

ORIGINAL ARTICLE



Should adjuvant radiotherapy be used in atypical meningioma (WHO grade 2) following gross total resection? A systematic review and Meta-analysis

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ABSTRACT

Background: The role of adjuvant radiotherapy (RT) following gross total resection (GTR) in atypical meningioma (AM) is not well established and its benefit remains unclear. We aim to evaluate the survival benefit of adjuvant RT in AM following GTR.

Methods: We searched biomedical databases for studies published between January 1964–February 2021 and included studies reporting primary outcomes of 5-year PFS, 5-year OS and had survival curves for restricted mean survival time (RMST) calculations. Data extracted from survival curves were pooled and analyzed using a random-effects model. Hazard ratio (HR) was calculated for sensitivity analysis.

Results: We included 12 non-randomized studies comprising 1,078 patients. 803 (74.5%) patients were treated with GTR alone and 275 (25.5%) patients received adjuvant RT. In 9 studies, RT included 3 D conformal RT, intensity modulated RT, or fractionated stereotactic radiotherapy; in 3 studies, stereotactic radiosurgery was also used. Median dose of RT was 59.4 Gy. Adjuvant RT resulted in an increase of 3.9 months for restricted mean PFS truncated at 5 years (95% CI 0.23–7.72; $p = 0.037$) and a 22% reduction in the hazard of disease progression or death (hazards ratio 0.78; 95% CI 0.46–1.33; $p = 0.370$). Restricted mean OS, truncated at 5 years, was improved with adjuvant RT by 1.1 months (95% CI 0.37–1.81; $p = 0.003$) and a 21% reduction in the hazard of death from any cause (HR 0.79; 95% CI 0.51–1.24; $p = 0.310$). Meta-regression analysis of the RMST of EBRT dose did not reveal any significant difference in PFS or OS between studies reporting median dose of <59.4 Gy vs. ≥ 59.4 Gy.

Conclusion: Adjuvant RT following GTR in patients with AM improved restricted mean PFS and OS. While we await the results from ongoing randomized controlled trials, adjuvant RT should be recommended.

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KEYWORDS

Atypical meningioma; WHO grade 2 meningioma; gross total resection; adjuvant; radiotherapy

Background

Meningiomas are the most common form of primary intracranial tumors with an estimated incidence of ~ 8 in 100,000 persons per year [1,2]. The World Health Organization (WHO) classifies and grades meningiomas as benign (grade 1), atypical (grade 2), or anaplastic/malignant (grade 3). WHO grade 2 or atypical meningioma (AM) represents approximately 30–35% of all cases of meningioma [3]. Since it was first introduced by WHO in 1993, the diagnostic criteria for AM has been redefined. This include mitotic count of ≥ 4 and additive criteria of 3 of the other 5 histological features: spontaneous necrosis, sheeting (loss of whorling or fascicular architecture), prominent nucleoli, high cellularity and small cells (tumor clusters with high nuclear:cytoplasmic ratio) [4]. The 2007 classification suggested brain invasion as an indicator of increased risk of recurrence, however it was only in 2016 that brain invasion was formally introduced as an independent histological criterion for atypical (grade 2) meningioma [4,5]. These changes have broadened the diagnostic criteria of atypical meningioma resulting in the increased frequency of its diagnosis from 5% to 35% [6–9]. With AM being such a heterogeneous category, clinical behavior and response to treatment may be variable. The most recent WHO

classification in 2021 recommends changing all CNS WHO tumor grades to Arabic numerals and in view of higher likelihood of recurrence, chordoid and clear cell meningioma have been assigned to WHO grade 2 meningioma [10]. The use of molecular biomarkers have also been recognized in the classification and grading of meningioma with some being used as a prognostic factor in guiding management decisions.

To date, there is no consensus guideline on the role of adjuvant radiotherapy (RT) in atypical (grade 2) meningioma. Decisions are often at the discretion of individual physician after taking into consideration patient's age, performance status, co-morbidity, location of tumor, likelihood of recurrence, and feasibility of repeating surgery should recurrence occur [11]. Gross total resection (GTR), usually defined as Simpson grades 1 to 3, is the surgical goal for atypical meningioma. However, recurrences still occur despite macroscopic clearance. Previous studies have reported recurrence rates in the range of 30–50% with surgery alone [5,12–14]. Whilst the benefit of adjuvant RT following subtotal resection is well established, survival data on the benefit of adjuvant RT following GTR have been conflicting with some reporting improved local control (LC), progression free survival (PFS)

and/or overall survival (OS) and others reporting no benefit with adjuvant RT [14–18]. The average time to recurrence with GTR alone and adjuvant RT has been reported as 45 months and 67 months, respectively [19,20]. As recurrences are challenging to treat, and may involve critical structures, establishing a treatment regimen to ensure the best possible outcome should be the ultimate aim in the management of atypical meningioma at first diagnosis.

Previous meta-analysis and systematic reviews have evaluated the role of adjuvant RT in atypical meningioma with hazards ratio (HR), however this assumes the ratio between the two hazard functions remain proportional during the study period. Restricted mean survival time (RMST) is the average time to an event (e.g., recurrence or death) and has been shown to be more suitable for analysis of a time-to-event outcome on a standard time scale [21,22]. Our study aims to evaluate the role of adjuvant RT in atypical (WHO Grade 2) meningioma following GTR using RMST, by comparing the PFS and OS of patients who underwent immediate post-operative RT.

Methods

A systematic review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23,24].

Search strategy

Biomedical databases such as Medline, EMBASE and CENTRAL were searched for studies published between January 1964 to February 2021. In addition, manual searching of references were performed in included studies. All studies retrieved were imported into EndNote X9. Duplicates were removed accordingly.

Inclusion criteria and exclusion criteria

Inclusion criteria were: 1) studies, either prospective or retrospective, which reported primary outcomes (5-year PFS and 5-year OS) of patients with atypical meningioma (WHO grade 2). We specifically selected studies which included survival curves so RMST could be calculated to provide an average event-free survival period up to a pre-specified time which is 60 months for our study. 2) studies comparing the effects of adjuvant RT following GTR versus GTR alone; 3) randomized controlled trials (RCTs) and cohort studies.

Exclusion criteria were [1]: studies involving patients with metastasis of meningioma [2]; studies where patients underwent GTR or STR and separate outcomes were not reported [3]; studies of patients receiving systemic treatment; and [4] articles that were not original studies such as commentaries and reviews.

Data extraction and assessment of quality

Two reviewers (CW, BV) independently reviewed all included studies to extract data using a pre-designed data sheet. The following data was extracted from each study [1]: general

information: author, publication year, title, source, country of origin and language [2]; study characteristics: study design and follow-up duration [3]; inclusion and exclusion criteria for study participants, number of study arms, size of each study arm, and baseline characteristics of each study arms [4]; prescription of adjuvant RT with doses normalized using the linear quadratic model [5]; techniques of external beam RT utilized (3D conformal RT, intensity modulated RT, fractionated stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS) [6]; outcomes of interest.

Quality assessment were independently assessed by the authors (CW, BV) using the Robins-I tool to evaluate the risk of bias in non-randomized studies [25].

Outcome measures

The primary outcomes were PFS and OS. PFS was defined as the time from surgical resection to disease progression or death from any cause. OS was defined as time from surgical resection to death.

Statistical analysis

Extracted data was analyzed using random-effects meta-analysis of time to event using the DerSimonian and Laird (DL) methods. It is a reliable approximation as the number of studies is large.

For the analysis of PFS and OS, we estimated the HRs and 95% confidence interval (CI) directly or indirectly from the given data. RMST was used to compare survival outcomes as we anticipated the proportional hazards assumption for the Cox Proportional Hazard model analysis of the PFS and OS outcomes would be violated in majority of the individual studies. Hence, we used HR as supplementary analysis. All calculations and synthesis of data were conducted using Stata version 15.0.

Results

Results of literature search

Initial literature search through Pubmed, Medline, and Embase identified 2026 studies (see PRISMA flow diagram in Figure 1). After removing 245 duplicate studies and excluding 1558 studies based on their titles, we screened through the abstracts of 223 studies, of which 71 studies met our study criteria for full-text article review. We excluded 59 studies due to various reasons including studies which combined the analysis of atypical meningioma with other grades, recurrences, previous RT, mixed cases GTR & STR. Studies with no survival curves available were also excluded as our statistical analysis requires data extraction from survival curves. After all the above exclusions, we finally included a total of 12 retrospective studies in our meta-analysis (see Table 1).

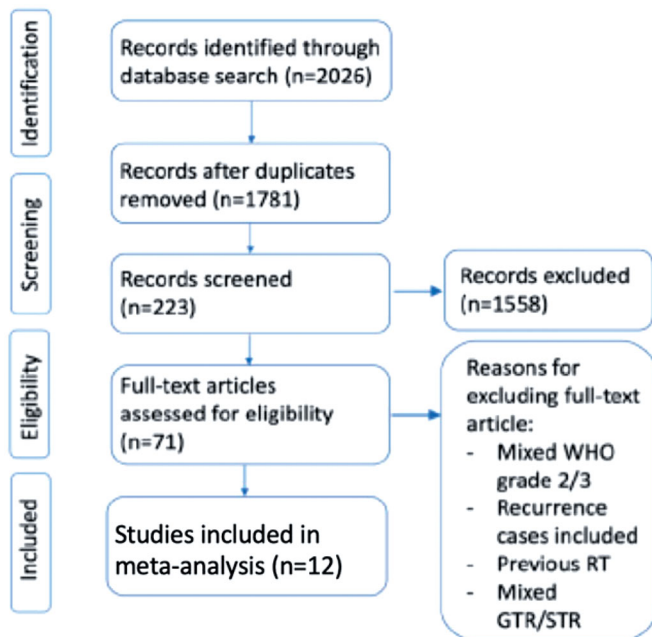


Figure 1. PRISMA flow diagram.

Characteristics of included studies

Twelve studies comprising of 1,078 patients met our inclusion criteria and had study period ranging from 1988 to 2017. All 12 studies were of retrospective nature with only WHO grade 2/AM in their study population. WHO 2007 classification criteria for AM was used in 7 studies [26–32], one study used both 2000 and 2007 classification [33], one study used the 2016 classification [34]. Two studies applied the WHO classification in place at the time of diagnosis [15,35] and one at the time of surgery [36].

Median follow-up of these studies ranged from 31 to 104 months. Only two studies reported the intervals of the follow-up imaging; Dohm *et al.* reported that patients had 6-monthly MRI for the first 2 years then annually thereafter [26]. Shakir *et al.* stated that all patients had follow-up imaging ranging from 3- to 6-monthly in the first 3 years, then 10- to 12-monthly thereafter [31]. GTR was the only treatment received in 803 (74.5%) patients and adjuvant RT following GTR was given in 275 (25.5%) patients. Eight studies defined GTR as resection with Simpson grade 1–3 (15, 26, 29–32, 35, 36), two studies only included those with Simpson grade 1–2 as having GTR [28,33], one study strictly defined GTR as Simpson grade 1 only [27], and in another study, GTR was defined as ‘absence of nodular enhancement at first post-operative magnetic resonance imaging’ [34].

In 9 studies, adjuvant RT was delivered in the form of external beam RT including 3D conformal RT (3D-CRT), intensity modulated RT (IMRT), fractionated stereotactic radiotherapy (SRT) [15,27–29,31–35]. In the remaining 3 studies, RT was given in the form of stereotactic radiosurgery (SRS) and/or fractionated RT [26,30,36].

Survival outcomes

We included studies which reported 5-year PFS and/or 5-year OS (see Table 2) and obtained the RMST up to 5 years.

Table 1. Baseline characteristics of included studies.

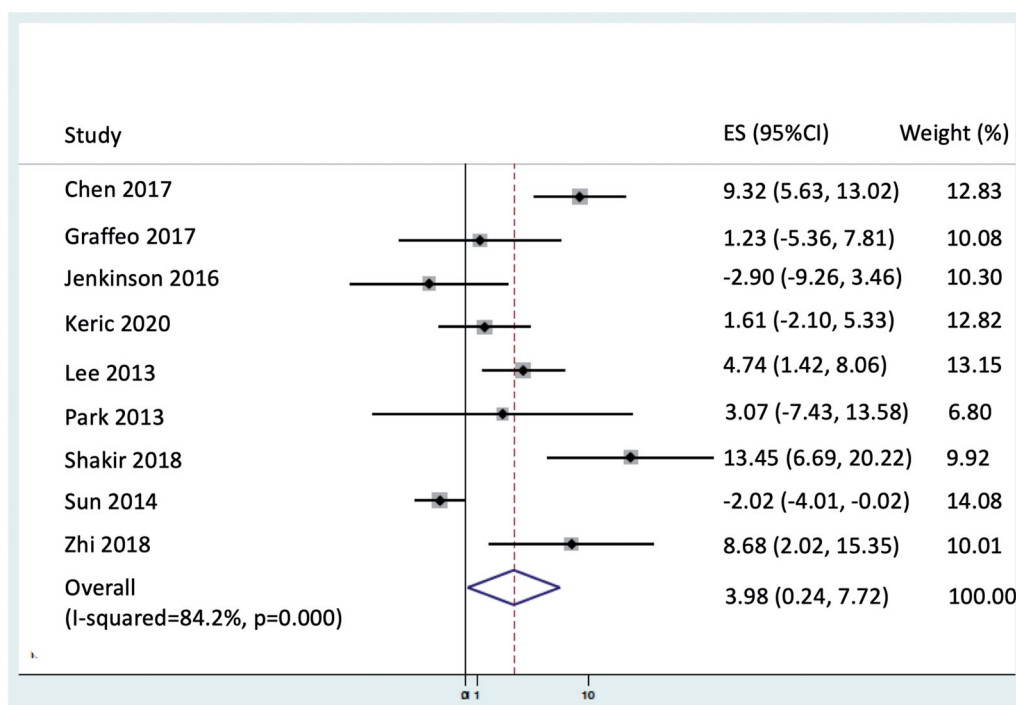
Study (ref)	No. of patients	Median age (yrs)	Study design	Study period	WHO classification	Simpson grades included as GTR	Sub-analysis of Simpson grade	GTR alone	GTR + adj RT	Median EBRT dose (Gy)
Chen <i>et al.</i> 2018 [36]	182	57	Retro-spective	1993–2014	At surgery	1 to 3	No	104	10	59.4
Dohm <i>et al.</i> 2017 [26]	117	63	Retro-spective	1993–2014	2007	1 to 3	No	37	41	55.7
Grafano <i>et al.</i> 2017 [34]	69	60 (no RT); 62 (RT)	Retro-spective	1988–2011	2016	1 to 3 ^b	No	61	8	54
Hammouch <i>et al.</i> 2014 [27]	79	58 ^a	Retro-spective	1996–2009	2007	1	Grade 1	25	9	56.2 ^c
Jenkinson <i>et al.</i> 2016 [15]	133	62	Retro-spective	2001–2010	At diagnosis	1 to 3	No	81	32	60
Keric <i>et al.</i> 2020 [28]	258	60	Retro-spective	2007–2017	2007	1 to 2	No	168	26	56.6 ^c
Lee <i>et al.</i> 2013 [29]	90	56.9 ^a	Retro-spective	1999–2009	2007	1 to 3	No	54	17	59.4
Park <i>et al.</i> 2013 [33]	83	52	Retro-spective	1997–2011	2000/2007	1 to 2	No	38	17	61.2
Pant <i>et al.</i> 2018 [30]	86	51	Retro-spective	2007–2014	2007	1 to 3	No	23	38	59.4
Shakir <i>et al.</i> 2018 [31]	70	62	Retro-spective	1992–2013	2007	1 to 3	No	28	12	54
Sun <i>et al.</i> 2014 [32]	151	54 ^a	Retro-spective	1993–2012	2007	1 to 3	No	112	39	53.8
Zhi <i>et al.</i> 2018 [35]	149	64	Retro-spective	2000–2012	At diagnosis	1 to 3	No	72	26	59.4

^amean age; ^bGTR defined as absence of nodular enhancement at first post-operative MRI; ^cmean EBRT dose. EBRT: external beam radiotherapy. GTR: gross total resection. NR: not reported.

Table 2. Survival outcomes of GTR alone vs. GTR with adjuvant RT.

Study (reference)	5-year PFS (%)		5-year OS (%)	
	GTR alone	GTR + adjuvant RT	GTR alone	GTR + adjuvant RT
Chen <i>et al.</i> 2018 [36]	70	100	90	90
Dohm <i>et al.</i> 2017 [26]	30	48	63	63
Graffeo <i>et al.</i> 2017 [34]	79	88	83	89
Hammouche <i>et al.</i> 2014 [27]	67	100	NR	NR
Jenkinson <i>et al.</i> 2016 [15]	79.3	82	75.7	77
Keric <i>et al.</i> 2020 [28]	68.8	70.7	NR	NR
Lee <i>et al.</i> 2013 [29]	65	74	NR	NR
Park <i>et al.</i> 2013 [33]	70	55	NR	NR
Pant <i>et al.</i> 2018 [30]	35	80	NR	NR
Shakir <i>et al.</i> 2018 [31]	54.1	100	NR	NR
Sun <i>et al.</i> 2014 [32]	86	100	NR	NR
Zhi <i>et al.</i> 2018 [35]	62	84	87	92

GTR: gross total resection. OS: overall survival. PFS: progression free survival. RT: radiation therapy. NR: not reported.

**Figure 2.** Restricted mean survival of progression free survival.

Hazards ratio was calculated for the purpose of supplementary analysis.

Progression free survival

Adjuvant RT resulted in an increase of 3.9 months for restricted mean PFS truncated at 5 years (95% CI 0.23–7.72; $p = 0.037$; see Figure 2) and a non-statistically significant 22% reduction in the hazard of disease progression or death (hazards ratio 0.78; 95% CI 0.46–1.33; $p = 0.370$; see Figure 3).

Meta-regression analysis of the RMST of EBRT dose (< 59.4 Gy vs. ≥ 59.4 Gy) did not reveal any significant effect modification on PFS ($p = 0.073$) or OS ($p = 0.85$).

Overall survival

Restricted mean OS, truncated at 60 months, was improved with adjuvant RT by 1.1 months (95% CI 0.37–1.81; $p = 0.003$; see Figure 4) and a non-significant 21% reduction in the

hazard of death from any cause (HR 0.79; 95% CI 0.51–1.24; $p = 0.310$; see Figure 5).

Radiation toxicities

Radiation treatment-related toxicities were not reported in all studies. One study reported late toxicity with radiation necrosis in 4 patients (10%) receiving 46–54 Gy to the surgical bed at a median of 10 months after adjuvant EBRT [32]. Three out of those 4 patients underwent debulking surgery and had histological confirmation of radiation necrosis.

Risk of bias

The risk of bias in non-randomized studies of interventions (ROBINS-I) tool was used to evaluate the quality of these studies [25]. The overall risk of bias was assessed as serious in 8 studies [27–30,32,34–36], and critical in 4

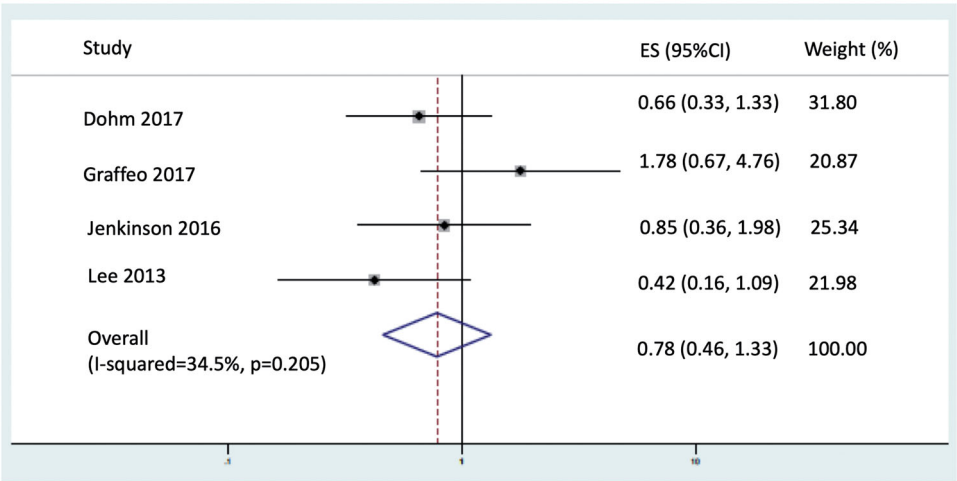


Figure 3. Hazards ratio of progression free survival.

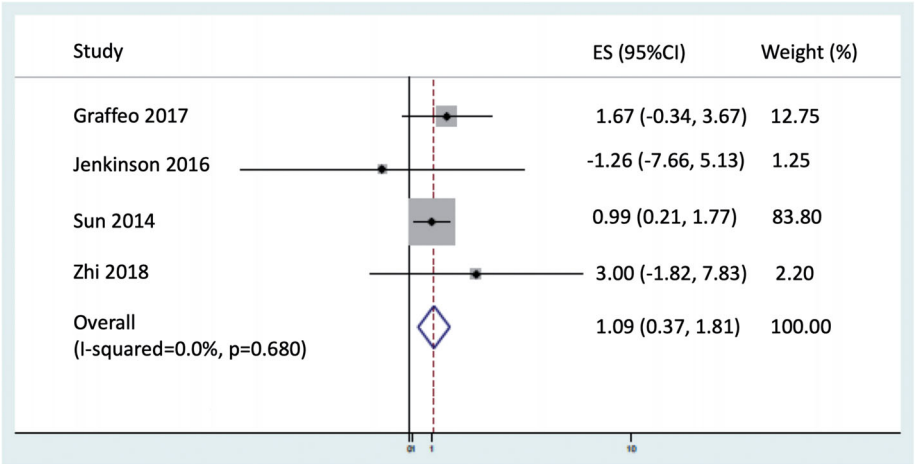


Figure 4. Restricted mean survival of overall survival.

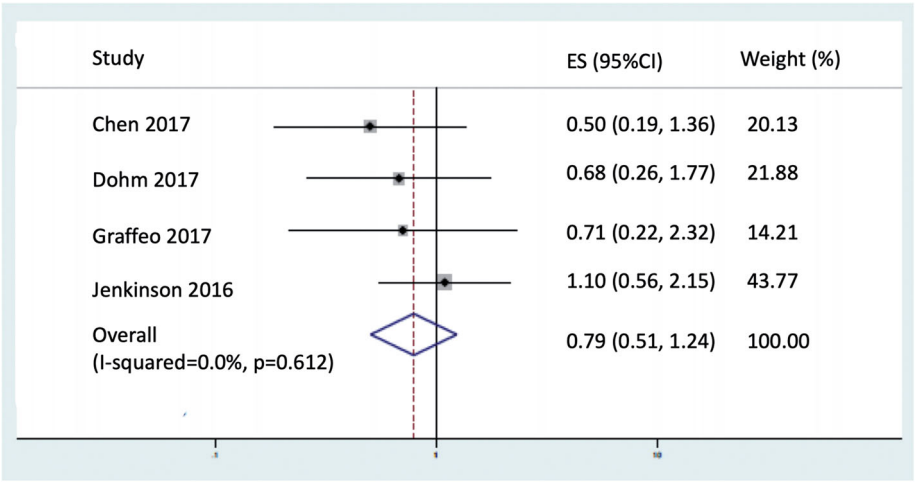


Figure 5. Hazards ratio of overall survival.

studies [15,26,31,33]. Please refer to [Supplementary Appendix 1](#) for the ROBINS-I tool evaluation of the studies included in our meta-analysis.

Discussion

We evaluated the role of adjuvant RT in AM following GTR in 12 studies which met our eligibility criteria and compared 5-year PFS and OS in those with and without adjuvant RT. We found that adjuvant RT was beneficial for patients with AM who had undergone GTR in that it significantly improved PFS by 3.9 months and OS by 1.1 month. Fewer data points were available to determine the reduction in hazard in PFS and OS. There was a non-significant reduction, of approximately 20%, in both these endpoints. Meta-regression analysis of EBRT dose did not show any significant difference between studies with median dose of < 59.4 Gy vs. ≥ 59.4 Gy.

The benefit of adjuvant RT following GTR in atypical meningioma remains debatable as class I evidence is not available. RT is the only form of adjuvant treatment that is currently known to reduce the risk of recurrence, and therefore it should be offered upfront to patients who are at higher risk with GTR alone [37]. Recurrences are likely to cause neurological dysfunction, detriment in Quality of Life, and necessitate a repeat resection, if feasible [8]. Such a risk-stratified approach is currently recommended by many society guidelines – based on the WHO grade and extent of resection [37]. However, patients with WHO grade 2 meningioma who have undergone GTR fall within a grey zone, as the risks of recurrence are balanced with the risk of adjuvant RT (e.g., cognitive decline, radiation necrosis, pituitary dysfunction) [32]. Further, advocates of the observation and early salvage strategy point to the lack of survival benefit with adjuvant RT. However, multiple surgeries for recurrent meningioma pose its own set of risks. A phase 2 non-randomized study (RTOG 0539), reported initial outcomes of 3-year PFS of 96% with local failure of 2.0% in 52 patients with intermediate risk meningioma who received adjuvant RT 54 Gy in 30 fractions [38]. In this study, intermediate risk meningioma include patients with WHO grade 2 meningioma who had GTR (36 patients) and patients with recurrent WHO grade 1 meningioma (16 patients). There was no difference in PFS between these two subgroups [38]. Another phase 2 trial (EORTC 22042–26042) reported 3-year PFS of 88.7% and 3-year OS of 98.2% with adjuvant RT following GTR [39]. In both trials, adjuvant RT was well tolerated with no significant effect on memory or cognitive function [38,39].

Over the years, meta-analysis and systematic reviews have reported the effectiveness of adjuvant RT in atypical meningioma following GTR to varying degrees (see [Table 3](#)). Hasan *et al.* reported that adjuvant RT after GTR (Simpson grade I–III) may improve LC but there was no significant benefit in the 5-year OS and no analysis on PFS was carried out [40]. Pereira *et al.* reported no difference in recurrence rate with or without adjuvant RT [41]. More recently, He *et al.* specifically selected studies that defined AM using the WHO classification criteria from year 2000 onwards and

found that adjuvant RT after GTR significantly improved LC and OS but not PFS [42]. Zoli *et al.* reported improvement in PFS, which were seen particularly at 3 and 5 years [43]. Song *et al.* reported significant improvement in PFS and OS with adjuvant RT in patients with GTR (Simpson grade I–III) however subsequent subgroup analysis revealed that only those with Simpson grade III had significant benefit from adjuvant RT [44].

The latest European Association of Neuro-Oncology (EANO) guidelines recommend adjuvant RT for Simpson 4–5 resection. Recommendation for Simpson 1–3 is uncertain and observation may be considered appropriate as no randomized trials are available to date with only level IV evidence currently available for this group [37]. Two highly anticipated phase 3 randomized controlled trials comparing adjuvant RT to observation following GTR in AM are currently in progress and their results are much awaited to help shed a light on the benefit of adjuvant RT in these cases. The ROAM/EORTC-1308 (Radiotherapy versus Observation following surgical resection of Atypical Meningioma/European Organization for Research and Treatment of Cancer-1308) trial will be the first multi-centre randomized controlled trial to evaluate the role of adjuvant RT in AM following GTR [45]. The NRG-BN003 study on observation versus irradiation for a gross totally resected grade 2 meningioma (clinicaltrials.gov NCT No: NCT03180268) is a phase 3 trial which randomized newly diagnosed AM patients with GTR to observation or early RT with photons or protons.

The benefit of adjuvant RT in our study was numerically small (PFS 3.9 months, OS 1.1 month) and still leaves unanswered questions about whether it should be offered to all patients with atypical meningioma undergoing GTR. The morphological classification of meningioma may soon give way to molecular classification. This may help to risk-stratify patients, aiding physicians to better select patients for adjuvant RT, where the benefit may be more pronounced. The group from Princess Margaret Hospital in Toronto have developed a new molecular classification based on the DNA methylation, somatic copy number aberration, point mutation and gene expression data from 121 patients [46]. They proposed 4 groups: MG1 (immunogenic), MG2 (benign NF2 wild-type), MG3 (hypermetabolic) and MG4 (proliferative). Other groups have suggested treatment algorithms considering other morphological features such as brain invasion, mitotic index and MIB-1. Adjuvant RT is recommended for AM with GTR where there is brain invasion as it carries a recurrence rate of up to 60% in 5 years with ~25% mortality rate. In cases where there is no brain invasion, adjuvant RT should be offered in AM with MIB-1 index of over 4.2% or more than 4 mitoses/10 HPF as this is deemed to be more aggressive with recurrence rate of more than 50% in 5 years [47,48]. A recent meta-analysis on the prognostic role of Ki-67 in meningioma reported worse OS in patients with high expression levels of Ki-67 (HR = 1.56; 95% CI: 1.217–2.013) [49].

All 12 studies included in our meta-analysis were of retrospective nature with limited number of patient population. This is in part due to our strict inclusion criteria, where only

Table 3. Comparison of meta-analysis and systematic reviews on post-operative RT in atypical meningioma.

Study (year)	Inclusion criteria	Statistical method	No. of studies (patients)	WHO grade	GTR alone	GTR + adjuvant RT	LC	PFS	OS	Toxicities	Authors' conclusion
Hasan et al. (2015) [40]	Age > 18, AM/WHO grade 2 meningioma, GTR	OR χ^2 test	14 (757)	II	549	208	OR 1.71; 95% CI 0.98–2.98; $p = 0.06$	NR	OR 0.97; 95% CI 0.39–2.4; $p = 0.95$	<10%	No significant benefit of post-op RT on survival.
Pereira et al. (2018)* [41]	(Simpson 1–3) Age > 18, AM/WHO grade 2 meningioma 2007/2016	OR	17 (1761)	II	NR	573	OR 1.0448; 95% CI 0.8318–1.3125; $p = 0.7062$	NR	NR	NR	RT does not significantly decrease the rate of recurrence in patients with AM.
He et al. (2021) [42]	AM/WHO grade 2 meningioma, WHO classification 2000 or after, 5-year prognostic data available	OR Cochrane's Q test /Z measurement	17 (2008)	II	1492	369	5-year LC OR 2.59; 95% CI 1.40–4.81; $p = 0.002$	5-year PFS OR 1.99; 95% CI 1.35–2.95; $p = 0.001$	5-year OS OR 1.07; 95% CI 0.60–1.91; $p = 0.828$	NR	PORT significantly improves 5-year LC and PFS.
Chun et al. (2021) [50]	Studies with GTR vs. adjuvant RT reporting LC, PFS, OS	HR	30 (2904)	II	2167	737	OR 0.50; 95% CI 0.36–0.68; $p < 0.0001$	5-year PFS HR 0.66; 95% CI 0.49–0.89; $p = 0.0072$	5-year OS HR 1.11; 95% CI 0.67–1.64; $p = 0.6548$	Mostly G1–2 2.1% G3 2.7% G4	Adjuvant RT confers significant benefits for LC and PFS.
Song et al. (2021) [44]	AM GTR, STR, RT	HR	24 (3078)	II	8 studies	16 studies	Reduced recurrence rate in patients with GTR (PFS); HR 0.69; 95% CI 0.52–0.92, $p = 0.01$	HR 0.73; 95% CI 0.39–1.34; $p = 0.31$	HR 0.55; 95% CI 0.36–0.85, $p = 0.007$	G3–4 in 1 study G2–3 in 1 study G2+ in 1 study G1–2 in 1 study	PORT significantly improved PFS and OS in GTR and STR. Subgroup analysis reported that within the GTR group, only Simpson 3 had significant improvement in PFS.
Zoli et al. (2022) [43]	AM GTR (Simpson 1–3), RT, Haenszel model	OR Mantel-Haenszel model	11	II	NR	NR	NR	1-year PFS OR 0.92 3-year PFS OR 0.31 5-year PFS OR 0.35	NR	NR	Possible protective role of PORT against long-term recurrences.
Our study	AM, GTR (Simpson 1–3), RT, PFS +/- OS reported with survival curves	RMST and HR	12 (1078)	II	803	275	NR	Restricted mean PFS 3.9 months $p = 0.037$ HR 0.78 $p = 0.370$	Restricted mean OS 1.1 months $p = 0.003$ HR 0.79 $p = 0.310$	Late toxicity: radiation necrosis in 4 patients	Significant PFS and OS benefit, albeit modest, hence there may be an option for close surveillance and early salvage for patients.

*Literature review. AM: atypical meningioma.

GTR: gross total resection. HR: hazards ratio. LC: local control. OS: overall survival. OR: odds ratio. PFS: progression free survival. RMST: restricted mean survival time. STR: subtotal resection.

studies which reported outcomes of GTR with or without adjuvant RT and included survival curves were selected. The long duration of study inclusion (on average about 10 years) also meant that the WHO classification for atypical meningioma have changed over that period of time, hence affecting the consistency of the diagnostic criteria used in the studies. GTR was not uniformly defined as most studies included Simpson grades 1–3 as GTR, however others only considered Simpson grades 1–2 or 1 only as GTR. With no standardized guidelines in place, there might have been some degree of bias in the selection of patients who were offered adjuvant RT following GTR as this depended on individual clinician's recommendation.

Conclusion

The use of adjuvant RT in patients with AM who have undergone GTR provided a modest PFS benefit (based on restricted mean survival). RT reduces the relative risk of recurrence and should be discussed with all patients. However, in view of the small OS benefit, there may be an option for close surveillance and early salvage for patients where repeat surgical resection can be easily performed. As such, no strong recommendation can be made for, or against, adjuvant RT. We anticipate better clarity with the ongoing RCTs addressing this question, and the increased use of molecular studies to better risk-stratify patients.

Authors contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by Caryn Wujanto, Balamurugan Vellayappan, and Soon Yu Yang. The first draft of the manuscript was written by Caryn Wujanto and Tabitha Chan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability statement

The data that support the findings of this study are available online from their respective journal website (please refer to Table 1 for a list of all the included studies and their references).

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