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TOPIC REVIEW

Meta-analysis of adjuvant radiotherapy for intracranial atypical and malignant meningiomas

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Abstract

Introduction Meningiomas comprise 33% of all CNS tumors. The World Health Organization (WHO) describes meningiomas as benign (BM), atypical (AM), and malignant/anaplastic (MM). High-grade meningiomas such as AMs and MMs are more aggressive, recur more frequently, and portend a worse prognosis than BMs. Currently, the standard treatment for high-grade meningiomas, especially AMs, is ill-defined. In particular, the benefit to survival outcomes of adjuvant radiotherapy post-surgical resection remains unclear. In this study, we investigated the effect of adjuvant radiotherapy (ART) post-surgery on survival outcomes compared to surgery alone for high-grade meningiomas.

Methods PRISMA guidelines were a foundation for our literature review. We screened the PubMed database for studies reporting overall survival (OS), progression free survival (PFS), and tumor recurrence for intracranial, primary AM and MMs treated with surgery+ART or surgery alone. Fixed and random effect models compared tumor control rate for AM aforementioned groups.

Results Mean 5-year PFS was 76.9% for AM (surgery+ART) and 55.9% for AM (surgery alone) patients. Mean 5-year OS was 81.3% and 74% for AM (surgery+ART) and AM (surgery alone) groups, respectively. Overall, the mean 5-year PFS for aggregated high-grade meningiomas AM+MM (surgery+ART) was 67.6%. Fixed effect models revealed tumor control rate as 76% for AM (surgery+ART) and 69% for AM (surgery alone) groups. ART induced toxicity incidence ranged from 12.0% to 35.5% for AM and MM patients.

Conclusions Our analysis suggests that (surgery+ART) may increase PFS, OS, and tumor control rates in high-grade meningiomas. However, further studies involving surgery+ ART should be conducted to fully evaluate the ideal radiosurgical candidate, modality, and dosage.

Keywords Atypical meningioma · High-grade meningioma · Malignant meningioma · Radiosurgery · Radiation therapy · Adjuvant

Introduction

Meningiomas possess the highest incidence rate, and comprise over one-third, of primary brain and central nervous system neoplasms [1, 2]. In the US, meningiomas occur in 7 per 100,000 people [2–5]. Meningiomas are thought to arise from arachnoidal cap cells, which form the arachnoid mater of the meninges [6]. The World Health Organization (WHO) categorizes meningioma into three molecular and histological groups: grade I/benign (BM), grade II/atypical (AM),

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and grade III/anaplastic/malignant (MM) [7]. According to the most recent 2016 WHO classifications, BMs must not invade the brain parenchyma, and they lack atypical features [8]. To be defined as AMs, the sample must exhibit increased mitotic rate (4–19 mitoses per 10 high powered field (hpf)) and invade the brain parenchyma. Additionally, AMs must possess at least three of the following features: increased cellularity, high nuclear-cytoplasmic ratios, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of spontaneous or geographic necrosis [8]. Finally, to be classified as an MM, lesions must display an even more elevated mitotic rate (≥ 20 mitoses per 10 hpf) and/or malignant characteristics resembling carcinoma, sarcoma, or melanoma [8].

Although 80% of meningiomas are benign and slow growing [5], 17% are AM, and 2% are MM [2]. High-grade meningiomas such as AMs and MMs are more aggressive, have an increased recurrence rate, and portend a worse prognosis than BMs [5, 6, 9–13]. Furthermore, a standardized treatment approach to high-grade meningiomas has not been established. Historically, meningiomas were considered resistant to radiotherapy, but more recent studies indicate that radiotherapy improves local control of AM and MMs [13–16]. The data for adjuvant radiotherapy (ART) in combination with surgical resection, however, remains unclear. This non-consensus contributes to the variation of treatment practices across institutions. In this meta-analysis, the authors investigated outcomes of patients with high-grade meningiomas treated with surgical resection and adjuvant radiotherapy (ART) compared to surgery alone to clarify the role of ART in the management of these aggressive lesions.

Materials and methods

Data collection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (www.prisma-statement.org) guidelines were used as a foundation for our literature review and analyses. The National Library of Medicine's MEDLINE database was queried through PubMed using combinations of Boolean operators and key terms, "atypical, grade II, grade 2, malignant, grade 3, grade III, anaplastic, meningioma, radio*, radiation, treatment, and adjuvant". Our last electronic search of the literature occurred in April 2020. Two independent reviewers screened titles, abstracts, and full-text manuscripts for pertinent studies (Supplementary Fig. 1). Bibliographies of relevant studies and review articles were manually queried for additional studies of interest missed by our electronic search. We included full English text studies, which reported patient outcomes following surgical resection and/or adjuvant radiotherapy for primary, intracranial AM and MM. Studies which aggregated AM and MM patients were also included. Case reports, reviews, non-English studies, non-human studies, and studies with insufficient data were excluded. We also excluded studies that contained pediatric patients (<18 years), non-primary lesions, prior radiotherapy, Neurofibromatosis type I and II and schwanomatosis, grade I (benign) meningiomas, mixed-histology tumors and aggregated adjuvant and salvage radiotherapies. Lastly, studies published prior to 2000 were excluded due to the rapid advancements in radiotherapeutic technology.

Data extraction

Initial demographics (i.e. patient age, gender, treatment modality, radiation dosage, follow-up time) were recorded for each study as available. To assess survival outcomes between AM and MM patients treated with (surgery alone) vs. those treated with (surgery + ART), we extracted overall survival (OS), progression-free survival (PFS), and tumor recurrence for each of the treatment groups. In most studies, PFS was defined as the time from surgery [14, 17–21] or ART [14, 17, 22] to detection of tumor regrowth, new lesions, or increase in tumor size [14, 18, 20, 21]. Of note, Weber et al. defined PFS and OS as beginning from study inclusion [23]. Zhi et al., Hammouche et al., Kaul et al., Aghi et al., and Goyal et al. did not explicitly define a starting time frame for PFS or OS [10, 24–27].

New lesions, tumor regrowth, or increase in tumor size was demonstrated by radiographic scans in all studies. Importantly, Weber, Bagshaw, and Dohm et al. characterized tumor regrowth as 25% size increase [14, 20, 23], while Lubgan and Chen et al. did so with 20% size [19, 22]. Of note, Masalha et al., Zhi et al., Detti et al., Hammouche et al., Kaul et al., Aghi et al., Goyal et al., and Kano did not specify a cut off size percentage increase to characterize tumor progression [10, 17, 18, 21, 24–27]. OS was majorly defined as the time between surgery [14, 17–21] or ART [14, 17, 22] and patient death from any cause. Zhi et al. defined PFS as, "absence of radiographic P/R and death from all causes and OS as absence of death from all causes" [27]. All included studies employed Kaplan-Meier techniques, with p values calculated by log-rank tests to estimate PFS and OS. We also noted toxicity and adverse events from radiotherapy.

Statistical analysis

Descriptive statistics of patient demographics and treatment modalities were displayed as means and standard deviation or 95% confidence intervals using standard methods. Statistical analysis was conducted using R Studio v.1.2.5019 (RStudio Inc., Boston, MA). Tumor control data across studies were aggregated under fixed and random effect models, summarized using a forest plot. Heterogeneity across studies

was measured using I^2, τ^2, and Cochran's Q, while publication bias was measured using Egger's test. A p value less than .05 was considered as significant for this study.

Results

Through combined electronic and manual bibliographic searching, we identified 659 deduplicated works. Of these, 126 papers remained after title-screen, and 63 abstracts were reviewed. Ultimately, 13 retrospective studies published between 2000 and 2019 met our inclusion criteria. These studies reported OS, PFS, and tumor recurrence after ART following surgical resection (Supplementary Fig. 1).

Patient characteristics and demographics

In total, 1113 patients (505M/608F) were reported with average age at treatment of 58 years and median follow-up time of 48.4 months (range: 12.5–80.4 months). Overall, patients were treated with a median radiotherapy dosage of 54 Gy (range:14–60 Gy). Of these 1113 patients, 1025 patients were diagnosed with AM, 409 of which underwent surgical resection and ART (Table 1). Of note, Kaul et al. aggregated the data for AM and MM patients [26]. Median ART dose for this group was 54 Gy. 615 patients received surgery alone. These patients were treated at a median age of 64 years with median follow-up time of 48 months. The remaining patient was treated with radiotherapy alone and was not included in our analysis. In addition, 33 patients were diagnosed with MM, of which 10 patients received surgical resection and ART (Table 2). For those MM patients who underwent ART, the average dose was 54 Gy. Compared to those with AM, the median age of treatment for MM patients was 61 years with median follow-up time of 40 months.

Survival outcomes

We compared mean PFS, mean OS at 5 years, and tumor control rates for AM, aggregated AM+MM, and MM patients (Table 3). Inverse logistic transformation of the fixed effect model coefficients was used to calculate 95% confidence intervals (95% CI) and tumor recurrence rates for AM patients, who underwent surgery+ART versus surgery alone. However, due to paucity of data, we could not similarly analyze MM or aggregated AM+MM groups.

Survival outcomes for AM patients

For AM patients treated with (surgery+ART), the mean PFS at 5 years was 76.1% (CI: [61.8%, 90.5%]) (range: 51–100%), compared to 55.6% (CI: [43.7, 67.5]) (range: 27–73%) for those treated with surgery alone. The mean OS at 5 years was 81.3% (CI: [74.5, 88.2]) (range: 71–86%) and 74% (CI: [55.0, 93.0]) (range: 55–87%) for ART+ surgery and surgery alone treatment groups, respectively.

Survival outcomes for aggregate AM+MM patients

Overall, the mean PFS at 5 years for aggregated high-grade meningiomas following ART and surgery was 67.6% (CI: [48.7, 86.6]) (range: 48.3–78.1%).

Survival outcomes for MM patients

Only two studies detailed outcomes for MM (surgery+ART) patients. Kano et al. reported an OS of 80.8% at 5 years [17], and Lubgan et al., 86% at 10 years [22]. For patients treated with surgery, one study, Detti et al. evaluated 5-year OS of 56.3% [18].

Surgery+ART or surgery on tumor control rates

We employed a generalized linear mixed model to compare the tumor control rates between surgery+ART and surgery alone groups. Tumor control rates for AM (surgery+ART) patients ranged from 20% to 100% with fixed and mixed effect model, showing a tumor control rate of 76.0% (95%CI: [0.71, 0.81]) (Fig. 1). Conversely, tumor control rates for AM (surgery alone) ranged from 40% to 80% across studies (Fig. 2). Fixed and random effects models demonstrated tumor control rate of 69.0% (95%CI: [0.65, 0.72]). Although not statistically significant, these models suggest that ART may improve tumor control rates in patients with AM. Lastly, aggregated AM+MM (surgery+ART) demonstrated a tumor control rate of 78.0% (95%CI: [0.74, 0.82]).

Treatment toxicity

Adverse effects secondary to radiation were reported in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) scale: grade 1 = mild grade 2 = moderate, grade 3 = severe, and grade 4 = life-threatening or disabling. In our study, the incidence of toxicity of all grades ranged from 12.0% to 35.5% [14, 17–20, 22–24, 26] for AM and MM patients. Of note, MM studies did not disaggregate the MM from AM data. Therefore, we cannot separately evaluate groups. Additionally, one study Kaul et al. reported radiation induced toxicities for their entire data set, which included BMs [26]. Grade 2 symptomology (headache, alopecia, dizziness, hearing and memory impairment, skin irritation, and fatigue) occurred in 5.1% [14], 16.7% [17], 16.0% [18], and 2.5% [19] of patients. 6.8% [14], 12.5% [24], 0.7% [26], 11.1% [20], 10% [19],

Table 1 Summary of study characteristics, radiation dose, survival outcomes, and toxicity related to radiotherapy in included studies of AM [10, 14, 17–27]

Author and publication year	Time period	Tumor definition	Total AM, n	Age, years	Female, n (%)	Received ART, n	Follow-Up time, mo.	Treatment modality	Dose, Gy, mean or median	PFS	OS	Tumor recurrence (%)	Patients with ART associated toxicity[a]
Weber et al. (2018) [23]	2008–2013	WHO (unspecified year)	56	54 median	27 (48)	56	61.2 median	Surgery+ EBRT[c] (IMRT[d], 3DCRT[e], FSRT[f])	60 median (range 60–70)	83.7% at 3 years (surgery+ART[g])	98.1% at 3 years (surgery+ART)	–	16.1%
Lubgan et al. (2017)[b] [22]	2002–2015	WHO (unspecified year)	34	60.46 mean; 61 median	70 (70)	34	36.15 median	Surgery+ SRS[h] or SRS alone	54.0 median	83% at 5 years and 8 years (surgery+ART)	–	–	26% worse QoL[i]
Chen et al. (2019) [19]	1993–2014	WHO 1993–2000	182	56.5 mean	111 (61)	42	52.8 median	Surgery+ EBRT or SRS, or surgery alone	59.4 median (range 36–60)	65% at 5 years (surgery alone); 82% at 5 years(surgery+ART)	87% at 5 years (surgery alone); 85% at 5 years (surgery+ART)	29%	12%
Dohm et al. (2017) [20]	1993–2014	WHO 2007	115	63.6 median	70 (61)	63	36.9 median	Surgery+ EBRT or SRS, or surgery alone	EBRT- 55.7 median (range 50.4–59.4) for; SRS- 14.5 median (range 12–18)	64% at 1 year and 49% at 2 years, and 27% at 5 years (surgery alone); 81% at 1 year and 73% at 2 years and 59% at 5 years (surgery+ART)	75% at 1 year and 72%at 2 years and 55% at 5 years (surgery alone); 98% at 1 year and 95% at 2 years and 71% at 5 years (surgery+ART)	–	12.7%
Masalha et al. (2017) [21]	2001–2015	WHO (unspecified year)	161	70.95 (surgery alone); 68.9 (ART+ surgery) median	85 (53)	33	62.4 mean	Surgery+ART or surgery alone	–	80% at 3 years, 73% at 5 years, 70% at 10 years (surgery alone); 76% at 3 years, 64% at 5 years, 57% at 10 years (surgery+ART)	–	29%	–
Bagshaw et al. (2017) [14]	1991–2014	WHO 2007	59	53 median	31 (53)	17	42 median	Surgery+ FSRT[j] or SRS or surgery alone	FSRT 54 median (range: 45–59.4) SRS 15 median (range: 12.5–15)	–	90.4%[b] unspecified time (surgery alone); 85.7%[b] unspecifiedtime (surgery+ART)	50%	12% RT related toxicity (grade 2 and above)
Zhi et al. (2018) [27]	2000–2012	WHO at time of diagnosis (2000–2007)	149	64 median	75 (50)	53	74.2 median	Surgery+ EBRT (IMRT or FSRT) or surgery alone	59.4 median (range:54–61.9)	63% at 3 years, 54% at 5 years, 41% at 10 years (surgery alone); 85% at 3 years, 76% at 5 years, 58% at 10 years (surgery+ART)	84% at 3 years, 80% at 5 years, and 67% at 10 years (surgery alone); 90% at 3 years 86% at 5 years, 68% at 10 years (surgery+ART)	35.40%	–
Detti et al. (2013) [18]	1993–2011	WHO (unspecified year)	30	58.5 median[k]	19 (50)	30	80.4 median[k]	Surgery+ EBRT (3DCRT or 2DCRT[l])	54.6 mean (range:50–60)	–	83.3% at 5 years (surgery+ART)	–	16% Grade <= 2 acute side effects (skin irritation, alopecia, fatigue, sickness, headache)[m]

Table 1 (continued)

Author and publication year	Time period	Tumor definition	Total AM, n	Age, years	Female, n (%)	Received ART, n	Follow-Up time, mo.	Treatment modality	Dose, Gy, mean or median	PFS	OS	Tumor recurrence (%)	Patients with ART associated toxicity[a]
Hammouche et al. (2014) [25]	1996–2009	WHO 2007	79	58 mean	36 (46)	36	50 mean	Surgery+ FSRT or surgery alone	56.2 mean (range:45–60)	95% at 1 year 56% at 5 years[b] reported as relapse free survival (surgery alone);87% at 1 year, 51% at 5 years (surgery+ART)		33%	–
Kaul et al. (2014) [26]	1995–2009	WHO (unspecified year)	20	60.13 mean	12 (38)	20	12.5 median	Surgery+FSRT, SRS, and hFRST[n] or FSRT, SRS, and hFRST alone	nFRST[o] −57.31 mean; hFRST−37.6 mean; SRS 17.31 mean; mean total dose 52.4	–	–	–	35.5% (entire data set including those with RT+ benign tumors) displayed late toxicity (group I–III symptoms)
Aghi et al. (2009) [24]	1993–2004	WHO 2000	108	55 mean	60 (56)	2	39 mean	Surgery+FRST or surgery alone	60.2 mean (range:59.4–61.2)	44% at 5 years (surgery alone); 100% at 5 years (surgery+ART)	–	28%	12.5% (radiation necrosis)
Goyal et al. (2000) [10]	1979–1995	WHO 1979	22	55.5 median	8 (36)	2	66 median	Surgery+FSRT or surgery alone	54 median (range:35–59.4)	70% at 5 years (surgery alone) 100% at 5 years (surgery+ART)	–	–	–
Kano et al. (2007) [17]	1997–2002	WHO 2000	10	58.5 mean; 63 median	4 (33)	10	44 median; 43.4 mean	Surgery+SRS	18 median (range:12–20 range)	–	–	–	16.7%

[a]Treatment toxicities are reported for adverse effects of grade 2 or above according to CTCAE guidelines

[b]Lubgan et al. reported number of lesions rather than number of patients

[c]External Beam Radiation Therapy

[d]Intensity-Modulated Radiation Therapy

[e]Three-Dimensional Conformal Radiotherapy

[f]Fractionated Stereotactic Radiotherapy

[g]Adjuvant Radiotherapy

[h]Stereotactic Radiosurgery

[i]Quality of Life

[j]Fractionated Stereotactic Radiosurgery

[k]Includes patients with recurrent meningiomas (they are not included in other data)

[l]Two-Dimensional Conformal Radiotherapy

[m]This also includes patients that received RT as primary treatment AND upon recurrence

[n]Hypofractionated Stereotactic Radiotherapy

[o]Narmofractionated Stereotactic Radiotherapy

Table 2 Summary of study characteristics, radiation dose, survival outcomes, and toxicity related to radiotherapy in included studies of MM [17, 18, 22, 26]

Author and publication year	Time Period	Tumor definition	Total MM, n	Age, years	Females, n	Received ART, n	Follow-up time	Treatment modality	Dose	PFS	OS	Tumor recurrence	Patients with complications associated with ART[a]
Lubgan et al. (2017)[b] [22]	2002–2015	WHO (unspecified year)	11	60.46 mean; 61 median	70	11	36.15 median	Surgery+SRS[c] or SRS alone	54.0 median	87% at 8 years (surgery+ART[d])	86% at 10 years (MM[e]+AM[f] surgery+ART)	–	26% worse QoL[g]
Detti et al. (2013) [18]	1993–2011	WHO (unspecified year)	8	58.5 years median[h]	19	8	80.4 median[h]	Surgery+EBRT[i] (3DCRT or 2DCRT)	54.6 mean (range: 50–60)	76.5% at 5 years, 69.5% at 10 years[b] reported as disease free survival (MM+AM surgery+ART)	56.3% at 5 years (surgery alone)	–	16% Grade <= 2 acute side effects (skin irritation, alopecia, fatigue, sickness, headache)[j]
Kaul et al. (2014) [26]	1995–2009	WHO (unspecified year)	12	60.13 mean	12	12	12.5 median	Surgery+FSRT[k], SRS, or hFSRT[l] or FSRT, SRS, or hFRST alone	nFSRT[m] 57.31mean; hFSRT 37.6 mean, and SRS 17.31 mean; mean total dose 52.4	87.6% at 3 years, 78.1% at 5 years, and 73.4% at 10 years (MM+AM surgery+ART)	–	–	35.5% (entire data set including those with RT[n]+ benign tumors) displayed late toxicity (group I–III symptoms)
Kano et al. (2007) [17]	1997–2002	WHO 2000	2	58.5 mean; 63 median	4	2	44 median; 43.4 mean	Surgery+SRS	18 median (range:12–20 range)	48.3% at 5 years[b] (MM+AM surgery+ART)	80.8% at 5 years (MM+AM surgery+ART)	–	16.7%

[a]Treatment toxicities are reported for adverse effects of grade 2 or above according to CTCAE guidelines

[b]Lubgan et al. reported number of lesions rather than number of patients

[c]Stereotactic Radiosurgery

[d]Adjuvant Radiotherapy

[e]Malignant/Anaplastic

[f]Atypical

[g]Quality of Life

[h]Includes patients with recurrent meningiomas (they are not included in other data)

[i]External Beam Radiation Therapy

[j]This also includes patients that received RT as primary treatment AND upon recurrence

[k]Fractionated Stereotactic Radiotherapy

[l]Hypofractionated Stereotactic Radiotherapy

[m]Normofractionated Stereotactic Radiotherapy

[n]Radiotherapy

and 16.1% [23], of all patients developed grade 3 adverse effects, which includes radiation necrosis, meningiomatosis, cognitive neuropathy, seizures, aphasia, and optic nerve disorders. Of note, one study Lubgan et al. describes 26.0% of patients that rated their quality of life as worse post irradiation [22].

Study heterogeneity

Analysis of Forrest plots show that both AM (surgery+ART) and AM (surgery alone) groups exhibited low heterogeneity, ($I^2 = 33\%$, $\tau^2 = 0.1024$, $\chi^2_9 = 12.42$, $p = .19$) (Fig. 1), and ($I^2 = 40\%$, $\tau^2 = 0.0429$, $\chi^2_7 = 13.67$, $p = .06$) (Fig. 2). Low heterogeneity indicates that the data from our studies overlap, increasing the data's validity.

Study bias assessment

To determine study bias, Egger's test for AM (surgery+ART) and AM (surgery alone) groups were run. No study bias was discovered in either group: AM (surgery+ART): $t = 0.43$, $p = 0.68$ and AM (surgery alone): $t = -1.45$, $p = 0.20$. Funnel plots graphically represent the relationship between study uncertainty and deviation of the study-wise tumor control rates from the fixed effect model (Supplemental Figs. 2 and 3). For both AM (surgery+ART) and AM (surgery alone) groups, the plots are symmetrical, with 50% reported tumor control rates higher than the fixed effects estimate and only one study falling beyond the 95% CI boundaries. This further illustrates absence of bias.

Discussion

The aim of our study was to evaluate whether ART following surgery improved survival outcomes for high-grade meningiomas compared to surgical intervention alone. Overall, we found that for AM patients treated with surgery+ART, mean 5-year PFS was 20.4% improved, mean 5-year OS was 7.1% increased, and tumor control rates were 7% higher than those respective outcomes in AM (surgery alone) patients. Our results suggest that surgery+ART, compared to surgery alone, may increase survival outcomes in patients with AM. Overall, our results are consistent with the existing literature [5, 10, 19–22, 24, 27, 29]. A subset of studies, however, did demonstrate a trend toward worsened outcomes in ART treated patients [14, 20, 21, 25]. It is the opinion of these authors that surgery+ART does, in fact, increase survival outcomes in high-grade meningioma patients. The limitations are inherent in the examined studies (retrospective natures, single-institution series, and heterogeneity of radiotherapeutic modalities and dosages) in addition to the lack of prospective randomized trials directly comparing surgery+ART with surgery alone [4, 5].

Dziuk et al., however, demonstrated that without ART, MM patients displayed 28.0% 5-year PFS compared to 57.0% with surgery+ART [28]. Additionally, Durand et al. reported a median overall survival rate of 62.0% and median PFS of 41.2% in MM (surgery+ART) groups and a correspondingly lower rate of 43.6% and 5.6% in MM (surgery alone) groups [30]. It is important to note that these studies were not included in this meta-analysis due to multiple confounding variables. Nevertheless, due to the numerous studies that suggested the benefits of surgery+ART in treating MMs [15, 28, 30–34], our data also concurs with the benefit of surgery+ART for primary MMs and combined AM+MM patients.

Heterogeneity of radiotherapy treatment, dosage, and toxicity

It is well documented that radiotherapy delivered to the brain can result in serious side effects like pituitary dysfunction [35], cognitive impairment [36], and secondary brain lesions [37]. Nevertheless, there are currently no established guidelines on radiosurgical modality or dosage for high-grade meningiomas. Within our study, AM and MM patients underwent external beam radiation therapy (EBRT) (IMRT, FSRT, 3DCRT, and 2DCRT) ($n = 307$), hypofractionated radiotherapy (hFRST) ($n = 10$), and SRS ($n = 70$). Historically, AM and MMs are largely treated with EBRT at about 60 Gy with daily fractions administered for 5–6 weeks [4]. This tendency is reflected in our meta-analysis, as the majority of the included patients received EBRT at an average dosage of 54 Gy. Despite this conventionality, compared to SRS, EBRT potentially generates more chronic neurocognitive and white matter adverse effects [4]. In our studies that exclusively employed EBRT, CTCAE grade III toxicities like (radiation necrosis and optic neuritis) were most frequently observed [19, 23, 24]. Conversely, in included studies utilizing SRS only, headache and short term perifocal edemas were more commonly displayed [17, 22]. This is in line with a subset of literature, which noted that SRS induced perilesional edema is transient, short-term, and often infrequent and mild [38–40]. Other retrospective studies examining SRS for meningioma, however, asserted that radiotherapeutic edema may engender seizures, especially in parasagittal regions [41, 42]. Nevertheless, numerous studies have shown that SRS has excellent local control, and therefore is a good option for tumors located near radiosensitive organs [41, 43, 44]. Compared to SRS's single dose, hFRST may deliver 3–6 fractions with good local control [45–47]. Due to its spaced fractionation scheme, hFRST may allow for tissue repair, and thus incur fewer ART induced complications [48]. Rogers et al. bolstered this claim by showing

Table 3 Survival Outcomes for AM+MM, AM, and MM (surgery+ART) and (surgery alone groups): Means and Confidence Intervals for 5-year PFS and OS and tumor recurrence rate [10, 14, 17–27]

	AM[a]		AM+MM[b]		MM	
	Surgery+ART[c]	Surgery Alone	Surgery+ART	Surgery Alone	Surgery+ART	Surgery Alone
PFS[d] at 5 year Mean %, (95%CI)	76.1 (61.8–90.5)	55.6 (43.7–67.5)	67.6 (48.7–86.6)	–	–	–
OS[e] at 5 year Mean %, (95%CI)	81.3 (74.5–88.2)	74.0 (55.0–93.0)	–	–	–	–
Tumor Control Rate, mixed effect model %	76	68	79	–	–	–

[a]Atypical

[b]Malignant/Anaplastic

[c]Adjuvant Radiotherapy

[d]Progress Free Survival

[e]Overall Survival

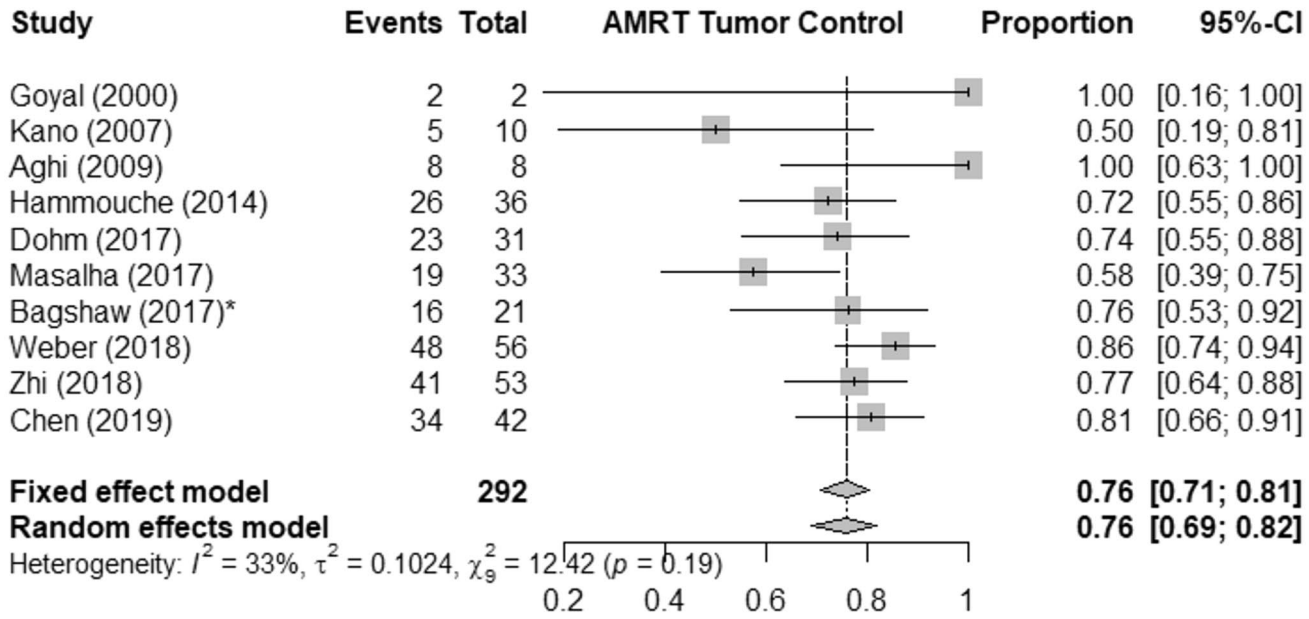

Fig. 1 Forest plot of tumor control rates for AM patients treated with surgery +ART. "Total" is the total number of patients that underwent surgery+ART for AM, whereas "Events" describes the number of patients with reported tumor control. A total of 292 patients with AMs treated with surgery alone were evaluated [10, 14, 17, 19, 20, 21, 23–25, 27]

that hFRST decreased edema and radiation necrosis in larger tumors [49]. In this study, meaningful examination of hFRST induced radiotoxicity was limited. Only one study by Kaul et al. examined this modality, and they reported radiation induced toxicities for their entire data set, which included BMs [26]. To these authors' knowledge, no study has directly compared various radiosurgical modalities nor dosages for meningioma patients. Therefore, to determine optimal dosage and modality for these patients, future exploration into this subject is merited.

Differences in the extent of surgery and tumor location

Meningioma location dictates the surgical approach and the extent of resection [4]. In our study, gross total resection (GTR) was achieved in 723 patients with 222 receiving ART [10, 18, 19, 22–24, 26]. The majority of tumors were located on convexity ($n = 398$). Therefore, they were more amenable to surgery, and thus gross total resection may have been a suitable intervention. In studies that directly compared (surgery+ART) to (surgery alone) per location, we observed

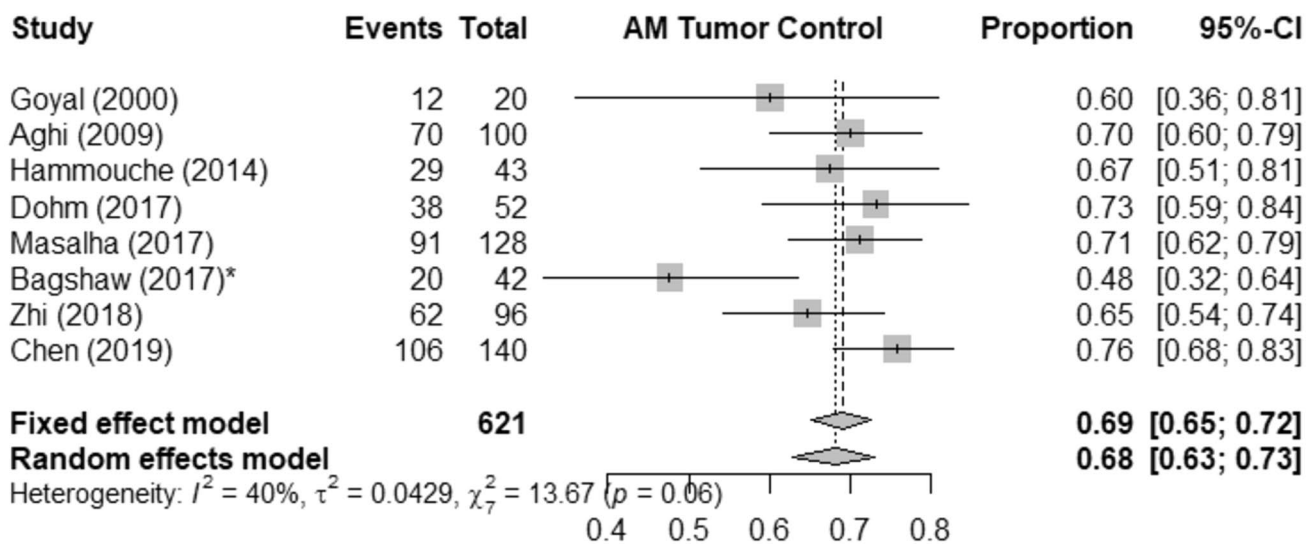

Fig. 2 Forest plot of tumor control rates for AM patients treated with surgery alone. "Total" is the total number of patients that underwent surgery for AM, whereas "Events" describes the number of patients with reported tumor control. A total of 621 patients with AMs treated with surgery alone were evaluated [10, 14, 19, 20, 21, 24, 25, 27]

that patients with meningiomas of the non-skull base (convexity and parasagittal/falcine) ($n = 303$), more frequently underwent surgical resection alone 65% [22], 63.5% [18], and 61.7% [23] compared to combination ART and surgery 45% [22], 62.3% [18], and 60.6% [23]. Conversely, patients with meningiomas in the skull base (sphenoid ridge/wing and anterior and posterior fossa) ($n = 162$) were more often treated with combination surgery and ART 54.7% [22] and 39.4% [23] compared to surgery alone 35.3% [22] and 38.3% [23]. Of note, Zhi et al. classified their tumor locations as "convexity" and "non-convexity", thus comparison was only obtained for non-skull base tumors [27]. This selection bias with more surgically amenable lesions forgoing ART may contribute to the difference in survival outcomes. That is, surgeons may influence survival outcomes by assigning more inoperable, aggressive meningiomas to combination surgery+ART over surgery alone. It is well documented the extent of surgical resection impacts the rate of meningioma recurrence [4, 12, 50]. Studies show that AM patients treated with GTR + ART have lower rates of tumor recurrence than those treated with subtotal resection (STR) + ART [5, 19]. Nevertheless, other studies report that ART reduced local progression of AM irrespective of GTR v STR [22]. Ongoing clinical trials, like that of Jenkinson et al., which compares AMs treated with GTR+ observation vs. radiotherapy, will help further elucidate the benefits of GTR + ART.

Limitations

An inherent difficulty in the evaluation of high-grade meningiomas is their relative rarity. Malignant meningiomas comprise between 1 and 5% of meningiomas [5, 25, 26], and the dearth of available data in conjunction with the aggregation of individual patient data hindered survival analysis. Nevertheless, ongoing studies should consider evaluating AM and MMs separately. Additionally, given the relative indolent growth of meningiomas, our study's relatively short follow-up times may have limited ability to capture statistically significant correlations. Furthermore, the included works did not report the FU length for each participant. Therefore, while tumor control rates were able to be analyzed using fixed and random effect models, we could only compare mean PFS and OS across studies. Furthermore, the heterogenous reporting of medians or means for survival metrics rendered our comparison limited to only the subset of most consistently reported outcomes. Other limitations include retrospective nature of the studies and their small sample sizes, which limited statistical power to detect significant differences between surgery+ART and surgery alone groups. Non-comparative designs with regard to treatment groups posed another challenge. Several studies treated all patients with adjuvant radiation, which precluded comparison of whether surgery+ART or surgery alone was more beneficial to high-grade meningioma patients [17, 18, 22, 23, 26]. Further confounding variables include slight variation in PFS and OS definitions, the aggregation of radiotherapeutic techniques [14, 18–20, 23, 26, 27], and the varying extent of surgical resection as mentioned above [10, 14, 17–27]. Lastly, nonuniform WHO tumor classifications mottled results. 2000, 2007, and 2016 each marked changes in WHO meningioma classification [8]. Because of the wide range of studies across time, institutions have

varied in adoption of meningioma classification, complicating data interpretation.

Conclusion

Our analysis suggests that ART+surgery, compared to surgery alone, may increase PFS, OS and tumor control rates in high-grade meningiomas. To not only further elucidate the benefit of surgery+ART, but also to develop a standardized treatment paradigm for high-grade meningioma patients, future trials should directly compare radiosurgical modalities, dosages, and extent of surgical resection.

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Code availability Statistical analysis was conducted using R Studio v.1.2.5019 (RStudio Inc., Boston, MA).

Compliance with ethical standards

Conflict of interest All 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: Not required for this study.

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