



Impact of radiotherapy in atypical meningioma recurrence: literature review

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Abstract

Evaluate whether radiotherapy (RT) after the neurosurgical treatment of atypical meningiomas (AM) has an impact on the reduction rate of recurrence. A Medline search through October 2017 using “atypical meningioma” returned 1277 papers for initial review. Inclusion criteria were as follows. We analyzed the database and included articles in which the anatomic pathological classification of atypical meningiomas was in accordance with WHO 2007 or WHO 2016 criteria, patients > 18 years of age, and there was postoperative external beam radiation to the tumor bed. Exclusion criteria were WHO grade I or III meningioma, patients who underwent whole-brain radiation, RT used as salvage therapy for recurrence, palliative dose of RT (< 45 Gy), recurrent AMs, and multiple AMs. Papers reporting outcomes in which atypical and anaplastic meningiomas were analyzed together were rejected, as were papers with small samples that may compromise evaluation. After filtering our initial selection, only 17 papers were selected. After reviewing the seventeen articles including a total of 1761 patients (972 female and 799 male; 1.21 female/1.0 male), the difference in proportion of tumor recurrence between patients with and without radiotherapy after neurosurgical procedure was 1.0448, 95% CI [0.8318 to 1.3125], *p* value = 0.7062. On the basis of this review, there is no evidence to suggest that RT decreases the rate of recurrence in patients with atypical meningiomas.

Keywords Atypical meningioma · Radiotherapy · Recurrence

Introduction

Atypical meningiomas (AM) represent up to 8% of all meningiomas [1], and their incidence is increasing (> 5–10% among all types of meningiomas); however, this number should increase given the new World Health Organization (WHO) 2016 criteria for the classification of this subtype of meningioma [2]. In fact, AM account for 20–25% of recurrent meningiomas [3, 4].

The rationale for advocating gross total resection (GTR) as the primary treatment for meningiomas is attributed to

effective local control post-GTR and avoiding the toxicity associated with postoperative radiation therapy, including the increased risk of radiation-induced malignancies [5]. In neuro-oncological management, complete resection must be pursued in this subtype of tumor [6], and a definitive cure after surgical resection is achieved in 16–18% of patients. Nevertheless, the disease will recur within a few months in up to 62–69% of cases [7, 8].

Adjuvant radiotherapy after the surgical resection of AM continues to be controversial. Compared to surgery alone, surgery followed by postoperative radiation lowers the incidence of local recurrence of AM, as reported in previous reviews [9]. However, opposite results have also been reported [10, 11]. In a recent retrospective case study of 45 patients with atypical meningioma, Endo et al. [11] showed no additional benefit of adjuvant radiotherapy concerning the long-term tumor control; results similar to those of Champeaux et al. [10], who showed that patients who received radiotherapy did not have a different overall survival nor difference in recurrence rate.

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Among the forms of radiotherapy treatment, we also did not observe consensus on the techniques. During the last two decades, stereotactic radiosurgery (SRS) has proved to be an effective treatment for WHO grade I benign meningioma [12, 13]. However, the efficacy of SRS in the treatment of grade II atypical meningiomas is still unclear [14]. Gamma knife radiosurgery (GKRS) for higher-grade meningiomas has been less well studied [15]. In the setting of recurrent atypical or malignant meningiomas, GKRS may provide durable palliation and local control for some but with poor long-term control overall [16].

Given the conflicting reports in the literature, we performed a systematic review to assess the impact of radiotherapy (RT) combined with surgical resection on the recurrence rate in patients with AM.

Methods

A Medline search from 2010 to October 2017 using “atypical meningioma” returned 1277 papers; we based our revision on this initial corpus. As a first selection step, we adopted the following inclusion criteria: (1) reports in which the anatomic pathological classification of AM was in accordance with WHO 2007 [17] or 2016 [2] criteria, (2) patients older than 18 years of age, and (3) postoperative external beam radiation to the tumor bed. Exclusion criteria were WHO grade I or III meningioma, patients who underwent whole-brain RT, RT used as salvage therapy for recurrence, definitive RT, palliative dose of RT (< 45 Gy), recurrent AMs, and multiple AMs.

All papers reporting outcomes in which atypical and anaplastic meningiomas were analyzed together were excluded, as were reports in the format of case reports with small series. Seventeen papers fulfilled the above criteria,

and these papers gathered data from 1761 patients, on whom the present analysis of the neuro-oncological management of AM was based.

Data evaluation

The patients’ clinical data and tumor-evolution (recurrence or not) data were tabulated, mainly, the data concerning tumor recurrence after neurosurgical procedure and the impact of RT in terms of preventing tumor recurrence in AM [see Fig. 1 for the PRISMA study flow diagram].

We calculated the weighted mean differences and the 95% confidence interval (CI). Dichotomous variables were presented as odds ratios (ORs) with a 95% CI. Matched analysis was performed as appropriate. Significance was set at $p < 0.05$.

Results

A total of 1761 patients (972 female and 899 male; 1.21 female/1.0 male ratio) reported in 17 manuscripts from worldwide centers during the period from 2010 to October 2017 were selected for the present analysis. Although the majority of the selected studies were from centers in the USA, we managed to analyze studies from each continent (see Table 1). Among them are 573 patients who underwent RT (32.5%) with a recurrence rate of 26% (149 patients). Comparatively, of the 1188 patients who were initially treated only with surgery, 299 patients presented tumor recurrence (25.16%). Thus, the difference in tumor recurrence between the two groups treated and not treated with RT after neurosurgical procedure was not significant (1.0448, 95% CI [0.8318 to 1.3125], p value = 0.7062) (see Table 1 and Fig. 2).

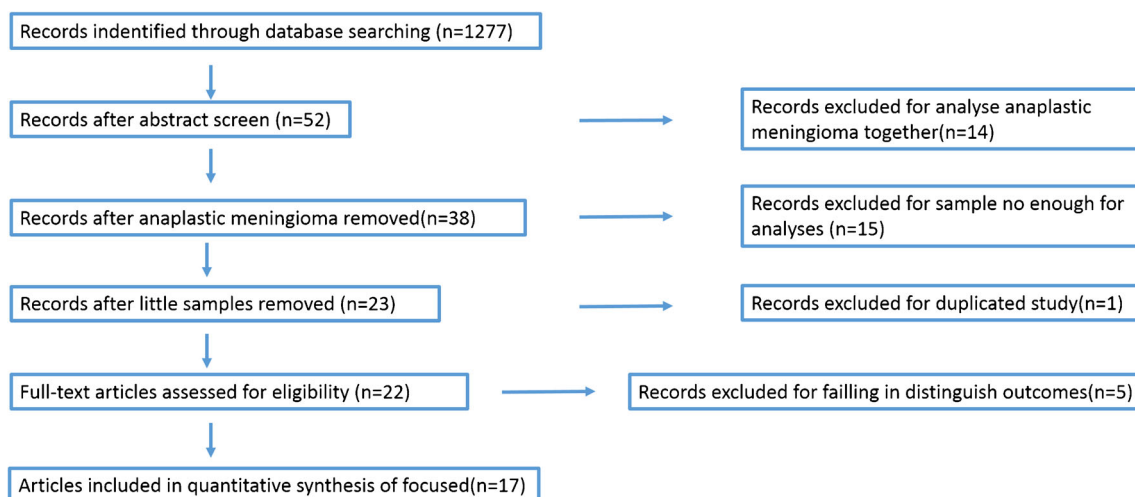


Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram

Table 1 Literature review

Author/year	RT without recurrence	RT with recurrence	RT total	No RT without recurrence	No RT with recurrence	No RT total	Male	Female	Country	Odds ratio	95% CI	<i>p</i>
Jo 2010 [18]	19	3	22	9	4	13	18	17	South Korea	2.25	0.4348 to 11.7084	0.3327
Komotar 2012 [19]	12	1	13	19	13	32	20	25	USA/Australia	5.28	0.6253 to 44.6056	0.1263
Lee 2013 [20]	28	3	31	45	14	59	34	56	USA	2.45	0.6546 to 9.1842	0.1831
Park 2013 [9]	21	6	27	32	24	56	33	50	South Korea	1.92	0.7055 to 5.2718	0.2005
Zaher 2013 [21]	22	4	26	6	12	18	22	22	Egypt	4.33	1.2033 to 15.6056	0.0249
Hardesty 2013 [22]	56	15	71	106	51	157	97	131	USA	1.53	0.8105 to 2.9169	0.1879
Sun 2014 [23]	30	9	39	108	4	112	63	88	USA	1.04	0.3182 to 3.4298	0.9426
Aizer 2014 [24]	30	4	34	38	19	57	41	50	USA	2.83	0.8892 to 9.0279	0.0782
Hammouche 2014 [25]	26	10	36	29	14	43	43	36	UK	11,721	0.4650 to 2.9542	0.7364
Yonn 2015 [26]	15	8	23	118	17	135	72	86	USA	0.3620	0.1401 to 0.9357	0.0360
Bagshaw 2016 [27]	17	3	20	16	23	39	28	31	USA	3.93	1.0520 to 14.6940	0.0418
Champeaux 2016 [10]	29	22	51	134	21	155	95	111	UK	0.3141	0.1597 to 0.6178	0.0008
Jenkinson 2016 [28]	27	9	36	74	22	96	67	65	UK/Ireland/I-taly	0.9167	0.3860 to 2.1770	0.8437
Endo 2016 [11]	15	11	26	11	8	19	20	25	Japan/Egypt	0.9952	0.3360 to 2.9482	0.9931
Dohm 2017 [29]	42	21	63	38	14	52	45	70	USA	0.8077	0.3741 to 1.7436	0.5865
Pereira 2017 [30]	16	6	22	15	2	17	25	14	Brazil	0.4314	0.0772 to 2.4113	0.3383
Masalha 2017 [31]	19	14	33	91	37	128	76	85	Germany	1.8122	0.8232 to 3.9894	0.1397
Total	424	149	573	889	299	1188	799	962		1.0448	0.8318 to 1.3125	0.7062

Recurrence for Atypical Meningioma

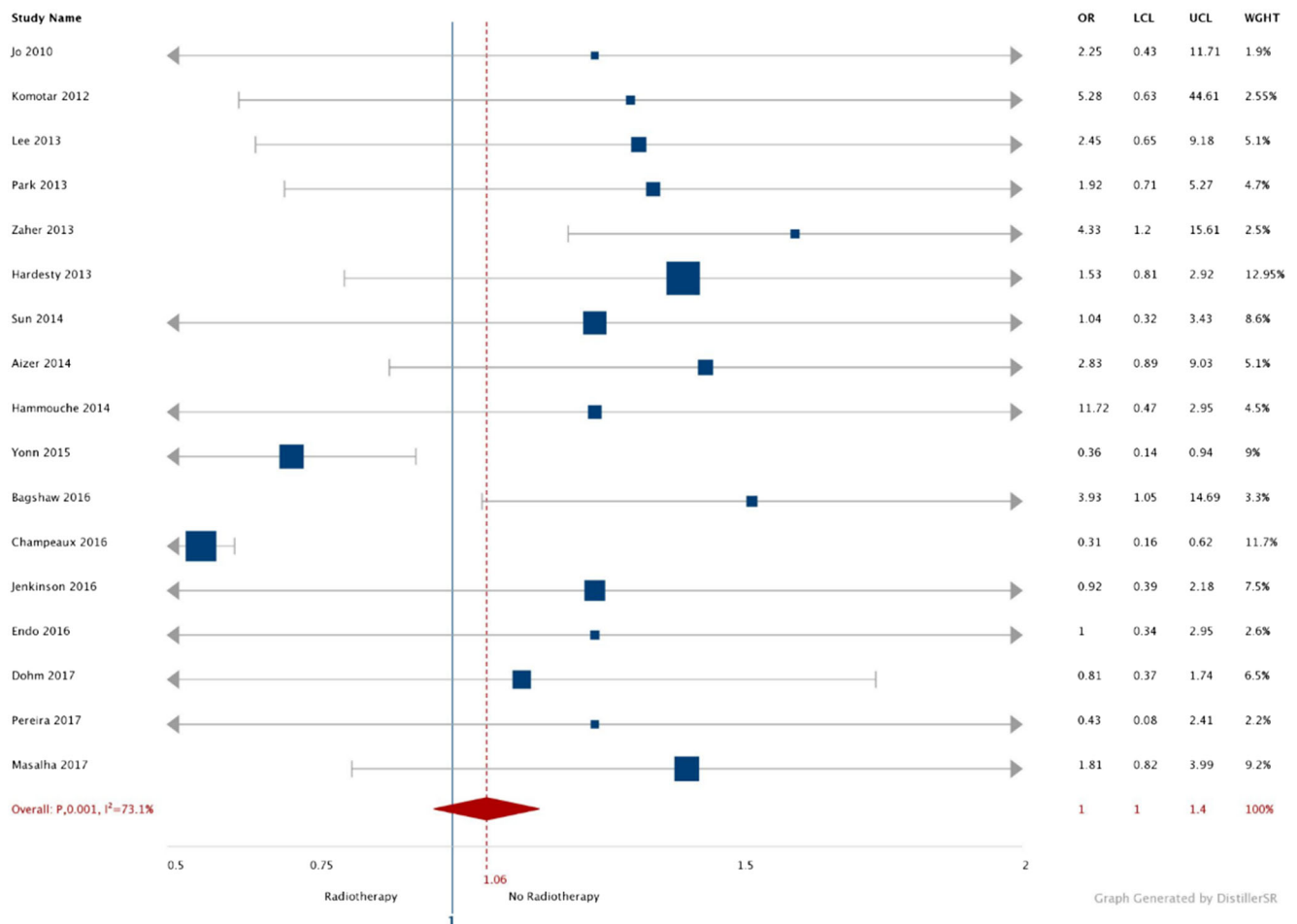


Fig. 2 Odds ratios of local control and recurrence in atypical meningiomas comparing surgery alone and surgery + RT among the studies

Discussion

Regarding the issue of the recurrence of meningiomas, some factors are already well established, such as the degree of surgical resection [32]. Since the initial work of Simpson [33] has proved that greater tumor resections lead to lower rates of tumor recurrence, other factors are still controversial, such as location. In our review, four of the articles selected [19–22] have an analysis of the subject, such as greater recurrence in tumors of convexity, but this result should reflect only the fact that this location is the most frequent. Despite technical and technological advances, the perioperative morbidity and mortality are high, because of their intimate anatomical relationship to the brain, cranial nerves, and essential blood vessels [34]. Another factor influencing the evolution of meningiomas is genetic alterations. Past studies have shown that the risk of meningioma recurrence is strongly correlated with the molecular profile of the tumor [35]. Genomic instability is one of the key differentiators between grade I and grade II–III meningiomas [36].

The clinical impact of AM recurrence is high, and the management of these patients poses specific challenges [37]. A robust analysis of large series of AM providing definitive guidelines for the neuro-oncological management of this type of meningioma is still missing; proof of this is that the management of these patients is still controversial and varies according to the group or center evaluated. In Germany, 74.1% of centers offer some form of RT following incomplete resection of AM, with 17.9% of centers offering postoperative RT even when tumor removal is complete [37]. In the UK, 59% of neurosurgeons would advise adjuvant radiotherapy in subtotal resection (STR), with only 20% doing so after gross total resection (GTR) [38]. Multicentricity varies from 19% at the first recurrence to 89% at the last follow-up, and marginal recurrence is progressively higher than the local type at the second and third recurrence, rendering management increasingly difficult [39, 40]. As the disease may be local, marginal, or distant with respect to the previous localization, a preferable indicator of treatment efficacy is disease-free interval [41, 42].

Radiotherapy was applied initially in the management of residual tumors after microsurgery. Its appropriate application proved to be successful when using all the available techniques, including linear accelerator (LINAC) [43–45], gamma knife [46, 47], proton beam [48], and conventional fractionated external beam radiation therapy (EBRT) [49]. As demonstrated in the literature, success rates of greater than 90% and with few associated complications can be achieved when stereotactic irradiation is performed in the management of intracranial meningiomas [16, 47, 50, 51]. The use of SRS alone has limitations that preclude its application in every case. These limitations are related to tumor size and proximity to eloquent structures especially the optic apparatus. Single-dose SRS is indicated for meningiomas smaller than 3 cm or 20 ml in volume and with a minimal distance from the optic apparatus of between 2 and 4 cm [52]. Although there are no long-term follow-up data for patients who underwent SRT for intracranial meningiomas, the expected success rate should be similar to that achieved using conventional EBRT, with fewer complications. A 5- and 10-year PFS rates of 92 and 83%, respectively, have been reported after EBRT [53]. The selection of the best treatment option for these lesions, however, should include consideration of tumor location, severity of presenting symptoms, and the long-term follow-up data of the available modalities.

There are several studies with conflicting results [9, 18, 19, 54, 55], and there are no randomized controlled trials, leading to a lack of class I evidence [56]. Our present systematic review failed to demonstrate a significant overall difference with respect to postoperative RT reducing tumor recurrence. However, there should be bias in the choice of patients who underwent radiotherapy, perhaps a point to be debated for future strategies to identify subgroups within the AM that present molecular characteristics at the level of biomarkers, so the patient is optimized and presents better results.

Conclusions

On the basis of this review, there is no evidence to suggest that RT decreases the rate of recurrence in patients with AM. Prospective studies on the effect of adjuvant RT for avoiding recurrence of AMs should be conducted to better address this question.

Limitations

Although this study had a large sample size, its limitations should be mentioned. Information on the extent of tumor resections, type of radiotherapy, and meningioma location is a limitation of our study; most of the articles do not present detail of these.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by our Institutional Review Board under registration CAPPESeq no. 200/05.

Informed consent All authors agree to the publication guidelines of the Neurosurgical Review.

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