54 (43–60); SRS, 15 (10–24)	EBRT, 48; SRS, 42	5-yr: EBRT, 100%, SRS, 100%	5-yr: EBRT, 87%, SRS, 100%	NA
Leenstra et al., 2007[4]	EBRT, 11; SRS, 5	GTR, 6; STR, 8; biopsy, 2	NA	EBRT, 56 (50–60); SRS, NA (14–20)	120	5-yr: NA; 10-yr: 79%	5-yr: 100%; 10-yr: 75%	Brain edema/memory deficits, 1 pt (20%, SRS group)
Genc et al., 2011[29]	GKRS, 22	Surgery, 18; biopsy, 4	7.55 (1–69)	16 (12–22)	24 (6–110)	NA	5-yr: 91.6%; 10-yr: 91.6	None
Chen et al., 2011[32]	GKRS, 14	Surgery, 14	20 (4–49)	12 (11–13)	65 (30–140)	NA	NA	None
Karlsson et al., 2012[30]	GKRS, 42	GTR, 2; STR, 33; biopsy, 1	8 (1–49)	13 (11–25)	59 (6–176)	NA	5-yr: 91%; 10-yr: 81%	Ventricular enlargement, 19 pts (45%)
Kim et al., 2013[21]	EBRT, 7; SRS, 17	GTR, 2; NTR, 1; STR, 11	8.2 (4–36 SRS group)	EBRT, 54 (50–56); SRS, 16 (9–20)	98 (13–245) (all pts)	5-yr: 93%; 10-yr: 90% (all pts)	NA	NA
Chen et al., 2014[12]	EBRT, 63	GTR, 24; STR, 28; PR, 9; biopsy, 2	NA	54 (46–60)	69 (15–129)	5-yr: GTR 94%, GTR, 96%, NTR, 100%	5-yr: GTR, 95%, STR, 100%, NTR, 91%	Overall no., 38 pts (60%); grade 1, 28 pts; grade 2, 7 pts; grade 3, 3 pts*
Pan & Lee, 2015[31]	GKRS, 23	Surgery, 20	13 (2–49)	12 (11–13)	75 (5–216)	NA	5-yr: 90%; 10-yr: 80%	NA
Yamanaka et al., 2016[14]	GKRS, 36	Surgery, 36	5 (0.1–23)	15 (10–20)	55 (3–180)	5-yr: 88%; 10-yr: 64%	5-yr: 94%; 10-yr: 86%	ICH, 2 pts; radiation injury/ memory disturbance, 1 pt (3%)
Lee et al., 2018[26]	GKRS, 28	Surgery, 23	NA	13 (11–15)	87 (3–194)	NA	NA	Memory impair, 1 pt; asymptomatic RIC, 2 pts
Current study	GKRS/CKRS, 60	GTR, 7; PR, 43; biopsy, 5	6 (0.2–49)	13 (10–30)	53 (3–241)	5-yr: 89%; 10-yr: 80%	5-yr: 93%; 10-yr: 87%	Grade I, 4 pts (7%)†

CKRS = CyberKnife radiosurgery; GKRS = Gamma Knife radiosurgery; ICH = intracranial hemorrhage; ITR = incomplete tumor resection; NA = not available; NTR = near-total resection; PR = partial resection; pt = patient; RIC = radiation-induced change.

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

† Grade I: RTOG Late Radiation Morbidity Scoring Schema.

Conclusions

SRS affords a favorable risk-to-benefit profile for the management of CNs, with high rates of local tumor control and low risks of symptomatic complications. A modest proportion of CN patients will have distant tumor recurrence after SRS, so long-term surveillance after treatment is prudent. Distant recurrence occurs more frequently in patients with previously irradiated CNs, which suggests that the tumors in these patients are more biologically aggressive or radioresistant. Patients with large CNs are more likely to require CSF shunt placement before SRS.

References

1. Hassoun J, Söylemezoglu F, Gambarelli D, et al. Central neurocytoma: a synopsis of clinical and histological features. *Brain Pathol*. 1993;3(3):297–306.
2. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol*. 2016;131(6):803–820.
3. Nader R, Gragnaniello C, Berta SC, et al, eds. *Neurosurgery Tricks of the Trade*. New York: Thieme; 2014.
4. Leenstra JL, Rodriguez FJ, Frechette CM, et al. Central neurocytoma: management recommendations based on a 35-year experience. *Int J Radiat Oncol Biol Phys*. 2007;67(4):1145–1154.
5. Rades D, Fehlauer F, Lamszus K, et al. Well-differentiated neurocytoma: what is the best available treatment? *Neuro Oncol*. 2005;7(1):77–83.
6. Rades D, Fehlauer F, Schild SE. Treatment of atypical neurocytomas. *Cancer*. 2004;100(4):814–817.
7. Vasiljevic A, François P, Loundou A, et al. Prognostic factors in central neurocytomas: a multicenter study of 71 cases. *Am J Surg Pathol*. 2012;36(2):220–227.
8. Rades D, Fehlauer F. Treatment options for central neurocytoma. *Neurology*. 2002;59(8):1268–1270.
9. Rades D, Schild SE. Treatment recommendations for the various subgroups of neurocytomas. *J Neurooncol*. 2006;77(3):305–309.
10. Schild SE, Scheithauer BW, Haddock MG, et al. Central neurocytomas. *Cancer*. 1997;79(4):790–795.
11. Chen KP, Lee CC, Liao CL, et al. Upfront Gamma Knife surgery for giant central neurocytoma. *World Neurosurg*. 2017;97:751.e15–751.e21.
12. Chen YD, Li WB, Feng J, Qiu XG. Long-term outcomes of adjuvant radiotherapy after surgical resection of central neurocytoma. *Radiat Oncol*. 2014;9:242.
13. Rades D, Schild SE. Value of postoperative stereotactic radiosurgery and conventional radiotherapy for incompletely resected typical neurocytomas. *Cancer*. 2006;106(5):1140–1143.
14. Yamanaka K, Iwai Y, Shuto T, et al. Treatment results of Gamma knife radiosurgery for central neurocytoma: report of a Japanese multi-institutional cooperative study. *World Neurosurg*. 2016;90:300–305.
15. Mozes P, Szanto E, Tiszlavicz L, et al. Clinical course of central neurocytoma with malignant transformation—an indication for craniospinal irradiation. *Pathol Oncol Res*. 2014;20(2):319–325.
16. Shrivastava A, Mohammed N, Xu Z, et al. Outcomes after gamma knife stereotactic radiosurgery in pediatric patients with Cushing disease or acromegaly: a multi-institutional study. *World Neurosurg*. 2019;125:e1104–e1113.
17. Yen CP, Sheehan J, Patterson G, Steiner L. Gamma knife surgery for neurocytoma. *J Neurosurg*. 2007;107(1):7–12.
18. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270–e278.
19. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31(5):1341–1346.
20. Brandes AA, Amistà P, Gardiman M, et al. Chemotherapy in patients with recurrent and progressive central neurocytoma. *Cancer*. 2000;88(1):169–174.
21. Kim JW, Kim DG, Kim IK, et al. Central neurocytoma: long-term outcomes of multimodal treatments and management strategies based on 30 years' experience in a single institute. *Neurosurgery*. 2013;72(3):407–414.
22. Lenzi J, Salvati M, Raco A, et al. Central neurocytoma: a novel appraisal of a polymorphic pathology. Our experience and a review of the literature. *Neurosurg Rev*. 2006;29(4):286–292.
23. Chen CL, Shen CC, Wang J, et al. Central neurocytoma: a clinical, radiological and pathological study of nine cases. *Clin Neurol Neurosurg*. 2008;110(2):129–136.
24. Hallock A, Hamilton B, Ang LC, et al. Neurocytomas: long-term experience of a single institution. *Neuro Oncol*. 2011;13(9):943–949.
25. Park HK, Steven D C. Stereotactic radiosurgery for central neurocytoma: a quantitative systematic review. *J Neurooncol*. 2012;108(1):115–121.
26. Lee CC, Chou CL, Chen CJ, et al. Stereotactic radiosurgery for hypervascular intracranial tumors. *J Neurooncol*. 2018;140(3):547–558.
27. Sharma MC, Sarkar C, Karak AK, et al. Intraventricular neurocytoma: a clinicopathological study of 20 cases with review of the literature. *J Clin Neurosci*. 1999;6(4):319–323.
28. Garcia RM, Ivan ME, Oh T, et al. Intraventricular neurocytomas: a systematic review of stereotactic radiosurgery and fractionated conventional radiotherapy for residual or recurrent tumors. *Clin Neurol Neurosurg*. 2014;117:55–64.
29. Genc A, Bozkurt SU, Karabagli P, et al. Gamma knife radiosurgery for cranial neurocytomas. *J Neurooncol*. 2011;105(3):647–657.
30. Karlsson B, Guo WY, Kejia T, et al. Gamma Knife surgery for central neurocytomas. *J Neurosurg*. 2012;117(suppl):96–101.
31. Pan DH, Lee CC. The management of incidental central neurocytoma. *Neurosurg Clin N Am*. 2015;26(1):57–66.
32. Chen MC, Pan DH, Chung WY, et al. Gamma knife radiosurgery for central neurocytoma: retrospective analysis of fourteen cases with a median follow-up period of sixty-five months. *Stereotact Funct Neurosurg*. 2011;89(3):185–193.
33. Martín JM, Katati M, López E, et al. Linear accelerator radiosurgery in treatment of central neurocytomas. *Acta Neurochir (Wien)*. 2003;145(9):749–754.
34. Tanaka H, Sasayama T, Yamashita H, et al. Rapid tumor growth with glial differentiation of central neurocytoma after stereotactic radiosurgery. *J Clin Neurosci*. 2016;31:188–192.

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