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REVIEW

Surgery versus stereotactic radiosurgery for the treatment of multiple meningiomas in neurofibromatosis type 2: illustrative case and systematic review

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Abstract Neurofibromatosis type 2 (NF2) is a genetic neoplastic disorder that presents with hallmark bilateral vestibular schwannomas and multiple meningiomas. Though the current standard of care for meningiomas includes surgery, the multiplicity of meningiomas in NF2 patients renders complete resection of all developing lesions infeasible. Stereotactic radiosurgery (SRS) may be a viable non-invasive therapeutic alternative to surgery. We describe a particularly challenging case in a 39-year-old male with over 120 lesions who underwent more than 30 surgical procedures, and review the literature. We also searched three popular databases and compared outcomes of SRS versus surgery for the treatment of multiple meningiomas in patients with NF2. A total of 50 patients (27 radiosurgical and 23 surgical) were identified. For patients treated with SRS, local tumor control was achieved in 22 patients (81.5%) and distal control was achieved in 14 patients (51.8%). No malignant inductions were observed at an average follow-up duration of 90 months. Complications in the SRS-treated cohort were reported in 9 patients (33%). Eight patients (29.6%) died due to disease progression. Six patients experienced treatment failure and required further management. For NF2 patients treated with surgery, 11 patients (48%) showed tumor recurrence and 10 patients (43.5%) died due to neurological complications. SRS may be a safe and effective alternative for NF2-associated meningiomas. Further studies are required to identify the ideal radiosurgical candidate.

Keywords Neurofibromatosis II · Multiple meningioma · NF2 · Surgery · Radiosurgery

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Abbreviations

NF2	Neurofibromatosis type II
NF2-M	Neurofibromatosis type II-associated meningioma
SRS	Stereotactic radiosurgery
GKS	Gamma Knife Surgery
LC	Local control

Introduction

Neurofibromatosis type 2 (NF2) is a neuro-oncological disorder caused by a mutation in the merlin gene on chromosome 22q.12 and leads to the formation of multiple lesions along the cutaneous, ophthalmic, and central nervous systems [4, 16, 19, 20]. NF2 is characterized by bilateral vestibular schwannomas, but meningiomas can occur in 45–58% of patients [4, 19, 59]. In these patients, the presence of meningiomas is associated with a multitude of other lesions and increases the risk of neurological deficits, surgical morbidity, and mortality [8].

NF2-associated meningiomas (NF2-M) are also thought to be more aggressive compared to sporadic meningiomas [59].

Conservative management and observation of NF2-M is often the preferred option until rapid growth is shown on imaging. However, treatment paradigms for these lesions in NF2 patients are absent. Although a total of 45–58% of patients with NF2 present with intracranial meningiomas, the progression of meningiomas is not axiomatic [4, 19, 47, 55, 57]. One large retrospective study reported no significant tumor progression in 66% of 287 meningiomas present in 74 patients [24]. Some authors have previously documented accelerated average growth potential (0.01–6.7 cm^3/year) in NF2-M, especially among the pediatric population, as compared with the growth rate of non-syndromic meningiomas (0.2–2.5 cm^3/year) [9, 16, 52, 54, 59]. Serial surveillance protocols for these patients have also not been described.

Currently, surgery is the primary treatment modality for meningiomas in NF2 patients, but there are concerns that surgery may prove to be impractical given the multiplicity of tumors and common locations in high-risk anatomical regions such as the skull base and optic nerve sheath. In recent years, stereotactic radiosurgery (SRS) has emerged as a potential alternative treatment because of its high local control (LC) rate, 60 to 100% in non-syndromic meningiomas [21, 27, 33–35, 39, 41, 42, 50, 51, 58, 72, 76, 77]. However, because of the underlying pathophysiology of NF2, there is concern for malignant induction and acceleration of tumor growth following SRS [7, 18, 45, 56]. Accordingly, there are limited studies examining the use of SRS as a primary treatment modality for NF2 patients afflicted with multiple meningiomas. Here, we present one such complex case of a 39-year-old male, where complete surgical resection of all meningiomas was infeasible. We also systematically analyze the review of literature to evaluate outcomes of SRS and surgery in patients with NF2-associated multiple meningiomas.

Case illustration

A 39-year-old male with a history of NF2 and 120 central nervous system lesions, who had undergone more than 40 surgical procedures, presented to our clinic for continued care of his complex pathologies. At age 15, the patient first sought medical care for sudden right-sided hearing loss, at which point he was diagnosed with bilateral vestibular schwannomas, as well as a small subependymal tumor. In the intervening years, the patient underwent 36 surgical resections for various tumors, including bilateral vestibular schwannomas, lumbar spinal tumor, right posterior tibialis sciatic nerve neuroma, and left cerebellopontine angle meningioma. Additional treatments included CyberKnife treatment for a T9 spinal cord ependymoma and jugular foramen schwannoma and shunt placement for hydrocephalus.

At age 35, the patient first presented at our institution for management of his complex disease process. One week prior, the patient suffered grand-mal seizures after halting an experimental drug therapy (SOM230) for his progressive intracranial meningiomas. A left parieto-occipital meningioma was suspected as the cause of his seizures and he was referred to neurosurgery for further management. Imaging studies confirmed enlargement of a right parieto-occipital and right tentoria/posterior fossa meningioma with adjacent edema, compared to imaging taken 16 months prior (Fig. 1a–c).

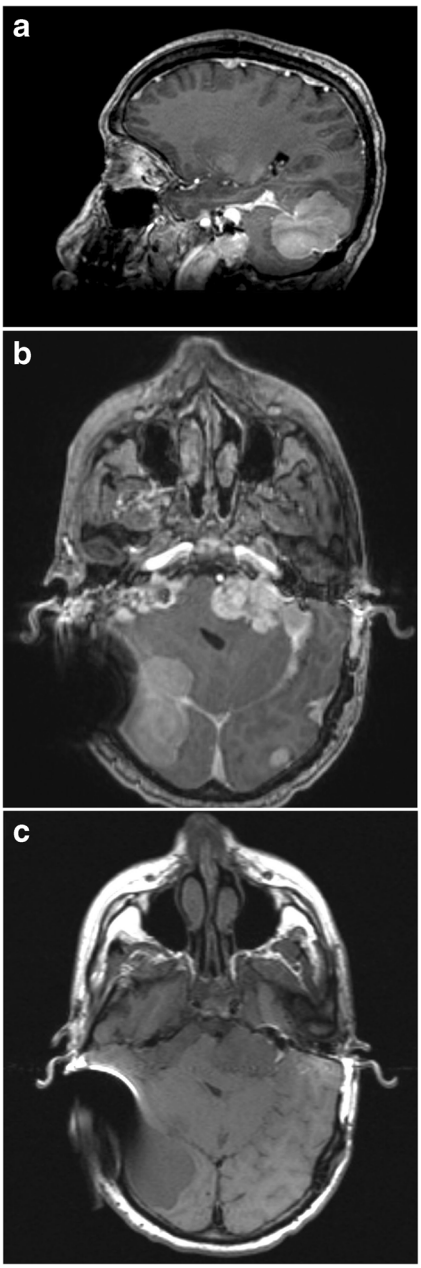

Fig. 1 Pre-operative images for our patient. **a** Sagittal T1-weighted MRI with contrast; **b** axial T1-weighted MRI with contrast; and **c** axial T1-weighted MRI without contrast showing multiple meningiomas. Patient's bilateral cochlear implants contribute to artifact and image degradation

Multiple large meningiomas along the cerebral and cerebellar convexities, tentorium, and cerebellar pontine angle cisterns were also noted with marked mass effect on the brainstem and pons. Surgical resection of the left parieto-occipital meningioma was performed. Postoperative imaging showed gross total resection and decreased mass effect (Fig. 2a–c).

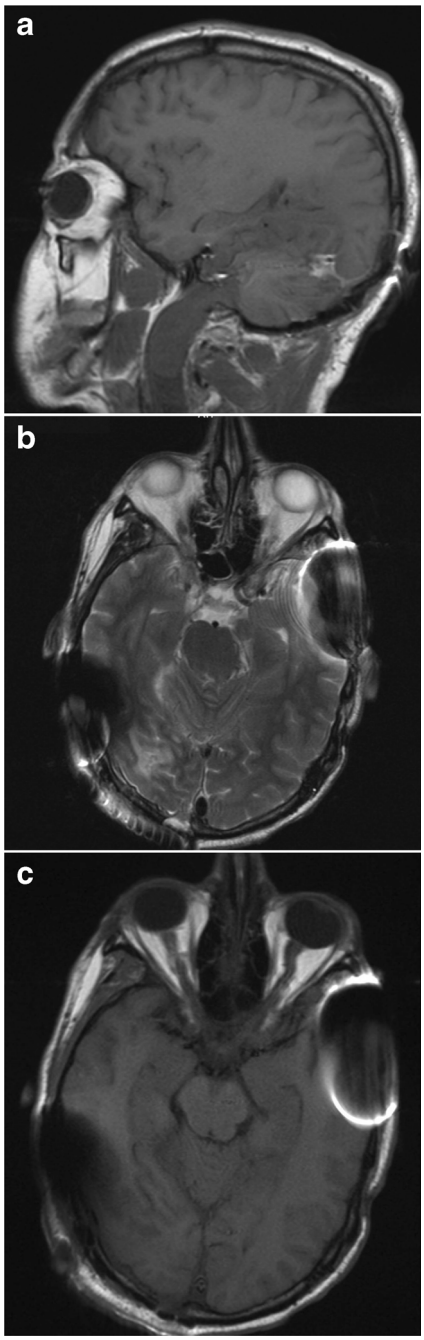

Fig. 2 Postoperative images for our patient. **a** Sagittal T1-weighted MRI without contrast resection of large meningioma along right posterior cerebellar and occiptal convexity; **b** axial T2-weighted MRI; **c** axial T1-weighted MRI without contrast showing reduced mass effect on the pons and brainstem

The patient was discharged home on postoperative day 5, only to re-present to the emergency department the following evening with a right femoral deep vein thrombosis and bilateral aspiration pneumonia, which evolved to sepsis. He was managed in the ICU for 9 days before being discharged home. In the ensuing 8 years, he underwent several other surgeries, including resection of a lumbosacral schwannoma, ulnar nerve decompression, and left eye alignment for double vision. The complex nature of this case served as the rationale for this review.

Material and methods

Article selection and data collection

Adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (www.prisma-statement.org) was maintained throughout this study. A strategic Boolean search was conducted by independent authors using the PubMed, Web of Science, and Scopus databases in the past 5 years through January 2017 (Fig. 3a, b). Search terms included a combination of "neurofibromatosis type 2" AND "meningioma" AND "surgery" or "neurofibromatosis" AND "meningioma" AND "radiosurgery" AND "radiation." English, full-text articles that included clinically diagnosed NF2 patients based on the Manchester criteria were included. Papers which aggregated NF2 patients with NF1 or sporadic meningiomas were excluded. For the PubMed database, our filter for article types included the following: case report, clinical study, and clinical trials. The bibliographies of the identified studies were queried for additional relevant studies. Demographics (age and sex), radiosurgery parameters, Simpson grade (for surgical patients), and follow-up were extracted. The outcomes of interest included the following: Karnofsky performance score, recurrence, and survival status for surgically treated patients, as well as local and distal control rates, complications, and survival status for SRS-treated patients.

Statistical analysis

Wilcoxon signed-rank and Pearson's tests were performed to determine significance in age between the treatment modalities. Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC). A P value less than 0.05 was considered statistically significant.

Results

Eleven retrospective studies published during the years 1996 to 2016 were identified. Two studies assessed SRS and nine

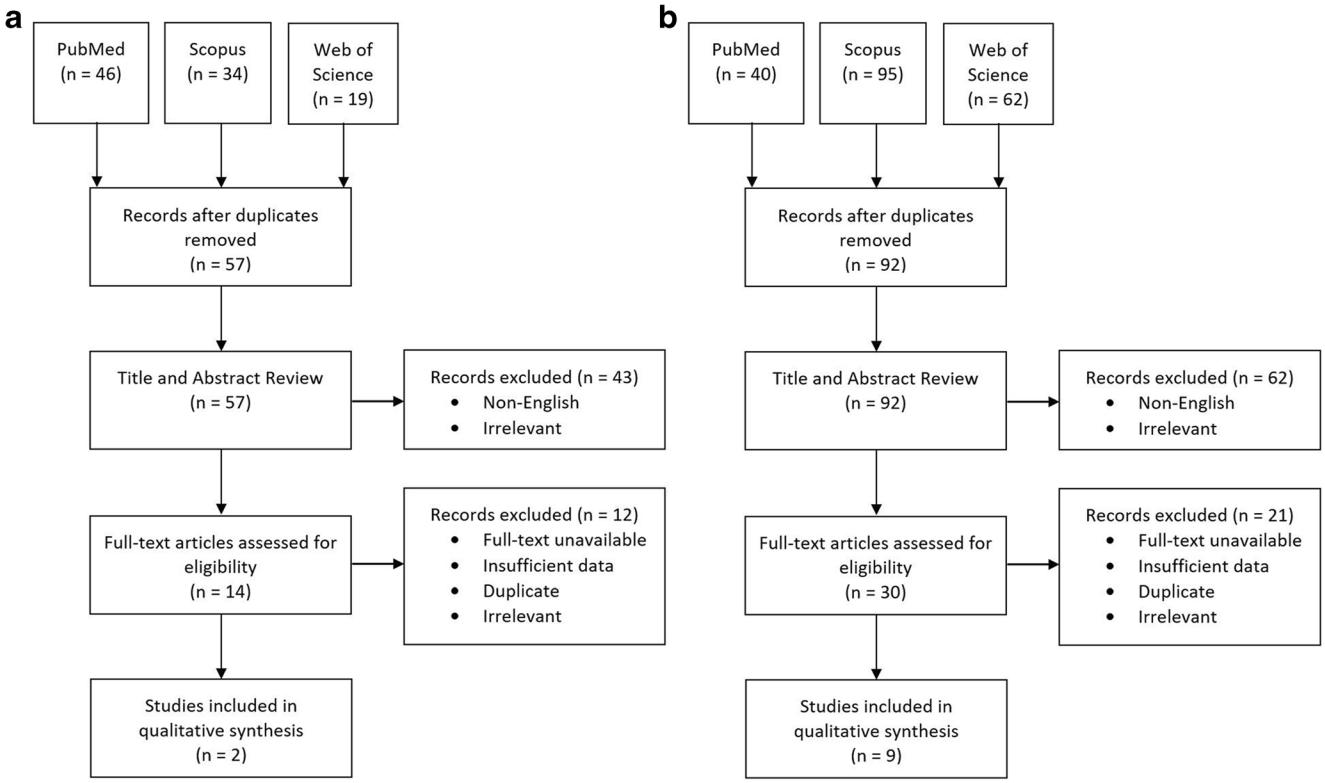

Fig. 3 **a** Search strategy for treatment of NF2-associated meningiomas with SRS; **b** search strategy for treatment of NF2-associated meningiomas with surgery

studies assessed surgery for multiple meningiomas in patients with NF2 [9, 10, 22, 26, 29, 43, 44, 62, 71, 75, 78, 80]. These studies are summarized in Table 1. Patient characteristics and clinical outcomes for both treatment modalities are displayed in Tables 2, 3, 4, and 5. A total of 50 patients were described; 27 (54%) patients were treated with SRS and 23 (46%) patients were treated with surgery. Compared to the surgical patients (12.6 ± 3.2 years; range 7–18 years), the radiosurgical patients (33.0 ± 11.4 years; range 13–54 years) were older at first treatment ($P < 0.0001$).

Surgery

In the surgical cohort, two patients (8.69%) underwent an additional surgery for progressive meningiomas. Gross total resections (GTR) were achieved in 14 cases, while 4 cases resulted in subtotal resections. Five cases had unreported outcomes. A total of 11 patients demonstrated tumor recurrence in cases of both gross total (72.72%) and subtotal resection (27.27%). World Health Organization (WHO) grades were available for 26 meningioma samples: WHO grade I (n = 20, 67.92%), WHO grade II (n = 4, 15.38%), and WHO grade III (n = 2, 7.79%) meningiomas. At last follow-up, 10 of 23 (43.47%) patients died as a result of neurological complications and 1 (4.35%) died after a motor vehicle accident.

SRS

The majority of meningiomas were distributed along three areas: convexity (n = 62 meningiomas), falcine/tentorium (n = 43), and parasagittal (n = 23). For NF2 patients treated initially with Gamma Knife Surgery (GKS), the mean marginal dose was 14.5 Gy (SD 2.2 Gy, range 12–20 Gy). Meningiomas that exhibited radiologic growth and caused symptomatic changes were treated with GKS. While two patients had prior GKS treatment, the remaining patients had not undergone any previous procedures—either SRS or surgery. Following the first GKS treatment, 13 patients required multiple subsequent GKS for treatment of other progressive meningiomas, achieving a distal control rate of 51.8%.

No cases of malignant induction were reported at an average follow-up duration of 90 months (SD 69.8 months, range 6–283 months). Five patients (18.5%) experienced complications including seizures, radiation necrosis, and peritumoral edema with one patient-related morality (3.7%) due to a major radiation-related complication of cerebral necrosis. Local tumor control was achieved in 22 patients (81.48%). Eight patients (29.63%) had disease progression and died. In nine histologically confirmed tumors, six (66.66%) were WHO grade I and three (33.33%) were WHO grade II. Nine patients had radiological diagnoses of meningiomas (without pathologic verification).

Table 1 Summery of data for NF2 patients treated with surgery and SRS [8, 9, 21, 25, 28, 40, 41, 59, 67, 71, 74, 76, 78]

Author	Treatment	NF2 patients, *n*	Average age at first treatment, years	Male, *n* (%)	Female, *n* (%)	Average follow-up, months
Stanuszek et al. [71]	Surgery	3	13.7	1 (33.3%)	2 (66.6%)	NR
Baumgartner and Sorenson [9]	Surgery	2	13	2 (66.6%)	1 (33.3%)	NR
Walter et al. [78]	Surgery	1	11	0 (0%)	1 (100%)	NR
Gao et al. [22]	Surgery	3	14.3	2 (66.6%)	1 (33.3%)	113.7
Greene et al. [26]	Surgery	5	13.6	4 (80%)	1 (20%)	120
Im et al. [29]	Surgery	4	10	1 (25%)	3 (75%)	116.3
Rochat et al. [62]	Surgery	3	10.6	1 (33.3%)	2 (66.6%)	115.2
Tufan et al. [75]	Surgery	1	13	1 (100%)	0 (0%)	96
Zwerdling and Dothoage [80]	Surgery	1	16	1 (100%)	0 (0%)	NR
Liu et al. [43]	SRS	12	32.3	2 (16.6%)	10 (83.3%)	105.4
Birckhead et al. [10]	SRS	15	33.3	6 (40%)	9 (60%)	63

SRS stereotactic radiosurgery, *NR* not reported

Discussion

NF2 is a multiple neoplasm syndrome caused by a mutation in the Neurofibromin oncogene and is characterized by bilateral vestibular schwannomas and other neoplasms, including multiple meningiomas. Current standard of care for NF2-M involves observation until radiological confirmation of tumor growth or symptom development. At which point, surgical resection is considered the primary treatment modality. SRS as an adjuvant therapy remains controversial [4]. Because of the underlying pathophysiology of NF2, the use of SRS as a primary treatment modality has been previously discouraged attributed to the concern of de novo meningioma formation or malignant transformation following treatment [9, 23].

To date, the only cases of malignant transformation of NF2-associated tumors occurred following radiosurgical treatment of vestibular schwannomas with studies reporting 5-year local control rates around 75% [6, 7, 14, 28, 48, 53, 63, 68, 73, 74]. Thus, the role and risks of SRS for NF2-M are not well-defined. Our systematic analysis suggests that continued investigation of SRS as a non-invasive treatment modality is needed. Clinical trials are underway to investigate the use of experimental drugs in cases of heavy tumor burden [2, 13, 25, 67].

Histopathological heterogeneity

The majority of meningiomas included in this study were benign. The distribution of grades in the SRS group is consistent with the literature, which reports an atypical histology in 29% of NF2-M and malignant histology in 6% of lesions [24]. Differential NF2 genotypes may contribute to different grades, and thus clinical prognoses in patients. Therefore, frequent treatment would be mandated to preserve neurological and motor function.

Other authors have shown that NF2-M are more often histologically benign, but can exhibit more variable growth patterns compared to sporadic meningiomas [11, 12, 22]. Even within the same patient, two separate meningiomas will exhibit idiosyncratic growth patterns and phenotypes [16]. Syndromic meningiomas may display extended periods of quiescence followed by punctuated growth [16, 43]. As a result of this saltatory growth pattern, NF2 patients with radiologically confirmed tumor growth and those in the pediatric population may require more frequent MRI surveillance and long-term follow-up post-treatment.

Although mutations in the NF2 gene underlie the pathophysiology for both NF2-associated and sporadic meningioma, the discrepancy in their aggressiveness phenotype may stem from biased sampling of these lesions [40, 61]. Since meningiomas are only surgically resected when they exhibit marked growth, these tumors are likely histologically over-represented. Accordingly, it is plausible that other NF2-M that are not resected are of low-grade histology, and because such low-grade meningiomas are not surgically removed, they are not documented in the literature. Furthermore, patients treated with SRS also previously underwent surgical resection for other tumors, again creating a tumor selection bias. This selective sampling, coupled with the increased tumor load in NF2 patients, may contribute to the notion that NF2-M exhibit a more aggressive phenotype.

Neuroanatomical distribution

NF2-M are commonly convexity, falcine/tectorial, and parasagittal. Small- to medium-sized meningiomas along the

Table 2 Characteristics of NF2 patients treated with surgery [8, 21, 25, 28, 41, 59, 67, 71, 74, 76, 78]

Patients by study, *n*	Age, years	Gender	Resection	Follow-up, months	WHO grade	Location of initially treated tumor(s)	Additional treatment
Stanuszek et al. (2014)							
1	15	M	Total	NR	1, 2	Parasagittal, skull base	Embolization
2	13	F	Total	NR	1	Thoracic intradural	
3	13	F	Total	NR	1	Parasagittal, skull base, intraventricular, thoracic intradural	fRST, embolization
Baumgartner and Sorenson (1996)							
4a	15	M	Total	NR	NR	Cervical	
4b	17	M	Total	NR	1, 2	Parasagittal, convexity	
5	11	F	Total	NR	2	Convexity	
Walter et al. (2008)							
6a	11	F	NR	NR	3	Coronary suture involving superior sagittalis sinus (falx meningioma), midline left sided occiptal lobe	SRS
6b	14	F	NR	NR	3	Falx meningioma	
Gao et al. (2009)							
7	18	M	Total	132	1	Convexity	fSRT
8	13	F	Subtotal	120	1	Lateral ventricle	fSRT
9	12	M	Total	89	1	Anterior fossa	
Greene et al. (2008)							
10	8	M	NR	312	1	Orbital	
11	14	F	NR	96	1	Foramen magnum	
12	10	M	NR	24	1	Orbital	
13	18	M	NR	12	1	Olfactory groove	
14	18	M	NR	156	1	Cervical spine	
Im et al. (2001)							
15	14	F	Total	3	2	Frontoparietal convexity	SRS
16	8	M	Total	234	1	Frontoparietal convexity	
17	11	F	Total	144	1	Intraventricular	
18	7	F	Subtotal	84	1	Intraorbital optic nerve sheath	SRS
Rochat et al. (2004)							
19	9	F	Total	122.4	1	Supratenorial/lateral	fSRT
20	12	F	Total	133.2	1	Supratenorial/midline	
21	11	M	Total	90	1	Supratenorial/midline	
Tufan et al. (2005)							
22	13	M	Subtotal	96	1	Left cerebellar pontine angle	fSRT
Zwerdling and Dothoage (2002)							
23	16	M	Subtotal	NR	1	Right frontal	

4b and 6b refer to the same patients as 4a and 6a treated for recurrent tumors, respectively

SRS stereotactic radiosurgery, *fSRT* fractionated stereotactic radiotherapy, *NR* not reported

falx and tentorium/parasagittal are thought to benefit the most from SRS, while convexity meningiomas are more amenable to surgery [33, 60]. SRS for convexity tumors may help limit the number of craniotomies [69]. Some authors caution against SRS due to the damage to small bridging veins, the potential of focal thrombosis, and a higher risk of radiation complications (e.g., edema) [30, 32]. SRS may trigger the release of hypoxic-dependent angiogenesis factor, resulting

Table 3 Outcomes for NF2 patients undergoing surgery for multiple meningioma [8, 21, 25, 28, 41, 59, 67, 71, 74, 76, 78]

Patients by study, *n*	KPS	Recurrence	Outcome
Stanuszek et al. (2014)			
1	NR	Yes	Alive
2	NR	No	Alive
3	NR	Yes	Alive
Baumgartner and Sorenson (1996)			
4a	NR	Yes	Alive
4b	NR		
5	NR	No	Alive
Walter et al. (2008)			
6a	NR	Yes	Alive
6b	NR		
Gao et al. (2009)			
7	0	Yes	Deceased
8	0	Yes	Deceased
9	60	Yes	Alive
10	0	No	Deceased
Greene et al. (2008)			
11	0	No	Deceased
12	0	No	Deceased
13	0	No	Deceased
14	0	No	Deceased
15	NR	No	Deceased[a]
Im et al. (2001)			
16	90	No	Alive
17	90	No	Alive
18	90	Yes	Alive
Rochat et al. (2004)			
19	0	Yes	Deceased
20	0	No	Deceased
21	0	Yes	Deceased
Tufan et al. (2005)			
22	< 30	Yes	Alive
Zwerdling and Dothoage (2002)			
23	NR	No	Alive

NR not reported, *KPS* Karnofsky performance score

[a] Patient 15 died from motor vehicle accident. All other patients died due to NF2-associated neurological complication

in swelling of the treated meningioma and blockage of cortical veins [70]. Thus, the risk of radiation-induced edema should be considered before consideration of SRS for multiple meningiomas in patients with NF2.

Surgery

Surgery is considered the first-line treatment for NF2-M [24]. In both non-syndromic and NF2-M, long-term prognosis is correlated to the extent of surgical resection. Patients who underwent subtotal resection often required subsequent surgeries due to meningioma recurrence [22, 44, 65]. As noted in our illustrative case, patients with NF2—in addition to the hallmark bilateral vestibular schwannomas—can present with multiple meningiomas. Due to the increased tumor burden, patients with NF2 require multiple surgical or radiosurgical procedures to excise developing lesions [22]. Our patient had over 120 lesions, necessitating over 40 procedures.

Surgical resection is limited by the potential to induce damage to surrounding structures and thus restricting the efficacy of treatment. Overall, we found an elevated recurrence rate of 47.8% for surgically treated NF2 patients. Two patients, who had first undergone surgery, were further treated with GKS. One of these patients required yet another GKS treatment following tumor recurrence. Depending on a meningioma's location, GTR may be achieved in only 38–80% of cases with complete resections often rendered impossible due to the proximity of neurovascular structures—leading to increased risk of iatrogenic injuries [1, 5, 15, 36, 37, 46, 49, 70]. Even if GTR was achieved, tumor reoccurrence remains a concern with 5-year recurrence rates of 4–14% and 10-year recurrence rates of 18–25% reported in sporadic meningiomas [1, 5, 15, 36, 37, 46, 49, 70].

SRS

Some studies argue against the use of SRS for the treatment of NF2-M due to the risk of malignant induction [7, 18, 20]. Our patient underwent CyberKnife treatment of a T9 spinal cord ependymoma in 2005 and a jugular foramen schwannoma early in 2006 at an outside hospital. One year after CyberKnife therapy, imaging showed no tumor regrowth but did show the presence of intratumoral hemorrhage without significant change in the surrounding T2 signal.

Though malignant change was not observed in the included studies, there were cases of de novo meningioma formation in sites distal to the treated area. Distal control was achieved in only 51.8% of patients and many patients subsequently developed progressive tumors away from the treated region. NF2 patients are predisposed to de novo tumor formation and additional exposure from SRS may further precipitate the formation of meningiomas [10, 43]. Of note, Dirk et al. in 2012 showed complete LC failure for two NF2-M following SRS first-line treatment [16]. Though those meningiomas displayed progression on radiological imagining, no further treatment was performed due to lack of symptom development. That case report displayed heterogeneity of NF2 lesions, which may have contributed to poor LC. Although the literature suggests high LC (81%) following SRS, this growth arrest may be attributed to the natural saltatory growth pattern of NF2-M.

Table 4 Characteristics of NF2 patients treated with SRS for multiple meningioma [9, 40]

Patients by study, *n*	Age at first GKS, years	Gender	Initial marginal dose, Gy	GKS, *n*	Follow-up, months	WHO grade	Tumor volume, CC	# of MM treated, *n*	Location of initially treated tumor(s)
Birckhead et al. (2016)									
1	22	M	17	1	87	NR	8.3	1	Olfactory groove
2	52	F	16	3	138	NR	0.9–2.6	7	Left cerebellopontine angle, pineal region, straight sinus, anterior inferior falx
3	29	F	16	1	98	NR	4.2	1	Left occipital parasagittal
4	29	F	18	8	213	NR	2.3–68.4	13	Right anterior frontal
5	27	F	18	4	163	NR	0.6–7.3	7	Right frontal, falx, left frontal, posterior falx
6	29	F	18	6	283	NR	0.6–9.6	9	Right cerebellopontine angle
7	33	M	18	2	156	2	7, 41	1	Left tentorial
8	23	F	18	1	22	NR	1.3–2.9	3	2 temporal convexity lesions Vein of galen
9	37	M	14	1	60	NR	2.9, 9.9	2	Left frontal, posterior right tentorial
10	20	M	13	2	20	NR	2–18.4	4	Right petrous ridge, right choroid plexus, left choroid plexus
11	32	M	14	3	91	1	8.1, 51	2	Falx staged treatments
12	54	F	15	1	61	NR	2.8–3.7	3	Anterior fossa, posterior falx, left temporal
13	34	F	15	1	6	NR	13.7	1	Left parafalcine
14	54	M	16	1	80	1	1.9, 1.9	2	Left transverse sinus, left posterior inferior cerebellar convexity
15	24	F	15	3	103	2	3.1–15.9	5	Straight sinus, torcula
Liu et al. (2015)									
16	27	F	12	1	48	NR	NR	3	NR
17	54	M	12	1	107	1	NR	3	NR
18	53	F	14	2	NR	NR	NR	7	NR
19	31	F	15	1	71	NR	NR	6	NR
20	26	F	14	3	168	NR	NR	11	NR
21	32	F	14	2	NR	1	NR	8	NR
22	23	F	12	3	NR	1	NR	18	NR
23	31	F	12	7	NR	1	NR	12	NR
24	34	M	14	1	22	2	NR	5	NR
25	13	F	NR	1	25	NR	NR	2	NR
26	41	F	12	1	35	NR	NR	6	NR
27	27	F	12	1	28	NR	NR	6	NR

Multiple GKS were used to treat multiple lesions

NR not reported

SRS is most often used and most effective for smaller, non-malignant, and sporadic meningiomas. Tumor control rates range from 60 to 100% with long-term tumor control rates as high as 93% at 5 and 10 years [21, 27, 33–35, 39, 41, 42, 50, 51, 58, 72, 76, 77]. The data falls within this range, exhibiting a LC rate of 81% (22/27). Given the growth heterogeneity, potentially more aggressive phenotype, and higher risk of malignant induction, it is surprising that the LC rate following SRS was comparable to that of sporadic meningiomas. We attributed this to the similarity in the underlying NF2 mutation for both sporadic and NF2-M [17]. The aggregated LC rate was similar to that of a large retrospective study performed between 1987 and 2003, yielding a LC rate of 87.2% at 5 years and 77.6% at 10 years [10, 64]. Santacroce et al. evaluated a total of 4565 NF2 and non-NF2 patients to determine the long-term effect of SRS on benign meningiomas and found a LC rate of 92.5%, with only 2.2% of lesions requiring a subsequent treatment [10, 64].

SRS for sporadic meningiomas exhibits lower complication rates, higher tumor control rates, and comparable progression-free survival as compared to Simpson grade I resection for small to medium sporadic

Table 5 Outcomes for NF2 patients undergoing SRS for multiple meningioma [9, 40]

Patients by study, *n*	Distal control achieved	Local control achieved	Additional treatment	Outcome
Birckhead et al. (2016)				
1	Yes	Yes		Alive
2	No	Yes	Phenytoin, GKS	Alive
3	Yes	Yes		Alive
4	No	No	GKS	Deceased
5	No	Yes	GKS	Alive
6	No	Yes	GKS	Alive
7	No	Yes	GKS	Alive
8	Yes	Yes		Alive
9	Yes	Yes		Alive
10	No	Yes	GKS	Alive
11	No	No	GKS, surgery	Deceased
12	Yes	Yes		Alive
13	Yes	Yes	Hospice	Deceased[a]
14	Yes	Yes	Surgery	Alive
15	No	Yes	GKS	Deceased
Liu et al. (2015)				
16	Yes	Yes		Alive
17	No	No	Phenytoin	Alive
18	No	Yes	GKS	Deceased
19	Yes	Yes		Alive
20	No	Yes	GKS	Alive
21	No	Yes	GKS	Deceased
22	No	No	GKS	Deceased
23	No	No	GKS	Deceased
24	Yes	Yes		Alive
25	No	Yes		Alive
26	Yes	Yes		Alive
27	No	Yes		Alive

GKS Gamma Knife Surgery

[a] Patient num. 13 died due to radiation-related complication of cerebral necrosis. All other patients died due to NF2-associated neurological complication

meningiomas [41]. Though our LC rate for NF2-M compares similarly with the findings by Santacroce et al., their higher LC rate for non-syndromic meningioma suggests that sporadic meningiomas are less aggressive and more susceptible to SRS compared to their NF2 counterparts, which is confirmed by several other studies [52, 54, 64, 79]. Consequently, SRS treatment for NF2-M may prove to be less effective compared to sporadic cases.

In addition to SRS, fractionated stereotactic radiotherapy (fSRT) may be considered for NF2-M treatment, because of its non-invasiveness, comparable tumor control rate, and management of larger tumors. In NF2-associated vestibular schwonnomas, Kim et al. reported similar local control rates between fractionated GKS (75% at mean follow-up of 5.1 year) and single-session GKS (50% at mean follow-up of 8.4 year), despite fractionated GKS's use in treating larger sized tumors [31]. Furthermore, for NF2 and non-syndromic vestibular schwannomas, Arribas et al. noted comparable local control rates of 91% for larger tumors (> 25 mm) treated with fSRT, as compared to local control of 95% for smaller lesions (≤ 25 mm) treated with SRS at 10-year follow-up [3]. Importantly, Arribas et al. and other fSRT studies did not observe malignant transformation of any treated lesion [3, 38, 66]. These studies suggest that larger meningiomas or those in critical areas of high surgery-associated morbidity may benefit from fractionated radiotherapy regimes. However, because of limited follow-up, differential tumor type and dearth of literature, further studies must be performed to better evaluate fSRT's efficacy in managing NF2-M.

Limitations

Several limitations were made apparent and attributed to the paucity of available literature. The deficiency in disaggregated data restricted the sample size. Many studies aggregated non-syndromic with NF2-M patients, or delineated different outcome metrics, which limited the quantitative synthesis. Metrics like tumor volume for the surgery cohort or tumor location for the SRS cohort were either unreported, confounded with non-NF2 patients or not individually delineated. A majority of the literature pertaining to surgical treatment of NF2 patients were from the pediatric population, which may also influence the data. In addition, selection and publication biases are also concerns associated with the retrospective study design.

Conclusions

Surgery is the current standard of care for treatment of multiple meningiomas in patients with NF2. SRS may be a safe and effective alternative for NF2-M. However, further studies are required to identify the ideal radiosurgical candidate.

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Compliance with ethical standards

Conflict of interest Dr. Isaac Yang is a consultant for BrainLab. All other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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