Neuro-Oncology

Neuro-Oncology 16(5), 628–636, 2014
doi:10.1093/neuonc/nou025

Adjuvant radiotherapy for atypical and malignant meningiomas: a systematic review

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Atypical meningiomas (AMs) and malignant meningiomas (MMs) are tumors with a lower incidence and poorer prognosis than benign meningiomas. The role of radiotherapy as an adjuvant to surgical resection, especially for AMs, is incompletely defined. In this study, the English-language literature was systematically reviewed for studies that reported tumor characteristics, treatment parameters, and clinical outcomes after adjuvant radiotherapy for AM and MM, including overall survival, progression-free survival, and/or time to recurrence or mortality. Clinical outcomes were further assessed in the context of resection status, timing of administration, and radiation dose. Outcomes after stereotactic radiosurgery were also examined. Treatment toxicity and other potential prognostic or confounding factors were appraised. Ten and 11 studies for AM and MM, respectively, met the inclusion criteria. The median 5-year progression-free survival and overall survival after adjuvant radiotherapy were 54.2% and 67.5%, respectively, for AM and 48% and 55.6% for MM. The complication rates were 11.1% for AM and 5.1% for MM. Incomplete resection and radiation dose $<$50 Gy conferred significantly poorer 5-year progression-free survival. Most studies were unable to demonstrate a statistically significant prognostic benefit for adjuvant radiotherapy in AM. In conclusion, adjuvant radiotherapy significantly improved local control of AMs and MMs, especially after subtotal resection. Study limitations, including inadequate statistical power, may underlie the studies' inability to demonstrate a statistically significant benefit for adjuvant radiotherapy in AM. Because these tumors preferentially recur within 5 years of surgical resection, future studies should define whether early adjuvant therapy should become part of the standard treatment paradigm for completely excised tumors.

Keywords: atypical meningioma, high-grade meningioma, malignant meningioma, radiotherapy, radiation therapy.

Meningiomas are the most commonly reported primary intracranial neoplasms in adults, comprising over one-third of all central nervous system tumors.[1] Meningiomas have an incidence of ~6 in 100 000 but are often incidentally discovered during autopsy or on neuroimaging.[2] Their incidence increases with age and peaks after the fifth decade of life. They are histologically characterized as benign, atypical, or malignant (also known as anaplastic) by the 3-tiered World Health Organization (WHO) classification scheme. Meningiomas are thought to originate from the arachnoidal cap cells[3] that form the outer layer of arachnoid mater and the arachnoid villi, of which the latter facilitate cerebrospinal fluid drainage into the dural sinuses and veins. While most are slow-growing, benign meningiomas (BMs), atypical meningiomas (AMs) and the rare malignant meningiomas (MMs) are considerably more aggressive.[3] While their precise incidence is difficult to ascertain,[4] AMs and MMs have a higher recurrence rate and poorer overall prognosis than BMs.[3] Although as few as 2% of primary BMs undergo malignant transformation, 28.5% of all recurrences of BMs are found to be atypical or malignant.[2]

The WHO scheme has been dramatically reworked in recent years, including a major revision in 2000. The latest update in 2007 resulted in the redistribution of many meningiomas into different classes.[4] Some previously benign meningiomas have been reclassified as AMs, while the incidence of MMs has fallen due to stricter criteria for this subtype.[5] According to previous classification schemes, ~90% of meningiomas were classified as benign, 5%–7% as atypical, and 3%–5% as malignant.[6] The new WHO 2000 and 2007 criteria have been gradually but not reliably adopted into clinical practice, and the use of inconsistent

Received 12 December 2013; accepted 8 February 2014

definitions of malignant pathology has complicated interpretation of published data.[7] However, when these criteria have been applied, ~20%–35% of meningiomas have been classified as grade II.[8–12] The recent adoption of modern WHO grading criteria and the rarity of the malignant subtype have limited the amount of available data on the clinical behavior, outcomes, and optimal management of meningiomas.[13]

A particularly controversial management issue is the optimal role and timing of radiotherapy (RT) for AMs treated with gross total resection (GTR). Though meningiomas were historically considered radioresistant,[14] RT has since been shown to improve local control of AM and MM.[7] The treatment approach to AM has largely been extrapolated from data on BM and MM, leading to nonuniform practice across institutions. While adjuvant RT is standardly used at many institutions after subtotal resection (STR) of AM, its role after GTR is controversial.[15–17]

In this article, the literature was systematically reviewed to determine the prognostic impact of adjuvant RT on the whole and in the context of resection status (GTR vs STR), timing of administration (initial diagnosis vs recurrence), and radiation dose, as these are incompletely defined for AM and MM.[5] Outcomes after stereotactic radiosurgery (SRS) were also examined. The treatment toxicity of adjuvant RT was further appraised. Lastly, an attempt was made to identify other potential prognostic or confounding factors in this patient population.

Histopathologic Classification of Atypical and Malignant Meningiomas

Since these high-grade forms of meningioma were first recognized by Cushing and Eisenhardt in 1938,[18] the histopathologic classification of AMs and MMs has been controversial. The histologic pattern of meningiomas is highly variable: 16 subtypes are recognized, and a single tumor may contain an admixture of these.[3] Published studies have employed multiple subjective grading schemes over the years,[16] complicating comparison of treatment data for these less common tumors.[16] In 1993, the WHO designated AM as an intermediate category between BM and MM.[15] A substantial revision by the WHO 7 years later made the criteria more objective, reproducible, and precise,[4] with the implementation of mitotic activity, proliferation index, and brain invasion as diagnostic variables.[2] The present 2007 WHO criteria have added minor changes such as designating brain-invasive meningiomas as grade II.[4] The broadened definition of AM, using necrosis as a criterion, increased the reported incidence of AM from 18% to 23% of all meningiomas.[15] With these latest standards, large series have shown grade and outcome to correlate better than before.[11,19,20] In spite of these strides, recent series remain susceptible to significant diagnostic variability.[4]

Tumors that lack atypical or malignant features or brain invasion are classified as benign (WHO grade I).[3] Criteria for atypical (WHO grade II) meningiomas include increased mitotic activity (4 or more mitoses within any 10 consecutive high-power fields under 40× objective magnification) and/or 3 or more of the following properties: sheetlike growth, spontaneous necrosis, hypercellularity, prominent nucleoli, and presence of small cells with a high nucleus-to-cytoplasm ratio.[3] It should be noted that cytological atypia is neither required nor common within this group of tumors.[3] Four variants of AM have been recognized: atypical, chordoid, clear-cell, and atypical with brain invasion.[3]

Malignant (WHO grade III) meningiomas are characterized by the classical malignant features of substantially elevated mitotic activity (20 or more mitoses within any 10 consecutive high-power fields under 40× objective magnification) or frank anaplasia with histology resembling carcinoma, melanoma, or sarcoma.[3] A diagnosis of MM is typically established in the presence of meningothelial histology within the tumor, a prior diagnosis of lower-grade meningioma in the same location, and/or supportive immunohistochemical, ultrastructural, or genetic data.[3] Although vascular invasion is common in meningiomas, metastasis occurs in only 0.1% of cases and is generally limited to grade III tumors. The lungs and pleura are the most common sites of metastatic seeding, followed by the musculoskeletal system, liver, reticuloendothelial system, and kidneys.[4]

In addition to the aforementioned cellular features, an important histopathologic feature in high-grade meningioma is mouse intestinal bacteria 1 (MIB-1; Ki-67), an immunohistochemical marker. A high MIB-1 labeling index may indicate increased malignancy and a poorer prognosis, although significant overlap exists in the MIB-1 labeling ranges for the 3 classes of meningioma.[2] Thus, the MIB-1 labeling index may be most useful when evaluating tumors with borderline atypia.[21] In the future, histopathologic classification might also be aided by the evaluation of genetic losses and telomerase activation on chromosomes 1p, 10q, 14q, and possibly 9p.[22]

Materials and Methods

A systematic review of the English-language literature was performed by 2 independent reviewers. Therapeutic studies were identified via a PubMed search using the keywords “atypical meningioma” and “malignant meningioma” in combination with “treatment,” “radiotherapy,” and “radiation” using Boolean operators. After individually reviewing the titles and abstracts of these preliminary results, full manuscripts were obtained for studies that reported clinical outcomes after adjuvant RT for AM or MM. The citation lists of these articles were manually screened to identify additional articles. The exclusion criteria were as follows: (i) lack of clinical outcome data at follow-up, namely overall survival (OS), progression-free survival (PFS), and/or time to recurrence or mortality; (ii) median follow-up interval less than 2 years; (iii) mixed-histology tumors; and (iv) incomplete description of treatment parameters. In total, 14 studies dating from 1994 to 2011 analyzing AM, MM, or both were included in the review. The aforementioned clinical outcomes were analyzed in patients treated with adjuvant RT for AM or MM. The impact of adjuvant RT on clinical outcomes was further evaluated in the context of resection status (STR vs GTR), time of administration (initial diagnosis vs recurrence), and radiation dose. When studies contained patient cohorts who were treated with adjuvant RT versus a control group (surgery alone), it was possible to assess the prognostic impact and statistical significance of adjuvant RT. For studies whose entire cohort was treated with adjuvant RT, no comparison was possible, and thus clinical outcomes were simply reviewed, as were any statistical analyses of the radiation dose. In studies that treated a portion of patients with SRS, the clinical outcomes associated with this therapeutic modality were assessed. The rate

of RT-related treatment toxicity was appraised. Lastly, the included studies were assessed for potential prognostic or confounding factors according to univariate or multivariate analyses.

Results

Study Characteristics

Fourteen total studies dating from 1994 to 2011 met the eligibility criteria for this systematic review.[5,7,13,15,16,23–31] Their study populations carried diagnoses of AM, MM, or an aggregate of these. Ten AM studies were included with initial diagnoses occurring between 1966 and 2005.[7,13,15,16,25–27,29–31] The mean or median follow-up interval for these studies ranged from 28 to 63.6 months. Eleven MM studies were included with initial diagnoses occurring between 1967 and 2009.[5,7,13,23,24,26–31] The mean or median follow-up interval for these studies ranged from 28 to 60 months. When it was reported, the proportion of WHO grade II or III meningiomas among all meningiomas was below 10% in all but 2 studies.[24,27] The radiation dose was reported for all but 1 study and ranged between 40 and 65 Gy. Stereotactic radiosurgery was utilized in 5 studies.[5,15,16,29,31] Progression was variably defined in 8 studies as pathological[23,27] or radiological[5,16,23–27,29–31] evidence of tumor growth or recurrence and/or clinical neurologic decline.[23,24,27,29,30] Twelve studies[5,7,13,15,16,23,25,27–30] performed univariate or multivariate regression analyses in order to identify potential prognostic or confounding factors.

Impact of Adjuvant Radiotherapy on OS, PFS, and Time to Recurrence or Mortality in Atypical Meningioma

In RT-treated patients with AM, the median 5-year PFS was 54.2% and ranged from 38% to 100% (Table 1). The median 5-year OS was 67.5% and ranged from 51% to 100%. No study was able to demonstrate a statistically significant improvement in any of the clinical outcomes with adjuvant RT for AM. Goyal et al[25] ($n = 22$) could not detect a statistically significant improvement in the local control ($P = .4$) or survival rates ($P = .5$) in their sample of 8 patients who received adjuvant RT. Yang et al[29] ($n = 40$) showed that complete excision without postoperative RT was sufficient to achieve effective PFS and OS, while RT-treated patients ($n = 23$) had statistically similar PFS and OS relative to the strong baseline outcomes in the surgery-only group (*P*-values not given). In a sample of GRT- and RT-treated AMs ($n = 8$), Aghi et al[15] reported that none experienced tumor recurrence. Although there was a trend toward clinical benefit, adjuvant RT use had no statistically significant effect on OS in univariate ($P = .10$) or multivariate ($P = .10$) analysis. Thirty of 114 patients in the series of Mair et al[16] received adjuvant RT following first-time resection. Administration of adjuvant RT at initial resection was a nearly significant negative predictor of radiological tumor recurrence or progression (hazard ratio [HR] = 2.052; $P = .108$). However, a statistically significant benefit was revealed when the researchers' analysis excluded 5 patients who received postoperative radiosurgery for a tumor remnant. In the study by Pasquier et al[13] ($n = 30$), the 5-year PFS and OS were 62% and 67.5%, respectively, but the analysis of adjuvant RT was limited to the radiation dose. In the study by Hug et al[7] ($n = 15$), the actuarial rates of local control and OS in their RT-treated cohort were 38% and 89% at 5 years, respectively, and 19% and 89% at 8 years. As the entire study population received RT, the prognostic impact of adjuvant RT could not be analyzed. In the study by Boskos et al[30] ($n = 19$), the 5-year rates of local control and OS in their RT-treated, mostly subtotally resected (18/24 for entire study sample) cohort of high-grade meningioma patients were 46.7% and 53.2%, respectively. As with the previous studies, no analysis was possible for surgery plus adjuvant RT versus surgery alone. The mean local relapse-free interval was 28.3 months for their group of AM patients, and intracranial metastatic disease developed in 2 patients.

Impact of Adjuvant Radiotherapy on OS, PFS, and Time to Recurrence or Mortality in Malignant Meningioma

In RT-treated patients with MM, the median 5-year PFS was 48% and ranged from 29% to 80% (Table 2). The median 5-year OS was 55.6% and ranged from 27% to 80.8%. Two of 11 studies found improved clinical outcomes with adjuvant RT. In the study by Dziuk et al[23] ($n = 38$), RT was associated with significant improvement in 24-month PFS (94% vs 61%) and a trend toward improved 60-month PFS (40% vs 16%; *P*-value not given). Adjuvant RT was an independent prognostic factor in their multivariate analysis involving 13 RT-treated patients. Additionally, the time to recurrence was significantly increased (38.9 vs 27.2 mo). Yang et al[29] ($n = 40$) also found adjuvant RT to be a significant positive prognostic factor for both OS and PFS in the 17 patients who received it. However, overall outcomes were dismal, with a 5-year OS of 35% and PFS of 29%.

Nine of 11 studies found no improvement in clinical outcomes with adjuvant RT or did not analyze it. Goldsmith et al[24] ($n = 23$) noted favorable outcomes, including a 5-year survival rate of 58% and 5-year local control rate of 48%, although the lack of a nonirradiated control group precluded statistical comparison. Milosevic et al[27] ($n = 42$) reported a median actuarial OS of 32 months and a 5-year survival rate of 28%; the PFS was not reported, and the statistical analysis of RT was limited to the radiation dose. Mahmood et al[26] ($n = 22$) were unable to demonstrate a reduction in recurrence or regrowth of MM in their 5 RT-treated patients, with mean regrowth times of 14 versus 10 months after STR ($P = 1.00$). The study by Sughrue et al[28] ($n = 63$) was not designed to assess the value of adjuvant RT, but the authors detected no improvement in OS with the use of focal adjuvant RT in 29 patients (*P*-value not given). In the study by Pasquier et al[13] ($n = 9$), the 5-year PFS and OS were 48% and 60%, respectively, but the analysis of adjuvant RT was limited to the radiation dose. Rosenberg et al[5] found a trend toward increased median actuarial OS that was 5.4 years for patients who received adjuvant fractionated RT after their first surgery ($n = 3$) versus 2.5 years for those who did not ($n = 10$) (risk ratio [RR] = 5.10; $P = .13$). The effect of adjuvant RT on recurrence trended toward statistical significance (RR = 3.35; $P = .13$). In the RT-treated cohort of Hug et al,[7] the local control and survival rates ($n = 16$) were 46% and 51%, respectively, at 5 years. However, given the lack of a nonirradiated control group, the prognostic impact of adjuvant RT could not be analyzed. In the study by Boskos et al[30] ($n = 5$), the 5-year rates of local control and OS in their RT-treated, mostly subtotally resected cohort (18/24 for entire study sample) of high-grade meningioma patients were 46.7% and 53.2%, respectively. Once again, the study design precluded comparison of surgery plus adjuvant RT versus surgery alone. The mean local relapse-

Table 1. Summary of study characteristics, radiation dose, survival outcomes, and complications in selected studies of atypical meningioma

Study	Period	Total AM, *n*	Received RT, *n*	Malignancy Definition	Proportion of All Meningiomas	Median Follow-up	Treatment Modality	Dose	Progression-free Survival	Overall Survival	Complications
Milosevic et al[27]	1966–1990	18	18	WHO 1979	68.6% (grade II/III)	40 mo (7–114)	Surgery + RT ($n = 17$)	50 Gy (40–60)	n/a	51% at 5 y	3.39% related to RT
Pasquier et al[13]	1971–2005	30	n/a	WHO 2000	n/a	4.1 y	Surgery + RT	54 Gy (40–66)	62% at 5 y	67.5% at 5 y	12.6% related to RT
Hug et al[7]	1973–1995	15	15	WHO 1993	n/a	28 mo (7–155)	Surgery + photon RT ($n = 4$) vs surgery + photon + proton RT ($n = 11$)	62 Gy (50–68)	38% at 5 y	89% at 5 y (90% for >60 Gy vs 0% for <60 Gy)	6.67% related to RT
Mahmood et al[26, a]	1976–1990	22	3	WHO 1993	8.0% (grade II/III)	38 mo (3–186)	Surgery ($n = 14$), surgery + RT ($n = 6$)	50–62 Gy	48% at 5 y; 33% at 10 y	58.33% at 5 y; 41.67% at 10 y	n/a
Goyal et al[25]	1979–1995	22	8	WHO 1979	6.7% (grade II)	5.5 y (1.5–14.8)	Surgery ($n = 14$), surgery + RT ($n = 8$)	54 Gy (35–59.4)	Surgery: 70% at 5 y; surgery + RT: 80% at 5 y	Surgery: 81% at 5 y; surgery + RT: 100% at 5 y	n/a
Kano et al[31]	1997–2002	10	10	WHO 2000	n/a	44 mo (6–84)	Surgery + SRS	18 Gy (12–20)	48.3% at 5 y[a]	80.8% at 5 y[a]	16.7% related to SRS[a]
Yang et al[29]	1986–2004	40	23	WHO 2000	7.2% (grade II/III)	63.6 mo (0.6–154.5)	Surgery, surgery + RT	n/a	87.1% at 10 y	89% at 10 y	n/a
Aghi et al[15]	1993–2004	108	8	WHO 2000	n/a	39 mo (1–168)	Surgery ($n = 100$), surgery + RT ($n = 8$)	60.2 Gy (59.4–61.2)	Surgery + RT: 100% at 5 y; surgery: 44% at 5 y	n/a	12.5% related to RT
Boskos et al[30]	1999–2006	19	19	n/a	n/a[b]	48 mo(1–87)	Surgery + RT	65 CGE (proton = 34.1 CGE; photon = 31 Gy)	46.7% at 5 y[a]	53.2% at 5 y[a]	16.7% related to RT[a]
Mair et al[16]	2001–2010	114	30	WHO 2000	n/a	n/a	Surgery ($n = 83$), surgery + RT ($n = 31$)	51.8 Gy	Surgery: 40%; surgery + RT: 60%	n/a	n/a

Abbreviation: CGE, cobalt gray equivalent.
[a]In this study, atypical and malignant meningiomas were aggregated into the same group. Boskos et al[30] and Kano et al[31] reported PFS, OS, and the complication rate for their aggregated group of atypical and malignant meningiomas, rather than separately.
[b]Boskos et al[30] cited the WHO 1993 classification scheme but did not explicitly report which scheme was used.

Table 2. Summary of study characteristics, radiation dose, survival outcomes, and complications in selected studies of malignant meningioma

Study	Period	Total MM, *n*	Received RT,*n*	Malignancy Definition	Proportion of All Meningiomas	Follow-up Interval, mo (range)	Treatment Modality	Dose	Progression-free Survival	Overall Survival	Complications
Milosevic et al[27]	1966–1990	42	42	WHO 1979	68.6% (grade II/III)	40 (7–114)	Surgery + RT ($n = 29$)	50 Gy (40–60)	n/a	27% at 5 y	3.38% related to RT
Goldsmith et al[24]	1967–1990	23	23	Unique grading scale	16.4% (grade III)	40 (2–213)	Surgery + RT	5400 cGy (4462–6926)	48% at 5 y (63% for >53 Gy vs 17% for <53 Gy)	58% at 5 y	3.6% related to RT
Pasquier et al[13]	1971–2005	9	n/a	WHO 2000	n/a	49.2	Surgery + RT (all recurrent)	54 Gy (40–66)	48% at 5 y	60% at 5 y	12.6% related to RT
Hug et al[7]	1973–1995	16	16	WHO 1993	n/a	28 (7–155)	Surgery + RT ($n = 11$), surgery + RT + proton RT ($n = 5$)	58 Gy/CGE (40–72)	46% at 5 y; 17% at 8 y	51% at 5 y (100% for >60 Gy/CGE vs 0% for <60 Gy/CGE)	12.5% related to RT
Mahmood et al[26, a]	1976–1990	22	5	WHO 1993	8.0% (grade II/III)	38 (3–186)	Surgery ($n = 1$), surgery + RT ($n = 4$)	50–62 Gy	48% at 5 y; 20% at 10 y	60% at 5 y; 30% at 10 y	n/a
Dziuk et al[23]	1984–1992	38	13	Russell/ Rubinstein classification (1997)	n/a	3–144	Surgery alone ($n = 19$), surgery + RT ($n = 19$)	5400 cGy (3060–6300)	Surgery: 15% at 5 y; surgery + RT: 80% at 5 y	n/a	n/a
Kano et al[31]	1997–2002	2	2	WHO 2000	n/a	44 mo (6–84)	Surgery + SRS	18 Gy (12–20)	48.3% at 5 y[a]	80.8% at 5 y[a]	16.7% related to SRS[a]
Boskos et al[30]	1999–2006	5	5	n/a	n/a[b]	48 mo (1–72)	Surgery + RT	65 CGE (proton = 34.1 CGE; photon = 31 Gy)	46.7% at 5 y[a]	53.2% at 5 y [a]	16.7% related to RT[a]
Yang et al[29]	1986–2004	24	17	WHO 2000	7.2% (grade II/III)	63.6 (0.6–154.5)	Surgery, surgery + RT	13 Gy (10–21)	29% at 5 y	35% at 5 y	n/a
Rosenberg et al[5]	1984–2006	13	13	WHO 2007	n/a	n/a	Primary disease: surgery ($n = 10$), surgery + RT ($n = 3$); recurrence: surgery ($n = 3$), surgery + RT ($n = 4$), SRS ($n = 3$)	Primary RT: 5900–5940 cGy; salvage RT: 5040–6000 cGy	52% at 1 y; 17% at 2 y; 8.7% at 3 y	47.2% at 5 y; 12.2% at 8 y	23% related to surgery; 7% related to RT or SRS
Sughrue et al[28]	1986–2009	63	29	WHO 2000	6.5% (grade III)	5 y (1–22)	Surgery + RT	n/a	57% at 5 y; 40% at 10 y	61% at 5 y; 40% at 10 y	19% related to surgery; none reported for RT

Abbreviation: CGE, cobalt gray equivalent.

[a]In this study, atypical and malignant meningiomas were aggregated into the same group. Boskos et al[30] and Kano et al[31] reported PFS, OS, and the complication rate for their aggregated group of atypical and malignant meningiomas, rather than separately.

[b]Boskos et al[30] cited the WHO 1993 classification scheme but did not explicitly report which scheme was used.

free interval was 23 months for their group of MM patients, and intracranial metastatic disease developed in 1 patient.

Subtotal Versus Gross Total Resection

Goyal et al[25] found that STR without postoperative RT for AM was associated with a significantly higher local failure rate and a trend toward lower OS ($n = 19$; $P = .8$). Mair et al[16] found that regardless of resection status, adjuvant RT at initial resection ($n = 30$) had no beneficial impact on radiological tumor recurrence or progression. Yang et al[29] reported that the extent of resection ($n = 40$) was associated with significantly reduced PFS and a trend toward increased OS ($P = .057$) in AM patients. Aghi et al[15] unexpectedly found a high recurrence rate (44% at 5 y; 52% at 10 y) of AMs after GTR alone ($n = 100$), most within 5 years of resection, suggesting marked clinical aggressiveness. In contrast, local control was achieved for all 8 AMs treated with RT after GTR.

Dziuk et al[23] observed that RT following GTR of MM was associated with decreased recurrence (37% vs 60%). Conversely, the recurrence rate after STR was high irrespective of RT use (100% vs 80%), with no disease-free survivors at 60 months in either treatment group. Neither Rosenberg et al[5] ($n = 13$; RR = 0.61 and $P = .67$ for OS; RR = 0.70 and $P = .75$ for PFS), Hug et al[7] ($n = 16$; *P*-value not given), Boskos et al[30] ($n = 24$; *P*-value not given), nor Pasquier et al[13] ($n = 9$; $P = .19$ for OS, $P = .36$ for PFS) found the extent of resection to be a significant prognostic factor for OS or PFS in their RT-treated cohorts. Milosevic et al[27] ($n = 42$) reported recurrence rates of 47% and 72% following GTR and STR, respectively (*P*-value not given), in their RT-treated cohort of MM patients. There was also a trend toward higher OS for totally excised tumors (47% vs 28%; $P = .3$). The extent of resection independently predicted increased PFS and OS in MM patients in the study by Yang et al.[29] In contrast, Sughrue et al[28] ($n = 63$) unexpectedly found that STR conferred a significantly higher median OS than GTR in MM patients receiving adjuvant RT after both initial surgery (107 vs 50 mo) and second surgery (77 vs 42 mo).

Initial Diagnosis Versus Recurrence

This analysis varied considerably across studies. Aghi et al[15] found that RT after initial GTR prevented recurrence in all 8 AM patients, while recurrent patients died whether or not they received RT at recurrence. Dziuk et al[23] ($n = 38$) found that adjuvant RT at initial diagnosis was associated with a reduced recurrence rate of MM (20% vs 67%), while patients with recurrent disease fared poorly regardless of adjuvant RT administration (75%, RT treated vs 78%, untreated). Recurrence status was shown to be an independent predictor of recurrence after tumor multicentricity was excluded from the multivariate analysis. Milosevic et al[27] noted a trend toward improved cause-specific OS (44% vs 28%; $P = .4$) in both their MM and AM subgroups when RT was administered immediately upon diagnosis (24 of 42 patients). Similarly, in their group of recurrent MM patients, Rosenberg et al[5] ($n = 13$) also noted a trend toward a longer interval to second recurrence using adjuvant fractionated RT (12.4 mo) and SRS (8.1 mo) versus surgery alone (3.8 mo), but no analysis of initial diagnosis versus recurrence was performed. Hug et al[7] ($n = 31$, total) did not find primary versus recurrent disease status to be significantly correlated with local control in their regression analysis (*P*-value not given). Boskos et al[30] reported that 8 of 24 AM and MM patients in their study underwent adjuvant RT after the initial surgery, while 12 and 4 patients received RT after the second and third surgery, respectively; however, the prognostic significance of this timing was not statistically analyzed. Mahmood et al[26] were the only authors to report that RT failed to reduce tumor recurrence or growth in MM patients regardless of administration at initial resection versus recurrence, though the sample size of the latter analysis was only 5 ($P = .23$).

Radiation Dose

Seven of 8 studies found that higher radiation doses were associated with improved clinical outcomes. Dziuk et al[23] reported that for both AM and MM, a dose of $\geq$50 Gy was independently associated with a higher 5-year cause-specific OS of 42%, compared with 0% using lower doses. These authors also linked radiation doses $<$54 Gy to poorer long-term outcomes in their STR group. Goldsmith et al[24] reported a 5-year PFS of 63% in MM patients receiving at least 53 Gy versus 17% with lower doses. Milosevic et al[27] similarly found a dose of $\geq$50 Gy to be strongly associated with improved cause-specific OS in their group of AM and MM patients. Hug et al[7] reported significantly better 5-year and 8-year PFS and OS for both AM and MM using target doses $\geq$60 Gy. Analyzed separately, the actuarial 5- and 8-year local control rates for AM were significantly higher using doses $\geq$60 Gy (90% and 45%, respectively) versus $<$60 Gy (0% and 0%). Actuarial 5- and 8-year local control rates for MM were also significantly higher using doses $\geq$60 Gy (100% and 33%, respectively) versus $<$60 Gy (0% and 0%). Akin to the findings of Hug et al, Boskos et al[30] reported that doses $>$60 Gy with combined proton-photon RT significantly improved PFS ($P < .05$) and OS ($P < .05$) in their cohort of AM and MM patients, according to univariate analysis. Multivariate analysis confirmed this positive association between doses $>$60 Gy and improved OS (RR = 8.3; $P = .029$). There was also a trend toward increased OS with doses $>$65 Gy according to univariate analysis. Using SRS, Kano et al[31] observed that a marginal dose $>$20 Gy ($n = 13$) was a significant positive prognostic factor in the univariate analysis ($P = .0139$), as the 5-year PFS was 63.1% compared with 29.4% for those receiving $<$20 Gy ($n = 12$). In contrast, Pasquier et al,[13] who used a median dose of 54.6 Gy to treat AM and MM patients, found external beam (EB)RT not to be a significant prognostic factor for either OS ($P = .28$) or PFS ($P > .05$), but they did not define the doses that were compared.

Outcomes After Stereotactic Radiosurgery

Five studies treated patients with SRS. Aghi et al[15] administered single-fraction SRS to 16 patients with AM, with a mean tumor volume of 4.4 cm^3 and mean marginal dose of 18.0 Gy. Mair et al[16] administered SRS alone and SRS plus surgery in 7 and 3 patients, respectively, with AM who demonstrated radiological tumor recurrence or progression. No outcomes data or subgroup analyses were reported for the SRS-treated patients in these 2 studies. Rosenberg et al[5] administered 1–3 treatments of SRS to 3 patients with MM in their series. There was a trend toward a shorter interval to second recurrence in these patients (8.1

mo) than in those treated with surgery plus fractionated RT (12.4 mo) but a longer interval than in those treated with surgery alone (3.8 mo) (*P*-value not given). One SRS-treated patient experienced cerebral necrosis. Kano et al[31] treated 10 AM patients and 2 MM patients using SRS, with a median tumor volume of 2.87 mL and median margin dose of 19 Gy; the median 80% dose-coverage volume was 98.5%. The 5-year PFS and OS for the entire cohort of high-grade meningioma patients were 48.3% and 80.8%, respectively. Two of the 12 patients experienced asymptomatic perifocal edema from radiation-induced angiopathy after doses of 17.6 Gy and 20 Gy. Yang et al[29] treated 5 patients with 6 recurrent MMs using SRS, with a median tumor volume of 6.3 mL and median margin dose of 13 Gy. The result was local failure in 4 of the 6 meningiomas and mortality due to recurrence in 4 patients at a median follow-up interval of 14 months, while the fifth patient was recurrence free for 34 months. In the same study, 3 patients with recurrent AM were given palliative SRS alone, and all had died from tumor progression as of the latest follow-up.

Treatment Toxicity

The incidence of treatment toxicity ranged from 3.4% to 16.7%[7,13,15,16,25–27,29–31] for AM and 0% to 16.7% for MM[5,7,13,23,24,26–28,30,31] after adjuvant RT. Cerebral necrosis occurred in 0.1%,[13] 4.2%,[30] 12.5%,[15] and 23.1% of patients.[5] Blindness due to irradiation of the optic apparatus occurred in ∼5% of patients receiving 50 Gy radiation and in 50% of patients receiving 65 Gy. Hypopituitarism was reported in up to 50% of patients at 1–11 years, even after low-dose treatment. Hypogonadism and cognitive disturbance were reported in 1.7%–5.9% of patients.[13,27] Seizures and alopecia were reported in 4.2% and 8.3% of patients, respectively.[30]

Potential Prognostic or Confounding Factors

Other prognostic factors identified in AM and MM treated with RT included older age,[5,13,15,27] tumor multicentricity,[23] tumor location,[16] brain invasion,[29] malignant progression,[29] Karnofsky performance status,[13] treatment era,[27] p53 overexpression,[29] and histologic characteristics such as prominent nucleoli,[15] sheeting,[15] and high mitotic rate.[13] Univariate or multivariate regression analyses indicated that the following were not significant confounding factors: age,[7,15,28–30] sex,[5,7,13,15,25,30] tumor location,[15,29] tumor size,[15,30] Karnofsky performance status,[5,25,27,28] neurologic functional status,[13] MIB-1 labeling index,[15,29] histologic subtype,[30] brain invasion,[13] previous diagnosis of benign meningioma,[5,13] mitotic activity,[15] increased cellularity,[15] small cells with a high nuclear-to-cytoplasmic ratio,[15] necrosis,[13,15] and type of RT (cobalt vs linear accelerator).[13]

Discussion

The aim of this systematic review was to define the role of adjuvant RT in the management of AM and MM, which are clinically aggressive forms of meningioma. Fourteen studies met our inclusion criteria and were analyzed to determine the impact of adjuvant RT upon clinical outcomes, including OS, PFS, and time to recurrence or mortality. Outcomes in RT-treated patients were further analyzed in the context of resection status (GTR vs STR), time of administration (initial diagnosis or recurrence), and radiation dose. Outcomes after SRS were reviewed, although small sample sizes precluded comparison with EBRT. Lastly, we assessed RT-related treatment toxicity and potential prognostic or confounding factors in this patient population.

This systematic review revealed that adjuvant RT generally improves local control and OS in AM and MM, although available data did not support this paradigm in the controversial subset of totally excised AMs. It was apparent that AM treated with resection only, particularly when subtotal, was highly prone to recurrence. Studies reported disparate results with respect to the clinical course of completely excised AMs. In the view of the authors, the lack of statistical significance seen in these analyses is a result of flaws in the included studies. While several studies showed trends toward clinical benefit with adjuvant RT, the lack of statistical significance is likely a result of small sample sizes, limiting the statistical power to detect any differences between groups. Furthermore, the nearly universal association between increased radiation dose and improved prognosis in the included studies makes it improbable that adjuvant RT has no prognostic benefit relative to surgery alone.

The included studies were fraught with other limitations. This point was clearly illustrated by the lack of a statistically significant correlation between adjuvant RT and improved local control in the study by Aghi et al,[15] despite a local control rate of 100% in 8 totally excised, irradiated AMs. A number of studies treated all patients with adjuvant radiation, precluding any analysis of whether adjuvant RT improved outcomes relative to nonirradiated patients. The timing of RT administration, at initial diagnosis versus recurrence, was not clearly reported in the study by Goyal et al,[25] which further complicates interpretation of their results. Yang et al[29] achieved extremely effective local control with resection alone in their study, ostensibly making it more difficult to demonstrate a statistically significant risk reduction in the recurrence rate in patients who also received adjuvant RT. Moreover, it must be noted that the retrospective studies in this review cannot indicate improvements in clinical outcomes per se, but only correlations.

This review confirmed that MMs are highly likely to recur regardless of resection status, though less so after GTR. Most studies demonstrated some benefit to adjuvant RT, particularly at high doses. Another finding of this review was that adjuvant RT is significantly more likely to succeed when administered at initial diagnosis rather than at recurrence of AM, which led most study authors to recommend this practice. This is consistent with the overarching goal of preventing recurrence at all costs. There are a myriad of reasons for this, including transformation to a higher grade upon recurrence, as occurs in one quarter of AMs treated with surgery alone[32]; the morbidity risk of reoperation; and the elevated probability of second recurrence and/or mortality.

Adjuvant RT for AM and MM were found to cause modest treatment toxicity, most commonly in the form of cerebral necrosis and optic neuropathy. It is imperative to use a radiation dose that maximizes efficacy and minimizes toxicity. In this review, a commonly recommended protocol for MM and AM was 60 Gy with standard fractionation of 180–200 cGy per day in a single session.[7,15,23,30] Another study recommended 54 Gy for MM,[24] while 3 studies found no improvement or only situational efficacy using doses ranging from 51.8 to 54.6 Gy.[13,16,25] Doses below

50 Gy are considered inadequate for treating AM or MM.[13] However, the roles of both dose escalation (>55–60 Gy) and radiosurgery have yet to be explored in a controlled, prospective study.[13] Radiation oncologists must exercise proper patient selection and adherence to radiosensitivity thresholds for surrounding structures. Treatment planning should also incorporate patient age, clinical condition, tumor characteristics, and extent of resection.

Relatedly, the studies in this review provided limited insight into the efficacy of SRS relative to EBRT, as outcomes data were provided for only a total of 23 patients who were given this treatment. While their outcomes were generally poor, except for the cohort of Kano et al,[31] their recurrence status and the palliative intent of this therapy confound any interpretation of these data. It is unclear whether SRS is an appropriate therapeutic modality for high-grade meningiomas, which are more infiltrative than BMs, due to the use of small or no margins on the target volume.[33] Instead, radiosurgery conventionally emphasizes targeting the enhancing disease rather than the clinical tumor volume.[33] The optimal target volume definition for AMs and MMs has yet to be prospectively defined and is obfuscated by the scarcity of high-quality evidence. Thus, of particular interest is the prospective Radiation Therapy Oncology Group 0539 protocol, established in June 2009. This protocol utilizes very large margins for AMs and MMs, that is, the gross tumor volume plus 1 to 2 cm.[33]

This systematic review is limited by the evidence upon which it is based. Weaknesses of the included studies were their retrospective and noncomparative design with respect to treatment groups, low statistical power due to the paucity of AM and MM cases, aggregation of AM and MM into a single histologic category for analysis in some cases, the use of conventional megavoltage RT protocols with conservative dose regimens, and the obsolescence of older studies by modern advances in radiotherapeutic modalities and techniques. Importantly, many of the outcome differences reviewed here may be due to the use of heterogeneous grading systems at institutions and over time, as well as nonuniform use of the WHO guidelines. Indeed, few of the included studies actually used the 2000 or 2007 WHO grading criteria that form the basis for modern meningioma classification. This point is illustrated by the percentage of all meningiomas that were classified as atypical in the included studies, which was generally below the 20% or 25% that would be expected under current histopathologic guidelines.

Prospective multicenter trials should be undertaken to provide the statistical power necessary to clarify unanswered questions: the role of adjuvant RT in totally excised AMs and the upper limit of radiation dosing at the intersection of maximal efficacy and acceptable toxicity. Because these tumors preferentially recur within the first 5 years after surgical resection, future studies should define whether early adjuvant therapy should become part of the standard treatment paradigm for completely excised tumors.

Conclusion

Controversy exists as to the role and prognostic impact of RT as an adjuvant to surgical resection, especially for subtotally resected AM. This systematic review demonstrates that adjuvant RT significantly improves local control of AM and MM, especially in patients with STR, and produces modest treatment toxicity. Furthermore, the extent of surgical resection and radiation dose are positively correlated with the clinical outcome in RT patients. Although the studies in this review were unable to establish a statistically significant correlation between adjuvant RT and improved prognosis in completely excised AMs, these studies were fraught with several limitations, including the lack of a nonirradiated control group and inadequate sample sizes to detect statistically significant risk reductions, among others. These problems highlight the need for prospective randomized controlled trials with sufficient statistical power to discern differences between treatment groups.

Funding

This work was supported by grants from the Howard Hughes Medical Institute (G.K., E.T.S.), the Reza and Georgianna Khatib Endowed Chair in Skull Base Tumor Surgery at UCSF (A.T.P.), and the Michael J. Marchese Professor and Chair at Northwestern University (A.T.P.).

Conflict of interest statement. None declared.

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