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REVIEW

Gamma knife stereotactic radiosurgery for neurofibromatosis 2 (NF2)-associated meningiomas; a systematic review and meta-analysis

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Abstract

Background Neurofibromatosis type 2 (NF2)-related schwannomatosis is a rare genetic disorder associated with meningiomas. Stereotactic radiosurgery (SRS) has emerged as a potential non-invasive method. This study aims to synthesize the available evidence on using SRS to treat these tumors.

Methods PubMed/Medline, Embase, Scopus, and Web of Science were searched until March 21, 2024. This study was prepared by adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

Results Four studies were included comprising 101 patients with NF2-associated meningiomas treated with SRS. All included studies used gamma knife stereotactic radiosurgery (GKRS) as treatment modality. Overall survival rates remained high (100%) up to 3 years post-treatment, with slight declines at five years of 98% (95% CI: 0.95–1.01) and ten years of 68% (95% CI: 0.48–0.87). Progression-free survival rates were similarly favorable, with 95% (95% CI: 89-101%) at three years, 93% (95% CI: 86-99%) at five years, and 81% (95% CI: 51-111%) at ten years. The pooled radiation necrosis rate was 5% (95% CI: 3-7%), while the overall radiation toxicity rate was 16% (95% CI: 11-21%). Local tumor control rates were high at six months, and at 12 months, they were 100% (95% CI: 1.00–1.00).

Conclusion GKRS demonstrates high efficacy and a favorable safety profile for NF2-associated meningiomas, offering a valuable treatment option for this challenging patient population.

Keywords NF2-related schwannomatosis · Meningioma · Stereotactic radiosurgery · Gamma knife

Introduction

Neurofibroma type 2 (NF2)-related schwannomatosis is a rare clinical condition caused by an NF2 gene mutation in the 22-chromosome. Figure 1 represents the mechanism of action of the tumor suppressor gene of NF2. The incidence rate of this condition is approximately 1 per 33,000–40,000 individuals [2]. A hallmark of NF2-related schwannomatosis is meningioma tumors in the cranium and spine with progressive growth over time. Furthermore, approximately 70% of patients present with notable cutaneous manifestations, such as intracutaneous plaque, schwannomas, and subcutaneous lesions [6, 17].

Surgical resection is the main treatment of meningioma, which accounts for approximately 50% of NF2-related schwannomatosis cases. However, accurate assessment of the exact location of the tumor in the cranium and spinal is essential for surgical planning. Otherwise, radiotherapy and antiangiogenic are under performance evaluation in this therapeutic area [1]. For pediatric patients with NF2-related schwannomatosis biologically targeted therapy such as Imatinib, Erlotinib, Sorafenib, and Bevacizumab offer alternative treatment [21]. Another study claimed that the surgery approach is the first option for treating NF2-related schwannomatosis patients with meningioma; although investigations have shown that radiotherapy is a safe method, the efficacy of radiotherapy should be investigated more; the main concern of utilizing this option is its long-term effects, and especially the chance of malignment transformation in NF2-related schwannomatosis patients. Full resection is recommended in NF2-related schwannomatosis patients; nevertheless, radiotherapy can

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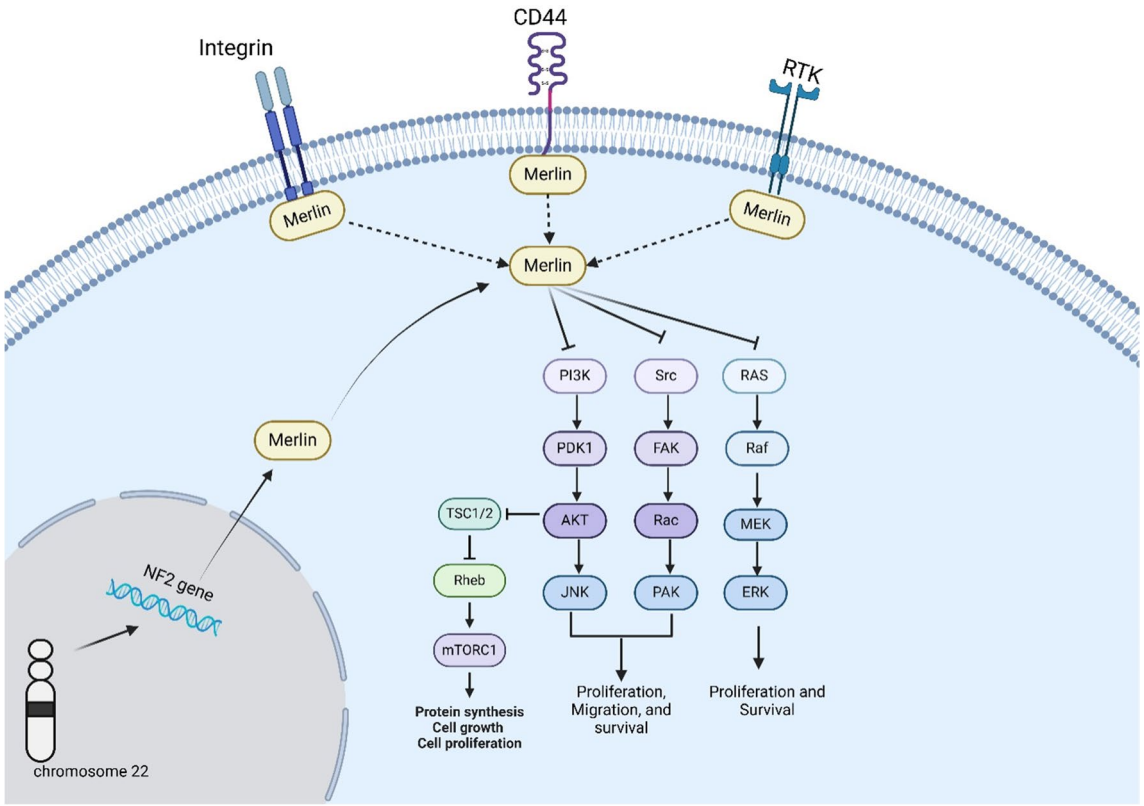

Fig. 1 The mechanism of action of tumor NF2 suppressor gene

be an alternative approach in unresectable, recurrent, and high-grade tumors [16]. Stereotactic radiosurgery (SRS) is a remarkable radiotherapy method that can be utilized as an alternative to surgery in a non-invasive way. SRS has a positive significant impact on complication management rate, tumor control, and tumor development compared with the surgery approach in NF2-related schwannomatosis patients with meningioma grade 1; however, because of limited studies in this field, further investigation to evaluate SRS efficacy is necessary [15]. Additionally, another study demonstrates that SRS has a few adverse event rates with high-level tumor management in NF2-related schwannomatosis patients. In this study, we aim to review the impact of gamma knife stereotactic radiosurgery (GKRS) as an essential radiotherapy approach for managing NF2-associated meningioma patients.

Method

This study was prepared adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [13]. PROSPERO approved the study's methodology, with the registration code of CRD42024583326.

Search strategy

The electronic databases of PubMed/Medline, Embase, Scopus, and Web of Science were individually searched from inception to March 21, 2024, without any restriction on date, type of publication, and language. The keywords "Radiosurgery," "Stereotactic Radiosurgery," and "Meningioma" were used to provide a search strategy in each electronic database. The full search syntax is shown in Supplementary Table S1.

Study selection process

The data from each electronic database was imported into EndNote v.20. After eliminating duplicate publications, two reviewers separately completed title/abstract screening to identify relevant research. Afterward, the full-text screening process was conducted to identify the papers that met the qualifying criteria. A third reviewer resolved the conflicts.

Eligibility criteria

We included studies focusing on patients with NF2-associated meningiomas (Population) and investigated the

clinical outcomes following SRS (Intervention/Outcome). The eligible studies were limited to English publications involving human subjects. We included original research articles, such as case series with more than five patients, cohort studies, cross-sectional studies, and randomized and non-randomized clinical trials (Study Design). We excluded non-English studies, studies involving non-human subjects or patients without NF2-associated meningiomas, studies that did not investigate clinical outcomes of SRS, and non-original research articles, including case reports, case series with fewer than five patients, book chapters, review articles, letters to the editor, and conference abstracts.

Data extraction

Two reviewers independently conducted the data extraction of the included studies. The information of studies was extracted, including name of author, year of publication, country, type of study, number of patients, mean age, gender of patients, duration of follow-up, number of tumors, prior treatment, mean Karnofsky Performance Scale (KPS) score, name of drug, dosage, cycle of treatment, concomitant therapy, overall survival (OS), progression-free survival (PFS), Local control (LC), Adverse radiation event.

Quality assessment

The Joanna Briggs Institute (JBI) quality appraisal checklist for non-randomized experimental studies scale was used to evaluate the methodological quality of each included study [3]. This checklist includes several important criteria, including the following: clarity of cause and effect; similarity of participants in each comparison; receiving similar treatment or care other than the exposure or intervention of interest; the presence of a control group in the study; the use of multiple measurement methods of the outcome both pre- and post-intervention/exposure; the completion of follow-up and an adequate description and analysis of the differences between groups at follow-up; measuring the outcomes of participants in any comparisons in the same order; reliable measurement; and suitable statistical analysis. In addition, two authors carried out independent quality assurance checks. During the data abstraction process, conflicts were settled through discussion and agreement (Supplementary Table S2).

Data synthesis

We followed the Cochrane Handbook for systematic reviews of interventions to determine appropriate effect sizes [5]. We combined various rates, including OS, PFS, LC, radiation necrosis, radiation toxicity, and mortality, using a random effects model with Restricted Maximum Likelihood (REML). High heterogeneity was defined as a Q test P-value less than 0.05 and I^2 greater than 40%. We provided 95% confidence intervals (CI) for all pooled estimates. We conducted sensitivity analyses using the leave-one-out method to assess the robustness of our meta-analysis results. Publication bias was evaluated using Egger's test. When significant heterogeneity was detected, we performed meta-regression to identify potential sources of variability (Supplementary Table S3). All analyses were conducted using Stata version 17.0.

Results

Study selection process

The initial searches on March 21, 2024, identified 5208 articles. After removing 2346 duplicate records, 2862 unique articles were left for screening. Two independent reviewers screened the titles and abstracts, excluding studies that were not relevant. Full texts of 28 potentially eligible studies were retrieved and assessed according to predefined criteria. Ultimately, four studies satisfied the inclusion criteria and were incorporated into the systematic review and meta-analysis [4, 8, 11, 14]. Figure 2 represents the study selection process.

Study characteristics

This review encompasses four studies focusing on GKRS for NF2-associated meningiomas, with 101 patients across all studies. The sample sizes ranged from 12 to 358 patients per study. Three studies were conducted in the USA and one in China. Three studies were retrospective cohorts, with one case series [4]. Where reported, there was a tendency towards more female patients (44 female and 18 male). The median ages of patients ranged from 31 to 40 years, with an overall age range of 10 to 72 years across all studies. Follow-up periods varied widely, from 43 to 102 months, with median follow-up periods ranging from 7.2 to 306 months. Study periods spanned from 14 years and nine months to 22 years and 7 months (Table 1).

The total number of meningiomas treated across studies ranged from 62 to 204, with one study reporting 125 meningiomas, of which 87 were treated [11]. Median tumor volumes varied considerably, from 1.31 ccs to 6.8 ccs, with an overall range of 0.1 ccs to 68.4 ccs across all studies.

All of the studies used GKRS as treatment modality. The median SRS margin dose was relatively consistent, ranging from 12 to 16 Gy, with an overall range of 10 to 25 Gy. The median number of lesions receiving GKRS per patient ranged from 6 to 8, with some receiving treatment for up to 46 lesions. In studies reporting the mean number of lesions treated per patient, values ranged from 2.8 to 7.25 (Table 2).

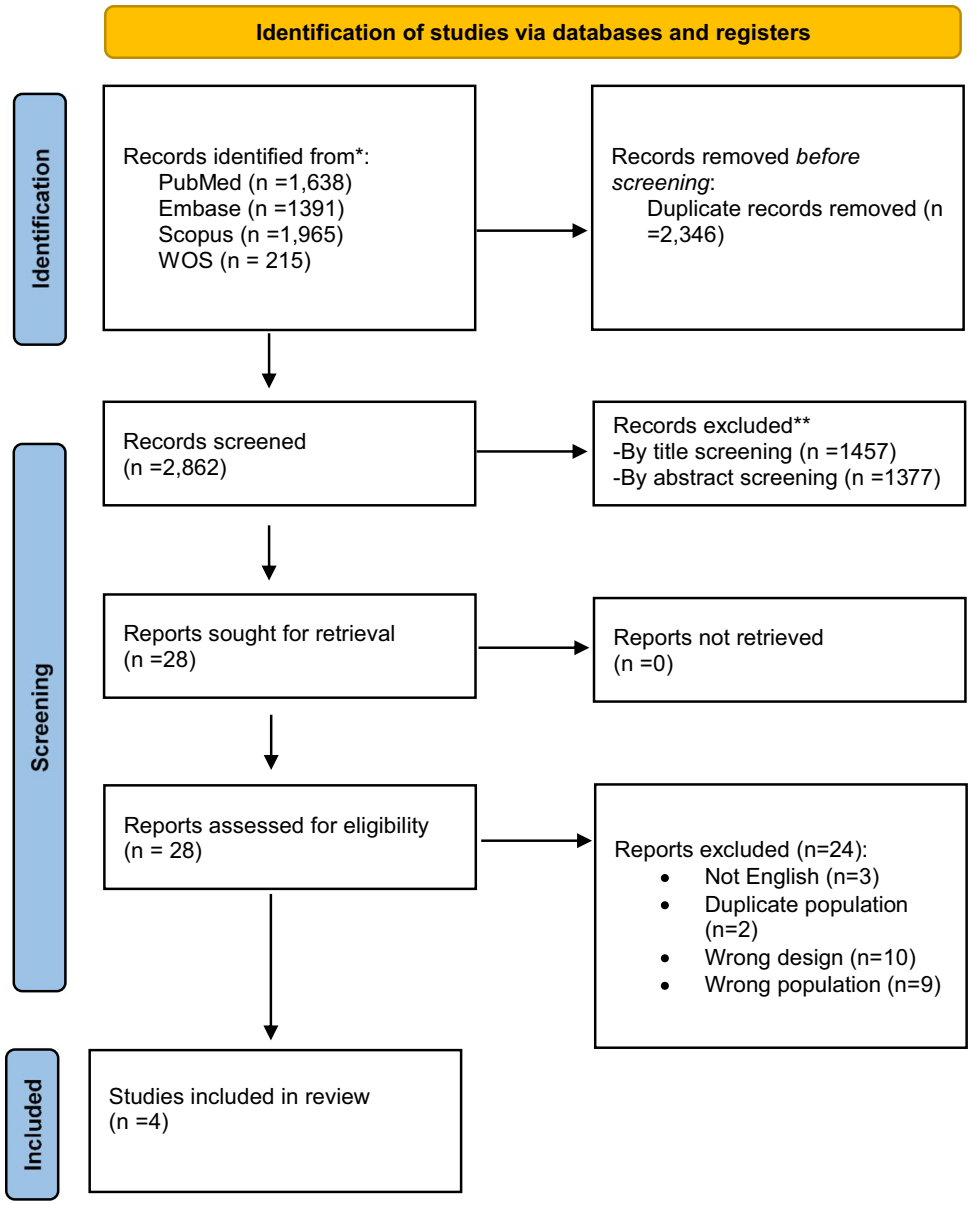

Fig. 2 PRISMA flowchart of the study selection process

Main outcomes

Overall survival

The combined 6-month survival rate across studies was 100%, and the heterogeneity was insignificant, with $I^2 = 0.02\%$, P-value = 0.57 (Figure S1). For the 1-year OS, the pooled estimate was also 100%, and heterogeneity remained insignificant with $I^2 = 0.02\%$, P-value = 0.57) (Figure S2). The overall pooled 18-month survival was 100% with insignificant heterogeneity ($I^2 = 0.02\%$, P-value = 0.57) (Figure S3). The 2-year OS rate was similarly pooled at 100% with a negligible and insignificant heterogeneity, indicated by $I^2 = 0.02\%$ and P-value = 0.57 (Figure S4). The pooled 3-year OS was 100% with heterogeneity insignificant ($I^2 = 0.02\%$, P-value = 0.57) (Figure S5).

In contrast, the 5-year OS showed a slight decrease, with a pooled estimate of 98% (95% CI: 95 − 101%) with $I^2 = 83.75\%$, P-value < 0.001 indicated high and significant heterogeneity (Fig. 3a). Finally, the 10-year OS estimate dropped to 68% (95% CI: 48 − 87%). The heterogeneity was considerable, with I^2 at 70.64% and P-value = 0.03 (Fig. 3b).

Meta-regression for 5-year OS highlighted that male gender (R2 = 100%), female gender (R2 = 100%), follow-up duration (R2 = 99.91%), and SRS margin dose (R2 = 99.89%) were the main source of heterogeneity of 5-year OS. Male gender ($r = -0.2631576$, P-value < 0.001), follow-up duration ($r = -0.0006619$, P-value = 0.001), and mean SRS margin dose ($r = -0.0277675$, P-value = 0.001) were inverse and significant factors and female gender ($r = 0.2631663$ and P-value < 0.001) was positively and significantly correlated

Table 1 Study characteristics

Author/Year	Study period	Country	Type of study	Number of patients	Male number	Female number	Median age (IQR or Q1 and Q3 or Range)	Median follow-up (months) (IQR or Q1 and Q3 or Range)
B. Birckhead 2016 [4]	22 years and 7 months	USA	Case series	15	6	9	NA	NA
F. Gao 2019 [8]	16 years	China	Retrospective	35	10	25	40 (14–61)	96 (25–224)
A. Liu 2015 [11]	14 years and 9 months	USA	Retrospective	12	2	10	31 (27–37)	43 (34–110)
N. Mohammed 2022 [14]	NA	USA	Retrospective	39	NA	NA	38 (10–72)	102 (7.2–306)

Birckhead, B., et al., *Gamma Knife radiosurgery for neurofibromatosis type 2-associated meningiomas: a 22-year patient series.* J Neurooncol, 2016. **130**(3): p. 553–560

Gao, F., et al., *Efficacy and Safety of Gamma Knife Radiosurgery for Meningiomas in Patients with Neurofibromatosis Type 2: A Long-Term Follow-Up Single-Center Study.* World Neurosurg, 2019. **125**: p. e929-e936

Liu, A., et al., *Gamma Knife radiosurgery for meningiomas in patients with neurofibromatosis Type 2.* J Neurosurg, 2015. **122**(3): p. 536 – 42

Mohammed, N., et al., *Neurofibromatosis type 2-associated meningiomas: an international multicenter study of outcomes after Gamma Knife stereotactic radiosurgery.* Journal of Neurosurgery, 2022. **136**(1): p. 109–114

Niranjan, A., et al., *199 Gamma Knife Radiosurgery to Treat Neurofibromatosis Type 2-Associated Meningiomas: A 35 Year Experience and Paradigm for Future Treatment.* Neurosurgery, 2024. **70**(Supplement_1): p. 51–52

Table 2 Meningioma and SRS characteristics

First author-name	Total number of meningiomas	Median tumor volume (IQR or Q1 and Q3 or Range)	Modality of SRS	SRS margin dose (median in Gy) (IQR or Q1 and Q3 or Rang)	Median number of lesions receiving GKRS per patient (IQR or Q1 and Q3 or Rang)	Mean number of lesions receiving GKRS per patient
B. Birckhead 2016 [4]	62	6.8 cc (0.6–68.4)	Gamma knife	16 (13–20)	8 (1–20)	NA
F. Gao 2019 [8]	99	6.8 cc (0.6–40)	Gamma knife	13 (12–15)	NA	2.8
A. Liu 2015 [11]	125 (treated = 87)	NA	Gamma knife	12 (10–15)	NA	7.25
N. Mohammed 2022 [14]	204	1.31 (0.1–21.2)	Gamma knife	12.5 (10–25)	6 (1–46)	NA

Birckhead, B., et al., *Gamma Knife radiosurgery for neurofibromatosis type 2-associated meningiomas: a 22-year patient series.* J Neurooncol, 2016. **130**(3): p. 553–560

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with 5-year OS rate. Meta-regression of 10-year OS showed that follow-up duration (100%) was the main source of heterogeneity. Moreover, follow-up duration is the significant factor of 10-year OS ($r = 0.0076603$, P-value = 0.010).

Local control

The overall pooled 6-month LC rate was 100% (95% CI: 1.00–1.00) with significant heterogeneity of $I^2 = 0.31\%$, P-value < 0.001 (Figure S6). The pooled 12-month LC rate was 100% (95% CI: 1.00–1.00), with an insignificant heterogeneity of $I^2 = 0.31\%$, P-value = 1.00 (Figure S7).

Progression-free survival

The pooled 6-month PFS rate was 96% (95%CI: 86–106%), with a moderate and insignificant heterogeneity ($I^2 = 45.92\%$, P-value = 0.17) (Figure S8). For the 1-year PFS, the pooled rate was 96% (95%CI: 86–106%), with a moderate and insignificant heterogeneity ($I^2 = 45.92\%$, P-value = 0.17)

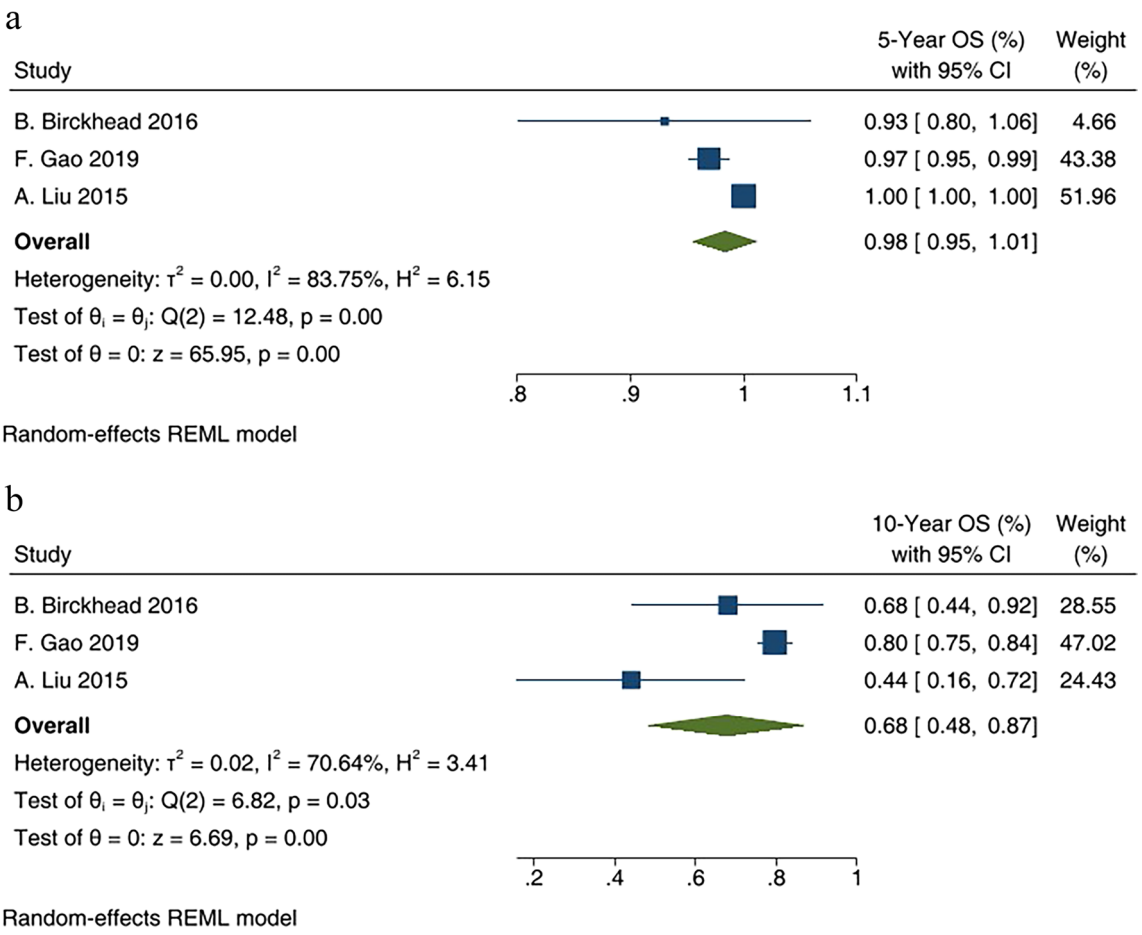

Fig. 3 **a** Forest plot of 5- year OS. **b** Forest plot of 10- year OS

(Figure S9). The pooled 2-year PFS rate was 96% (95%CI: 86–106%), with a moderate and insignificant heterogeneity (I^2 = 40.16%, P-value = 0.20) (Figure S10). At three years, the pooled PFS rate slightly decreased to 95% (95% CI: 89 − 101%), with a negligible and insignificant heterogeneity (I^2 = 00.02%, *P*-value = 0.33) (Fig. 4a). The pooled 5-year PFS was 93% (95% CI: 86 − 99%), with a negligible and insignificant heterogeneity (I^2 = 0.00%, *P*-value = 0.39) (Fig. 4b). Meta-regression showed that follow-up duration, total number of meningiomas, tumor volume, maximum dose of SRS, and SRS margin dose are the significant factors of 5-year PFS heterogeneity. Moreover, follow-up duration, median tumor volume, and maximum dose of SRS are significant factors of 5-year PFS. Finally, the 10-year PFS rate was pooled at 81% (95% CI: 51 − 111%), with a high and significant heterogeneity (I^2 = 82.72%, *P*-value = 0.02) (Fig. 4c).

Radiation necrosis and toxicity

The overall pooled radiation toxicity (total) rate was 16% (95% CI: 11 − 21%), with a low and insignificant heterogeneity (I^2 = 13.20%, *P*-value = 0.28) (Fig. 5a). The overall pooled radiation necrosis (total) rate was 5% (95% CI: 3 − 7%), with a negligible heterogeneity (I^2 = 0.04%, *P*-value = 0.53) (Fig. 5b). The overall pooled radiation toxicity (lethal) rate was 3% (95% CI: 1 − 5%), with a negligible insignificant heterogeneity (I^2 = 0.00%, *P*-value = 0.53) (Figure S11).

Mortality

The overall pooled total number of deaths rate was 16% (95% CI: 1– 30%), with a significant heterogeneity of I^2 = 96.68%, *P*-value < 0.001) (Figure S12). The overall pooled neurological death rate was 20% (95% CI: 8–32%), with a low and insignificant heterogeneity of I^2 = 39.92%%, *P*-value = 0.22 (Figure S13).

Meta-regression revealed that mean age (R2 = 32.89%), number of meningiomas (R2 = 100%), mean tumor volume (R2 = 100%), and mean follow-up (R2 = 91.55%) were the main sources of heterogeneity of death. Moreover, the total number of meningiomas (*r*=−0.0016724, *P*-value < 0.001), mean tumor volume (*r* = 0.022163, P-value < 0.001), and

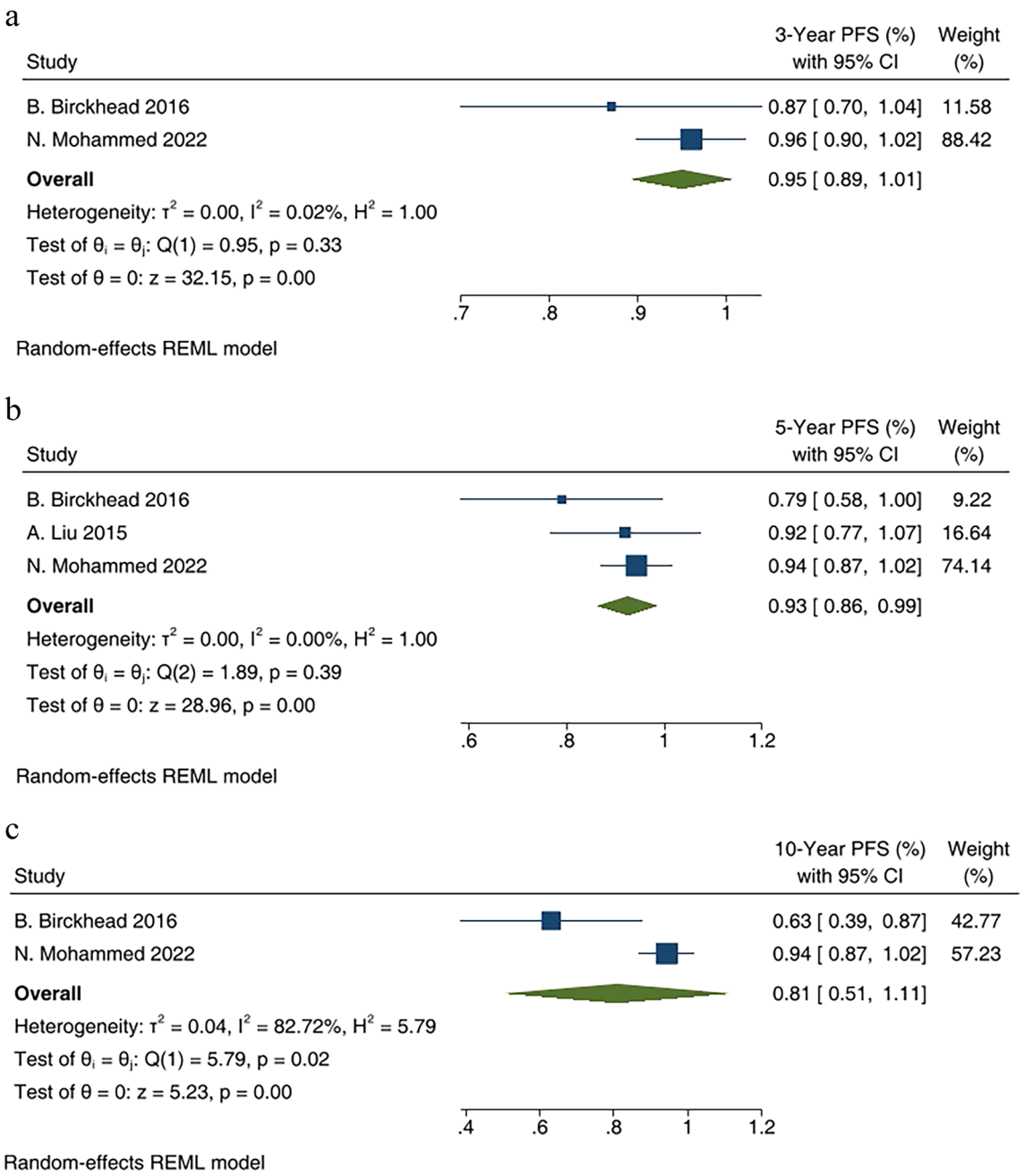

Fig. 4 **a** Forest plot of 3-year PFS. **b** Forest plot of 5-year PFS. **c** Forest plot of 10-year PFS

mean follow-up duration (r=−0.0065715, P-value < 0.001) were the significant factors of death.

Seizure and brain edema

The overall pooled seizure rate was 3% (95% CI: 1 − 5%), with low and insignificant heterogeneity of I² = 4.14%, P-value = 0.32) (Figure S14). The overall pooled brain edema rate was 7% (95% CI: 0 – 13%), with low and insignificant heterogeneity of I² = 0.01%, P-value = 0.76 (Figure S15).

Sensitivity analysis

The re-run analysis indicated that 1-year OS, 2-year OS, 3-year OS, 5-year OS, 10-year OS, 18-month OS, 2-year PFS, 3-year PFS, 5-year PFS, radiation toxicity(total),

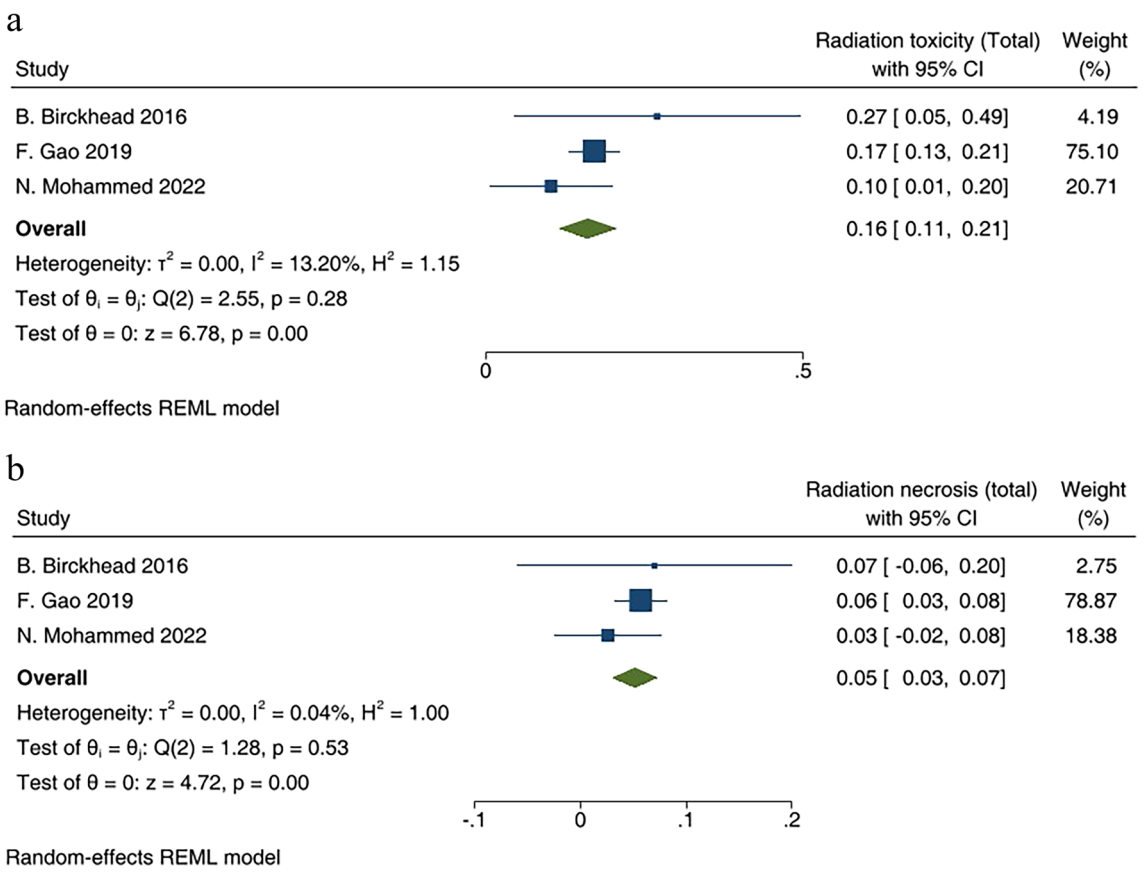

Fig. 5 **a** Forest plot of radiation toxicity(total) rate. **b** Forest plot of radiation necrosis(total) rate

seizure, 6-month LC, 12-month LC, and neurological death rate were robust (P-value < 0.05 for each study). However, other outcomes did not have robust outcomes, including the radiation necrosis (total) rate (*P*-value > 0.05 for one), radiation toxicity(lethal) (*P*-value > 0.05 for one study), the Systemic death rate (P-value > 0.05 for three studies), the total number of deaths rate (*P*-value > 0.05 for three studies). (Supplementary Figure S16).

Publication bias

Publication bias was assessed using Egger's test for various outcomes. No statistically significant evidence of publication bias was detected for 2-year PFS (t = −1.69, *P*-value = 0.2339), 6-months PFS (t = −1.60, *P*-value = 0.2500), 1-year PFS (t = −1.60, *P*-value = 0.2500), 3-Year PFS (t = −2.34, *P*-value = 0.1439), and Radiation toxicity (Total) (t = 0.20, P-value = 0.8522). Similarly, no significant bias was found for radiation necrosis (total) (t = −0.35, *P*-value = 0.7572) and Seizure (t = 2.45, *P*-value = 0.0707). The 5-year PFS (t = −1.19, *P*-value = 0.4444), 10-year PFS (t = −3.50, *P*-value = 0.0728), and Neurological death (t = 2.98, *P*-value = 0.0586) were close to the threshold for potential bias. Potential publication bias was detected for total deaths (t = 7.73, *P*-value = 0.0015).

Discussion

As Rogers et al. emphasize, managing meningiomas, especially in complex cases like NF2-related schwannomatosis, remains a significant challenge in neuro-oncology [20]. Traditional approaches often involve surgical resection, which can be particularly risky in NF2-related schwannomatosis patients due to the potential for multiple cranial nerve deficits and the frequent need for repeated surgeries. Our findings suggest that GKRS offers a viable and potentially superior alternative to traditional surgical approaches, particularly for patients with multiple or surgically challenging meningiomas. Moreover, the results of our study align with and expand upon the growing body of evidence supporting the use of SRS in meningioma treatment. Our study extends the finding of Pinzi et al. about radiosurgery in intracranial meningiomas for the management of NF2-related schwannomatosis population [18]. This is particularly important given the unique challenges posed by NF2-associated

meningiomas, including their tendency to be multiple and their potential impact on adjacent cranial nerves already compromised by vestibular schwannomas.

The high survival rates observed up to 3 years post-treatment are particularly encouraging, reflecting the immediate and short-term efficacy of GKRS in controlling NF2-associated meningiomas. However, the slight decline noted at 5 and 10 years warrants careful consideration. This trend aligns with findings from Pinzi et al., who reported similar long-term survival patterns in their meta-analysis of radiosurgery for intracranial meningiomas [18].

The observed decline could be attributed to several factors, including inherent progression of NF2-related schwannomatosis, the development of new tumors, or potential late effects of radiation. It's important to note that despite this decline, the survival rates remain favorable compared to historical data on untreated or surgically managed NF2-associated meningiomas, as suggested by Rogers et al. [20].

As revealed by our meta-regression analysis, the impact of SRS margin dose on survival rates is a crucial finding that merits further exploration. Optimizing the SRS margin dose could improve long-term survival outcomes. This concept is supported by Marchetti et al. in their practice guideline for SRS in benign meningiomas [12]. The dose-response relationship observed in our study provides valuable guidance for treatment planning. It suggests that while higher margin doses may improve tumor control, they must be balanced against the risk of toxicity, especially in the context of NF2-related schwannomatosis, where preserving neurological function is paramount.

The stability of PFS rates up to 3 years is a significant finding, demonstrating the effectiveness of GKRS in controlling tumor growth in the short to medium term. However, the observed decrease at 5 and 10 years requires careful interpretation. This pattern is consistent with the findings of Fatima et al., who noted similar trends in their comparison of SRS and radiotherapy for meningiomas [7].

The stability of PFS in the early years post-treatment is particularly valuable in the context of NF2-related schwannomatosis. GKRS can provide a period of tumor control during which patients may be spared the morbidity associated with surgical intervention. This "therapeutic window" could be crucial in maintaining the quality of life and neurological function in NF2-related schwannomatosis patients, who often face multiple tumor-related challenges simultaneously.

The low incidence of radiation necrosis and toxicity observed in our study is a key finding that emphasizes the safety profile of GKRS for NF2-associated meningiomas. This is particularly noteworthy given the concerns often associated with radiation treatment in NF2-related schwannomatosis patients, who may be more susceptible to radiation-induced complications.

Our findings compare favorably with the side effects associated with other treatment modalities, as discussed by Rafiq et al. in their meta-analysis of surgical outcomes for meningiomas [19]. The lower risk of complications with GKRS is especially significant in the NF2-related schwannomatosis population, where preserving neurological function is crucial given the multitude of tumors these patients often face.

The low toxicity profile observed in our study may be attributed to several factors. First, the highly conformal nature of GKRS allows for precise tumor targeting while minimizing radiation exposure to surrounding healthy tissues. Second, the typically smaller tumor volumes treated with GKRS in NF2-related schwannomatosis patients may contribute to the lower toxicity rates. Finally, advances in imaging and treatment planning technologies have likely played a role in improving the safety profile of GKRS over time.

Our analysis of mortality rates and influencing factors revealed variability related to tumor characteristics and treatment variables. This heterogeneity in outcomes is consistent with observations by Islim et al. in their review of prognostic factors for incidental meningiomas [9].

The mortality rates observed in our study were generally low. However, the variability in mortality rates highlights the importance of considering individual patient and tumor factors when planning treatment. Factors mortality rates included tumor size, follow-up duration, and the number of meningiomas present.

Birckhead et al. specifically commented on the lack of malignant transformation or secondary malignancies in their 22-year study of 15 patients [15]. Again, Liu et al. did not report any events of malignant transformation in their cohort of 12 patients with 87 treated meningiomas over a median follow-up of 43 months [13]. Mohammed et al. also found no post-GKRS malignant transformation in 39 patients with 204 meningiomas over 287 person-years of follow-up [18]. Although these results may suggest low malignant transformation risk, it has to be conceded that the studies are limited in the sample sizes and lengths of follow-up. It would require larger cohorts with longer observation to arrive at a definite conclusion about the long-term risks of radiation-induced malignancy.

Interestingly, our analysis suggested that patients with multiple meningiomas did not necessarily have higher mortality rates than those with single tumors, provided all tumors were adequately treated. This finding supports the use of GKRS in NF2-related schwannomatosis patients with multiple meningiomas, as it allows for treating several tumors in a single session or over multiple sessions with minimal cumulative toxicity.

Interestingly, our results on LC rates are comparable to those reported by Leroy et al. in their systematic review of radiosurgery for cavernous sinus meningiomas [10]. This suggests that GKRS may be equally effective for NF2-associated meningiomas in challenging locations, which is particularly relevant given the frequent occurrence of

multiple meningiomas in various intracranial locations in NF2-related schwannomatosis patients. GKRS should be considered a primary or adjuvant treatment for NF2-associated meningiomas, particularly when surgical resection carries high risks. Our study's high LC rates and favorable safety profile support this recommendation. Clinicians should evaluate the benefits of GKRS against other treatment based on individual tumor characteristics and the patient's clinical situation.

Conclusion

In conclusion, our study demonstrates that GKRS is the only SRS modality used in NF2-associated meningiomas. It is a safe and effective treatment option that provides high LC rates and favorable long-term outcomes. Future research should focus on optimizing treatment parameters and exploring the long-term effects of GKRS in larger cohorts of NF2-related schwannomatosis patients.

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Author contributions MA. H and MS.M contributed to the study conception and design, and edited the manuscript. MS.M , F.A, and MA. H analyzed the data. MA. H, MH. A and P. D wrote the first draft of the manuscript. O. A, F.AY and MT. AJ conducted the study selection process. F. AY, R. HR and A. D conducted the data extraction. M. M conducted the quality assessment. MA.AM, S.T, A.B, and B.H made a critical revision of the manuscript. F.A created the Fig. 1. All authors commented on previous versions of the manuscript and revised it. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval The study is deemed to exempt to received ethical approval.

Consent to participate Not applicable.

Consent to publish Not applicable.

Competing interests The authors declare no competing interests.

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