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REVIEW ARTICLE

Role of adjuvant radiotherapy in atypical (WHO grade II) and anaplastic (WHO grade III) meningiomas: a systematic review

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Abstract

The systematic adoption of the histopathologic criteria provided by the 2016 update of the WHO classification of brain tumors has markedly increased the relative proportion of atypical and anaplastic meningiomas. These tumors exhibit a much greater recurrence rate compared to benign meningiomas, which negatively impacts survival. In recent years, the publication of numerous retrospective case series, yet no randomized controlled trials, on the impact of radiation therapy in non-benign meningioma, has yielded conflicting evidence. At present, maximum safe resection, including the dural attachment, is the preferred primary treatment modality for all types of meningiomas. Adjuvant radiotherapy is currently recommended for subtotally resected grade II and for all grade III meningiomas. However, in grade II meningiomas achieving complete resection, close radiologic and clinical observation is a feasible option. Despite the great amount of non-benign meningiomas available and eligible for trials, there is a striking lack of prospective studies testing adjuvant therapies against observation for this subset of patients. An updated and systematic literature review is provided on the effectiveness and indications of radiotherapy on grade II and III meningiomas.

Keywords Meningioma · Atypical · Anaplastic · Grade II · Grade III · Radiotherapy

Introduction

Meningioma accounts for at least one-third of all primary intracranial neoplasms [1]. Overall incidence, about 6–7/100,000 persons [2], increases with age and prevalence estimations reach 2% of the population, acknowledging that many meningiomas are incidentally discovered thanks to neuroimaging [3, 4] or at autopsy [5]. The great majority of meningiomas are benign (grade I), yet with the potential for recurrence, even in the event of complete resection [6].

Atypical (grade II) and anaplastic (grade III or malignant) variants account for a variable percentage of all meningiomas depending on diagnostic criteria [7, 8]. The latest 2016 update of the World Health Organization (WHO) classification of central nervous system tumors maintained this 3-grade stratification of meningiomas (Table 1) based on specific histologic features [9]. Under previous classifications, atypical and anaplastic meningiomas comprised only 5–7% and 3–5% of all meningiomas, respectively [10, 11]. However, the systematic adoption of such newer criteria has increased the proportion of referred atypical meningiomas up to 20–35% [12, 13].

It is widely recognized that atypical and anaplastic meningiomas exhibit at least a 7- to eightfold increased risk of recurrence, and a marked increased risk of mortality, compared to benign meningiomas [13, 14]. As a general principle, maximum safe resection is the recommended primary treatment modality for all meningiomas [15]. However, at least one quarter to one-third of all meningiomas will eventually require adjuvant therapy, either after the first surgery or at the moment of recurrence [12, 13]. Therefore, it is important to confirm whether radiotherapy or other systemic therapies are clinically effective, especially among higher-grade tumors, and to identify what subset of patients benefit most.

Age, grade, and extent of resection remain the most relevant prognostic factors related to meningioma patient's survival [16, 17]. Currently, there is relative consensus that all anaplastic and subtotally resected (STR)

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Table 1 Definition of WHO grade II and III meningiomas according to the 2016 update of the WHO classification of brain tumors

WHO classification of non-benign meningiomas	Grade II (atypical)	Grade III (anaplastic)
Gender	Preferentially affect women	Preferentially affect men
WHO histopathologic diagnostic criteria	Mitotic index > 3 per 10 high power fields Or At least 3/5 of the following Sheeting architecture (loss of whirling and/or fascicles) Small cell formation (high n/c ratio) Prominent nucleoli Hypercellularity Spontaneous necrosis (not induced by embolization or radiation) Or, Brain invasion	Mitotic index > 20/10 high power fields Or, Frank anaplasia (sarcoma, carcinoma or melanoma-like histologic features)
Histologic subtypes (most common gene mutation involved)	*Atypical* (NF2, TRAF7, AKT1 TERT) *Clear cell* (SMARCE1) *Chordoid*	*Anaplastic* (NF2, TERT) *Papillary Rhabdoid* (BAP1)
Biological behavior and prognosis	Able to infiltrate brain parenchyma Overall 30–50% recurrence rate 10-year PFS and OS: 23–58% and 50–80%	Infiltrates brain parenchyma Overall 50–90% recurrence rate 10-year PFS and OS: 0% and 15–30%

WHO World Health Organization, *PFS* progression free survival, *OS* overall survival

atypical meningiomas should undergo adjuvant radiotherapy [18–20]. However, controversy remains on the optimal treatment of atypical meningiomas undergoing gross total resection (GTR) [12, 13, 19, 21]. At present, GTR is defined by most authors as macroscopically complete tumor removal with or without its dural attachment or underlying bone, that is, Simpson's grades I, II, and III [22].

Previous systematic reviews have synthesized the evidence regarding the impact of radiotherapy on atypical and malignant meningiomas, showing and discussing some conflicting results among studies. Kaur et al. [21] and Hasan et al. [23] thoroughly reviewed grade II and III meningioma case series published before 2014. More recently, Pereira et al. [24] have summarized the effectiveness of radiotherapy in atypical meningiomas according to studies published up to October 2017. Strikingly, several dozens of additional case series and a few non-randomized trials have been published since then. An updated systematic review on the impact of adjuvant radiotherapy in atypical and anaplastic meningioma patients according to published studies from 2017 to date is presented.

Methods

Search strategy

A systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines was performed [25]. Studies were searched and retrieved from PubMed, SCOPUS, Cochrane Controlled of Register Trials, EMBASE, and clinicaltrials.gov databases. The search terms were as follows: meningioma, atypical, anaplastic, malignant, grade II, grade III, radiotherapy, radiation therapy, adjuvant, high grade, irradiation, radiation, resection, gross tumor resection, gross total resection, subtotal resection, postoperative, overall survival, progression-free survival, local control, progression, and recurrence. The search strategy included combinations of these key words with appropriate Boolean operators. References lists from relevant papers and related articles were also screened to make the search as comprehensive as possible. Papers published from 2017 and thereafter were gathered, and no language restriction was applied. The search was performed on April 10, 2020, by the two authors (PDL and ECG) independently, and discrepancies were solved by consensus.

Inclusion and exclusion criteria

All types of study (either observational or intervention studies) published within the last 4 years, that included a minimum of ten patients (either atypical and/or anaplastic meningiomas), were included. Studies on exclusively grade II meningiomas and studies on grade II–III and grade III meningiomas were analyzed, separately. Studies not strictly related to adjuvant radiotherapy in atypical or anaplastic meningioma patients were excluded. Review articles on radiotherapy techniques, chemotherapy or other systemic therapies, histologic features of atypical/malignant meningiomas, and studies in which the clinical course and outcome of patients [local control (LC), progression-free survival (PFS) or overall survival (OS)] were not available were also excluded (Fig. 1).

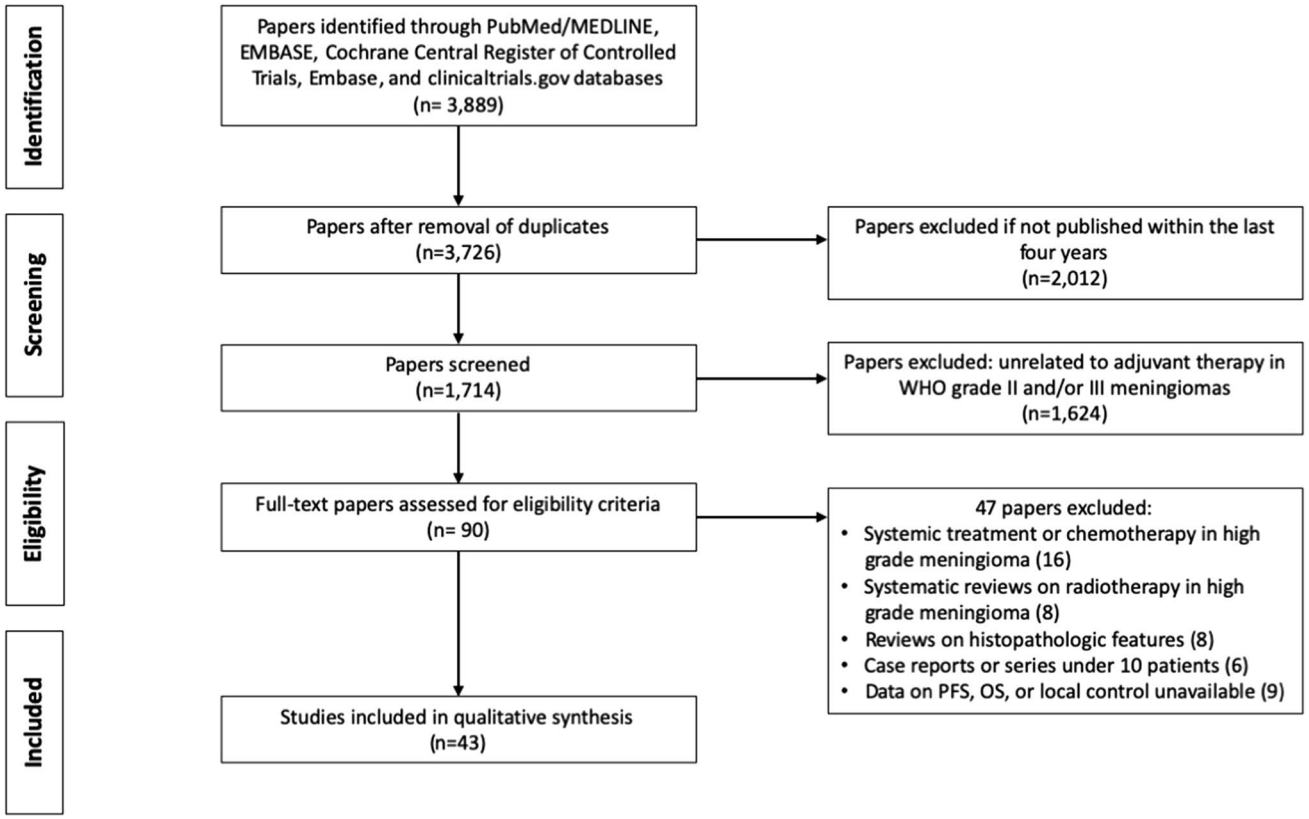

Fig. 1 PRISMA flow chart

Data extraction

Information extracted from studies included first author, year of publication, study design, number of participants, histologic grade, number of irradiated patients, median follow-up, extent of resection, outcome regarding LC, PFS, or OS, limitations of the study, and main conclusions. Data on adverse effects related to radiotherapy was beyond the scope of this review and was not specifically addressed. Due to the paucity of prospective trials and the great heterogeneity among studies, a quantitative analysis on the effectiveness of adjuvant radiotherapy was not attempted.

Results

Study selection and main characteristics

Out of the initially screened 3726 studies, 90 were full-text reviewed for eligibility. After applying inclusion and exclusion criteria, 43 studies were finally included in the qualitative synthesis, 22 studies on exclusively atypical meningiomas [12, 13, 20, 26–44], and 21 studies on anaplastic or atypical/anaplastic series [19, 45–64]. The main characteristics of the studies are summarized in Table 2 for atypical meningiomas, and Table 3 for anaplastic and atypical/anaplastic meningiomas.

Regarding atypical meningiomas, 20 studies were retrospective cohorts (three multi-center studies) and two were prospective trials. The median number of participants per study was 140, and the median percentage of irradiated patients per cohort was 24.8%. The median follow-up period of studies was 52 months. The RTOG 0539, a non-randomized phase II trial [34] testing the efficacy of postoperative radiotherapy (either intensity-modulated radiotherapy (IMRT) or 3D conformal, 54 Gy in 30 fractions) among the so-called Group 2 or intermediate-risk meningiomas (atypical undergoing GTR and recurrent grade I with any extent of resection), provided results in terms of LC and PFS/OS at 3 years, which were compared with historical controls. The EORTC 22,042–26,042 trial [32], a multi-cohort non-randomized phase II trial, tested the efficacy of postoperative high-dose radiotherapy on PFS at 3 years among atypical and anaplastic meningiomas separately. The majority of patients enrolled were grade II meningiomas undergoing GTR. The objective of the study was to demonstrate that 3-year PFS among completely resected and irradiated grade II patients was higher than 70%.

In the group of studies including grade II and III or exclusively grade III meningiomas, 20 studies were retrospective

Table 2 Summary of clinical characteristics of studies on WHO grade II meningiomas treated with adjuvant radiotherapy

Studies on radiation therapy in atypical WHO grade II meningiomas			
Author, year	Design, participants	Overall results	Comments
[26]	Multi-center retrospective study (4 neurosurgical departments). $N=258$ (46 received RT)	RT was preferentially applied after incomplete resection (37.7% vs. 13.4%). Shorter PFS associated with Simpson III–IV (HR 1.19, $p<0.001$) and age > 65 years (HR 2.89, $p=0.001$)	The impact of postoperative RT on PFS was not significant, including a propensity score-matched survival analysis ($n=46$; $p=0.438$; OR 0.710). The most important prognostic factors were EOR and age
[27]	Two-center retrospective study. $N=88$ (19 received RT)	Nineteen patients received RT during follow-up, without significant impact on OS ($p=0.27$)	Early postoperative RT is not mandatory in grade II meningioma with macroscopically GTR
[13]	Single center retrospective study. $N=149$ (53 received RT)	Median follow-up: 74.2 months. RT showed trend toward improved PFS ($p=0.066$) in GTR. Significant improvement of LC and PFS in STR	Adjuvant RT was independent factor of improved PFS. STR should receive RT and GTR can be actively observed or irradiated
[28]	Single-center retrospective study. $N=263$ (86 received RT)	Median follow-up: 41 months. Median PFS: 28 months. MIB-1 (HR 2.637; $p<0.001$), secondary tumor (HR 3.541; $p<0.001$), tumor size (HR 1.818; $p=0.032$) and EOR (HR 2.861; $p<0.001$) predicted recurrence	RT was associated with reduced tumor recurrence in STR ($p=0.023$) but not in GTR ($p=0.923$). Postoperative RT did not decrease the risk of recurrence in GTR patients
[29]	Single-center retrospective study. $N=302$ (75 received RT)	Median follow-up: 41.6 months. RFS was 55.2 months after the first surgery, with 1-, 3-, and 5-year RFS rates of 87.6%, 63.3%, and 47.7%, respectively. OS rates from first surgery at 1, 3, and 5 years were 97.0%, 90.6%, and 78.8%, respectively	In multivariate analysis, preop KPS ≥ 80, primary tumor, tumor invasiveness, and GTR showed increased RFS, whereas preop KPS ≥ 80, primary tumor, supratentorial location, lack of peritumoral edema, RT, and GTR were associated with increased OS
[30]	Single-center retrospective study. $N=1{,}014$ (315 received RT)	RT performed in 27% of GTR and 42% of STR. In STR, RT improved OS, in GTR did not. Survival time was similar in STR + RT and GTR + RT ($p=0.39$)	Adjuvant postoperative RT was not an independent predictor of increased OS in GTR, but patients undergoing STR + RT achieved equal OS as GTR + RT
[20]	Single-center retrospective comparative study. $N=99$ (19 received RT)	Median follow-up: 37 months. Median PFS after surgery plus RT was better than surgery alone (64 vs. 37 months, HR 0, 20, 95% CI 0.06–0.66)	Adjuvant postoperative RT improved PFS compared to wait-and-see in atypical meningiomas. Effect of RT on PFS confirmed in multivariate analysis
[31]	Single-center retrospective study. $N=131$ (25 received gamma knife surgery)	Actuarial OS at 1, 3, and 5 years were 88.6%, 48.8%, and 36.0%, respectively. Median PFS and OS were 34.5 and 61.7 months, respectively. In the treatment group, non-peritumoral edema, preop KPS (per 10 scores increase), and GKS was related to better OS	Short interval (< 24 months) from symptoms onset to intervention was related to better PFS. Surgery is recommended in patients with recurrence, and GKS is considered a promising therapeutic option
[32]	(EORTC 22,042–26,042 trial) Multi-cohorts non-randomized phase II and observational study. Prospective study. $N=78$ (56 received RT)	At a median follow-up of 5.1 years, the estimated 3-year PFS was 88.7%. The 3-year OS was 98.2%	3-year PFS in meningioma patients undergoing GTR (Simpson I–III) was > 70% if treated with high-dose adjuvant RT (60 Gy)
[33]	Single-center retrospective study. $N=75$ (gamma knife surgery)	Median follow-up: 70 months. OS rates at 2 and 5 years were 97.2% and 89.8%, respectively. PFS rates at 1, 3, and 5 years were 89.3%, 72.6%, and 59.3%, respectively. No statistically significant differences between the surgery-alone group and the surgery with adjuvant/salvage GKS group ($p=0.512$; $p=0.949$)	No significant PFS or OS benefit for meningiomas treated with postop adjuvant/salvage GKS. Convexity meningiomas with GTR tended to benefit PFS. Recommend maximum safe GTR followed by close observation

Table 2 (continued)

Studies on radiation therapy in atypical WHO grade II meningiomas			
Author, year	Design, participants	Overall results	Comments
[34]	Single-center retrospective comparative study (early versus late RT). $N=81$ (51 early RT, 30 late RT)	6/51 (12%) in the early adjuvant RT group recurred/progressed compared with 34/35 (97%) patients kept on observation after initial surgery. Post-RT 5-year PFS was better for early adjuvant RT compared to salvage RT (69% vs. 28%, $p<.001$)	Upfront early adjuvant RT reduced the risk of local recurrence/progression in atypical meningiomas compared with initial observation. Re-excision followed by salvage RT may not be as effective as early adjuvant RT
[35]	Single-center retrospective study. $N=128$ (33 received RT)	No significant benefit for PFS after adjuvant RT (HR = 1.48, CI (95%) 0.76–2.86, $p=0.22$). Anterior and posterior fossa meningiomas showed significantly longer PFS compared to other locations	Adjuvant postoperative RT showed no impact on PFS or recurrence/progression. EOR (Simpson I–II) was the most important prognostic factor for lower recurrence and higher PFS
[36]	National Cancer Database retrospective study. $N=3,611$ (private insurance patients were more likely to receive RT)	5-year OS was 77.6% and declined with increasing patient age. Surgery with adjuvant RT: 5-year OS was 93.7% in those ≤ 45 years and 54.1% in those > 75 years ($p<0.0001$)	A marginal OS benefit of adjuvant RT was observed for patients < 55 and > 75 years, while those between 55 and75 years had a slightly improved OS with surgery alone
[37]	RTOG 0539 trial, first report. Phase II clinical trial. Group 2: grade II + GTR and recurrent grade I + any extent of resection. $N=56$ (52 received RT)	3-year PFS was 93.8%, 3-year actuarial local failure rate was 4.1%, and 3-year OS rate was 96%. No significant PFS differences between grade II + GTR and recurrent grade I. Only grade 1–2 AE, not grade 3	Patients with intermediate-risk meningioma treated with RT had excellent 3-year PFS, with a low rate of local failure and a low risk of AEs. Adjuvant RT useful in GTR Grade II or recurrent Grade I meningiomas irrespective of EOR
[38]	Single-center retrospective study. $N=182$ (42 received RT)	Median follow-up: 4.4 years. Adjuvant RT improved local progression (RR 0.2, $p<0.001$) following either GTR and STR	Adjuvant RT improved LC irrespective of EOR. MIB1 > 7%, > 5 mitoses per 10 hpf, and brain/bone invasion, likely benefit most from postop RT
[39]	National Cancer Database retrospective study. $N=7,811$	5-year OS of entire cohort: 76% GTR + adjuvant RT independently and in unison, improved OS (HR 0.47, $p=0.002$). GTR patients used RT less frequently	GTR and/or adjuvant RT are independent prognostic factor of OS in univariate and multivariate analyses
[40]	Multi-center retrospective study (3 regional referral centers). $N=220$	Early progression (< 24 months) predicted by STR, parafalcine /parasagittal location, peritumoral edema, and mitotic index > 7	Adjuvant RT was negatively associated with early recurrence ($p=0.046$). Adjuvant RT not protocolized in this cohort, so impact unclear
[41]	Single-center retrospective study. $n=215$ (64 received RT)	Median follow-up: 4.5 years. Recurrence correlated with progression from grade I to grade II, incomplete resection and high Ki-67 index	Patients receiving RT did not demonstrate either a reduced risk of recurrence or a longer survival. Shorter survival in older age, incomplete resection, and re-intervention
[42]	Single-center retrospective comparative study. $n=115$ (63 received RT)	5-year OS: 55% in surgery alone, 75% in surgery + RT. 5-year PFS: 27% in surgery alone, 59% in surgery + RT. Early EBRT improved local control vs. surgery alone	Adjuvant RT improved OS and PFS at 5 years. Early (< 4 months postop) EBRT improved LC and PFS
[43]	Retrospective review of National Cancer Database. $N=2,515$ (propensity score matching)	GTR was associated with improved OS compared with STR. Adjuvant RT in STR had improved OS compared with no adjuvant RT (HR 0.590, $p=0.045$) but not if GTR (HR 1.09, $p=0.737$)	Significant improvement of OS in patients undergoing STR with adjuvant RT compared with no adjuvant RT, but unclear benefit after GTR
[44]	Single-center retrospective comparative study. $N=69$ (61 observation, 8 received RT)	15 observation and 3 RT recurred (5-year PFS 79% vs. 88%; $p=0.67$); 19 observation and 2 RT died (5-year OS 89% vs. 83%; $p=0.68$)	Observation alone after GTR was not associated with increased risk of tumor recurrence or mortality. Observation after GTR may be a safe alternative to RT

Table 2 (continued)

Studies on radiation therapy in atypical WHO grade II meningiomas

Author, year	Design, participants	Overall results	Comments
[12]	Single-center retrospective comparative study. $N=63$ meningiomas in 59 patients	Median follow-up: 42 months. Median time to local failure: 180 months in surgery + RT compared to 48 months in surgery alone ($p=0.02$). Benefit regardless of resection, except for Simpson IV	Adjuvant RT provided benefit in LC for GTR. Treatment at first recurrence yielded 26 months to local failure with or without RT. Toxicity of RT: 2 grade 3 and 1 grade 4

RT radiotherapy, *EOR* extent of resection, *PFS* progression-free survival, *OS* overall survival, *STR* subtotal resection, *GTR* gross total resection, *LC* local control, *RFS* recurrence-free survival, *KPS* Karnofsky Performance Score, *AE* adverse effects, *EBRT* external beam radiotherapy

case series (one multi-center study and five retrospective institutional database reviews) and one non-randomized prospective trial. The median number of participants per study was 60, and the median percentage of irradiated patients per cohort was 72.4%. The reported median follow-up period of studies was 48 months. The RTOG 0539 trial [46] conductors, which recently published the initial analysis of its *high-risk* cohort, recruited new or recurrent grade III meningiomas of any resection extent, recurrent grade II of any resection extent, and new grade II meningiomas after subtotal resection. Patients received IMRT (60 Gy high dose or 54 Gy low dose in 30 fractions) and PFS was assessed at 3 years.

Effectiveness of radiotherapy in grade II and grade III meningiomas

Among studies including exclusively grade II meningiomas, adjuvant postoperative radiotherapy was generally found beneficial for subtotally resected meningiomas in terms of LC, PFS, and OS [12, 13, 28, 30, 43]. In the case of GTR, the effect of radiotherapy was controversial, with few studies suggesting a clear benefit [29, 37, 39], the majority not confirming a clear influence on PFS or OS [13, 26, 27, 30, 33, 35, 36, 41, 43, 44], and even others suggesting a negative impact [40]. According to several studies, close observation of grade II meningiomas was considered a feasible option if they were completely resected [13, 27, 43, 44]. In general, a greater than 70% PFS rate at 3 years was expected following radiotherapy of grade II and completely resected meningiomas [32, 37]. The impact of radiotherapy on OS was not that clear, although some retrospective studies suggested a moderate or marginal beneficial effect [29, 30, 36, 39, 42, 43].

In general, authors do not recommend adjuvant radiotherapy as mandatory for grade II and GTR patients. In fact, close observation is a feasible and reasonable option, although it has been reported that salvage radiotherapy after re-intervention may not be as effective as early adjuvant radiation [34]. Patients considered of higher risk (advanced age, severe co-morbidities, tumors near critical structures, and lesions requiring large irradiation fields) are good candidates for observation. Likewise, lower-risk patients concerned about radiation-related toxicity can also be observed. Nevertheless, there seems to be relative consensus that local control is enhanced by postoperative adjuvant radiation in grade II meningiomas irrespective of resection extent [12, 34].

Regarding studies including grade II and III (15 studies) or exclusively grade III (6 studies) meningiomas, as expected, adjuvant radiotherapy was given to a larger proportion (near threefold) of patients compared to cohorts of solely grade II meningiomas. Among grade III meningioma

Table 3 Summary of clinical characteristics of studies on WHO grade II and III and exclusively grade III meningiomas treated with adjuvant radiotherapy

Studies on radiation therapy in WHO grade II and III and exclusively grade III meningiomas			
Author, year	Design, participants	Overall results	Comments
[45]	Single-center retrospective study. $N=32$ grade II (26) and III (6) meningiomas. All received GKS 56 Gy	Median follow-up:106.5 months. Overall LC in 50%. Tumor progression was observed in 28; 16 recurrences were local (12 grade II and 4 grade III), 8 were marginal (7 and 1), and 4 were distant (3 and 1)	21.8% developed AE Multivariate analysis: WHO grade (HR 5.051, $p=0.01$) and prior radiation (HR 5.763, $p=0.004$) were independently associated with OS
[46]	Phase II cooperative trial RTOG 0539. Analysis of the high-risk cohort: grade III, recurrent grade II and new STR grade II. Received IMRT. $N=57$ (53 received RT)	Median follow-up: 4 years. 3-year PFS was 59.2%. Three-year local control was 68.9%, and OS was 78.6%. Majority had grade 1–3 adverse effects, but 1 grade 5	Patients with high-risk meningiomas treated with IMRT (60 Gy/30) experienced 3-year PFS of 58.8%. Treatment-related toxicity acceptable
[47]	Single-center retrospective study. $N=127$ grade II (105) and III (22) meningiomas (127 received SRS by Ciberknife)	Median follow-up: 23 months. Estimated LC rates were 97%, 77%, and 67% at 12, 36, and 60 months in grade II, and 66% each at 12 and 24 months in grade III	PFS rates were 93%, 73%, and 59% at 12, 36, and 60 months, in grade II and 93% and 46% at 12 and 24 months in grade III. Aggressive treatment by high-dose single or multisession SRS of recurring malignant meningiomas provides satisfactory LC rates
[48]	Multi-center retrospective study (6 centers). $N=178$ grade III meningiomas (67 prior grade I or II). 129 received RT	Median follow-up: 4.5 years. Median OS was 2.9 years. OS rates at 1, 5, and 10 yr, were 77.7%, 40%, and 27.9%. Age at surgery < 65 yr, prior benign or atypical meningioma surgery, completeness of resection, and adjuvant RT were independent prognostic factors for OS	Patients under 65-yr-old with primary grade III meningiomas live longer after GTR and postoperative RT. Even with aggressive treatments, local control remains difficult
[49]	Single-center retrospective study. $N=36$ grade III meningiomas (21 received adjuvant RT)	11 received GTR and 18 STR. GTR (Simpson I-II) associated significantly improved PFS ($p=0.01$) and OS ($p=0.004$). Adjuvant RT improved PFS ($p=0.01$) but not OS ($p=0.16$)	EOR correlated with a better outcome, although it was insufficient for LC. Adjuvant RT was found essential even for GTR grade III meningiomas
[50]	US National Cancer Database retrospective comparative study in aged > 60. $N=254$ grade III meningiomas (151 received RT)	5-year survival rate was 57.8% in the adjuvant RT group and 38.1% in the group without RT. Adjuvant RT associated longer OS on both univariate and multivariate analyses	Adjuvant RT did not improve OS ($p=0.271$) matching by age, race, comorbidity, extent of resection, and tumor size. Adjuvant RT was not associated with improved OS in elderly patients undergoing GTR
[51]	National Cancer Database retrospective study 2004–2015. $N=2170$ grade III meningiomas (80 received RT, BED of 80.23 ± 16.6 Gy)	Median OS time was not significantly different: 32.8 months for adjuvant RT vs. 38.5 months for non-RT; $p=0.57$. BED of 81 Gy showed maximal difference in survival distribution	Age was a significant predictor for long-term survival. Conventional adjuvant RT improves LC. However, the effect of adjuvant RT on OS is unclear
[52]	Single-center retrospective comparative study. Surgery vs surgery + RT $N=98$ grade II–III meningiomas (53 received RT)	Greater proportion of grade III in RT group. Median follow-up: 74.3 months. Actuarial 5-year LC rates were 86.7% in RT and 59.3% in surgery ($p=0.002$)	Adjuvant RT reduced local failure in patients with grade II or III meningiomas compared with the surgery only group
[53]	Single-center retrospective study. $N=19$ grade II (15) and III (4) meningiomas. Received helical tomotherapy (> 60 Gy)	Median follow-up: 29.2 months. PFS rates at 1, 2, and 3 years were 89.2%, 83.6%, and 56.3%. OS rates at 1, 2, and 3 years were 94.7%, 94.7%, and 78.9%, respectively	Only 1 AE grade 3. Helical tomotherapy with doses exceeding 60 Gy associated good LC and acceptable OS
[54]	SEER (Surveillance Epidemiology and End Results) database study 2000–2015. $N=530$ grade II and III meningiomas Propensity score matching analysis	GTR did not result in better OS compared to STR. Multivariate analysis: worse OS if > 65 years, > 6 cm, and grade III	Adjuvant RT significantly improved OS for grade III meningiomas, but not for grade II meningiomas, regardless of EOR. In grade II GTR, RT was unable to improve OS and PFS

Table 3 (continued)

Studies on radiation therapy in WHO grade II and III and exclusively grade III meningiomas

Author, year	Design, participants	Overall results	Comments
[19]	Single-center retrospective study. $N=162$ grade II (99) and III (63) meningiomas (115 received RT)	Median follow-up: 76.5 months. Adjuvant RT showed prolonged PFS and OS in patients with newly diagnosed grade III meningiomas irrespective of EOR (PFS, $p=0.001$; OS, $p=0.003$). GTR was the only independent prognostic factor for those with newly diagnosed grade II (PFS, $p<0.001$; OS, $p=0.012$)	A survival benefit for adjuvant RT was also found in subgroup of patients with high-grade meningiomas who underwent STR (PFS, $p=0.023$; OS, $p=0.013$). Among recurrent high-grade meningiomas, RT offered no statistically significant improvement in either PFS or OS
[55]	Single-center retrospective study. Proton beam radiation therapy as re-irradiation. $N=9$ grade II (8) and III (1) meningiomas	Median time from prior RT (54 Gy) to proton therapy (60 Gy): 5.8 years. Median follow-up: 18.8 months. Median cohort PFS was 22.6 months, with 1- and 2-year PFS of 80% and 43%. 1- and 2-year OS were 94% and 73%	Longer interval between prior RT and proton therapy also predicted improved PFS ($p=0.03$) and OS ($p=0.049$). Two patients (13%) developed radionecrosis at 6 and 16 months after proton therapy; one was symptomatic
[56]	Single-center retrospective study. $N=26$ grade II (22) -III (4) meningiomas in lateral ventricles (12 received RT)	Overall recurrence rate of 38.5% (10/26 patients) and a mortality rate of 11.5% (3 deaths) Recurrence in 4/12 patients who received RT and 6/14 patients without RT ($p=0.58$)	STR was a risk factor for recurrence. Postoperative RT had little significance for high-grade meningiomas in the lateral ventricles
[57]	Single-center retrospective study. Intraoperative brachytherapy with I-125 or Cs-131 seeds. $N=15$ grade II (8) – III (7) meningiomas	Prior to brachytherapy: Median of 2 open surgery and local RT median dose of 55 Gy. 2.5-year OS was 56% for grade II and 17% for grade III. OS significantly associated with patient age but not with tumoral grade	40% reoperations due to wound complications following brachytherapy. Seed implantation is an alternative in recurrences by associated high rate of wound morbidity and need for reoperation
[58]	Single-center retrospective study. $N=23$ grade III papillary and rhabdoid meningiomas	Median follow-up: 38 months. Mean PFS was 37.6 months, with 1-year, 3-year, and 5-year PFS of 78.3%, 50.8%, and 43.6%. Mean OS was 48.8 months, with 1-year, 3-year, and 5-year OS of 95.7%, 82.6%, and 44.0%	Postop RT had longer OS than not RT (median, 60.7 vs. 35.1 months; $p=0.029$). Better PFS and OS if RT was given and rhabdoid histology in multivariate analysis. RT recommended regardless of EOR
[59]	Single-center retrospective study. $N=60$ recurrent grade II and III meningiomas	Median follow-up: 36.7 months. Inclusion of RT as primary or adjuvant therapy at first recurrence reduced the risk of progression or subsequent recurrence compared to surgery alone ($p=0.07$)	There was no effect of EOR at first recurrence on time to a subsequent recurrence. Better tumor control with the addition of RT
[60]	Single-center retrospective study. Boron neutron capture therapy (alpha particles). $N=31$ recurrent grade II and III meningiomas	Grades II–III exhibited 3.8 times higher boron accumulation than the normal brain. Transient increases in size in several cases, all lesions were found to decrease during observation	Median survival time of patients with skull base tumors post-RT and after being diagnosed as high-grade were 24.6 and 67.5 months, (vs. non-skull base: 40.4 and 47.5 months). Promising treatment
[61]	Single-center cross-sectional study. $N=43$ grade II (39) -III (4) meningiomas (24 received RT)	Follow-up: 15 years. 19 deaths (44.18%): 15 (38.46%) in grade II and 4 (100%) grade III. The 10-year OS was 35% in grade II and 0% of grade III	Role of RT controversial. Positive impact of RT in PFS
[62]	Prospectively collected data from SEER database $N=522$ grade II–III meningiomas	Multivariate analysis: age (HR 1.03, $p<0.001$), infratentorial location (HR 2.81, $p=0.017$), tumor size (HR 1.01, $p=0.032$), and radiation treatment (HR 1.52, $p=0.01$) were significantly associated with tumor-related death	Significant differences between groups. Age at diagnosis, tumor size, location, and RT impact OS

Table 3 (continued)

Studies on radiation therapy in WHO grade II and III and exclusively grade III meningiomas

Author, year	Design, participants	Overall results	Comments
[63]	Single-center retrospective study. $N=80$ grade II (64) and III (16) meningiomas (53 received postop stereotactic RT and 47 as definitive treatment)	Median stereotactic RT dose: 54 Gy. PFS at 8 years with adjuvant SRT after GTR of grade II were significantly better at 83% ($p=0.016$) compared to 46% after adjuvant SRT of recurrence	Postoperative RT in grade II after GTR can effectively reduce recurrence risk. Better PFS at recurrence if skull base or convexity compared to the falx
[64]	National Cancer Data Base retrospective comparative study on papillary grade III meningiomas $N=190$ papillary meningiomas (89 received RT)	2-year OS was significantly improved with RT vs. no RT (93.0% vs. 74.4%), as was 5-year OS (78.5% vs. 62.5%). Multivariate analysis: patients receiving RT had improved OS compared to observation	Benefit of RT vs. no RT was significant for patients ≤ 18 years with 2-year OS of 85.7% vs. 50.0% and for patients > 18 years with 2-year OS of 94.7% vs. 76.1%. RT associated improved OS for both adult and pediatric patients with papillary meningioma

GKS gamma knife surgery, *RT* radiotherapy, *EOR* extent of resection, *PFS* progression-free survival, *OS* overall survival, *STR* subtotal resection, *GTR* gross total resection, *LC* local control, *RFS* recurrence-free survival, *KPS* Karnofsky Performance Score, *AE* adverse effects, *EBRT* external beam radiotherapy, *SRS* stereotactic radiosurgery

patients, there was consensus on the beneficial effect of radiation on LC and PFS, and maybe on OS, irrespective of extent of resection [19, 45–49, 52, 54, 58, 59, 62–64]. Yet, adjuvant radiotherapy was found to have unclear or no impact on OS in some studies [50, 51, 56, 61]. Rhabdoid histology was reported to achieve better outcome after radiation in a multivariate analysis [58]. Among studies including both grade II and III meningiomas, the majority confirmed the efficacy of adjuvant radiation on LC, PFS, and likely OS, especially among subtotally resected tumors [19, 45–48, 52–54]. Less efficacy was reported regarding recurrent tumors, especially those located in the falx compared to convexity or skull base meningiomas [63]. Special radiation modalities, like proton therapy, brachytherapy, and boron neutron capture therapy, showed promising results, usually performed as re-irradiation or at the time of recurrence. However, these techniques reported non-negligible rates of radionecrosis and wound morbidity [55, 57, 60].

In general, it is widely accepted that grade III meningiomas need upfront postoperative radiotherapy regardless of the extent of resection. The majority of cohorts including both grades also showed benefit from adjuvant radiotherapy in terms of LC and PFS (although not so clear over OS), especially if performed immediately after the first operation. The impact of radiation at the time of recurrence seems to be less favorable and likely conditioned by the possibility of further resection. Figure 2 depicts a scheme of the current recommendations regarding grade II and III meningioma management according to the extent of resection.

Discussion

Since 2017, numerous grade II and III meningioma case series have been published, adding evidence toward the effectiveness of adjuvant radiation therapy in non-benign meningioma. Unfortunately, the great majority of studies were single-center retrospective cohort reviews. The synthesis of this systematic review confirms the usage and efficacy of adjuvant radiotherapy and underscores the need for prospective comparative trials. Atypical meningiomas can be cured by surgery only in 16–18% of the cases [24], and up to 70% recur within the next few months after surgery [65, 66]. Compared to benign meningiomas, atypical lesions carry a poorer overall prognosis, with 5- and 10-year PFS of 38–59% and 19–22%, respectively [12, 67], and a significantly reduced OS [65].

Application of adjuvant radiotherapy exhibits wide variability partly attributable to a lack of comparative prospective trials. Surveys among neurosurgeons indicate that a majority do not recommend routine adjuvant radiotherapy after GTR [18, 68]. The controversy about adjuvant radiotherapy in operated non-benign meningioma emanates from the

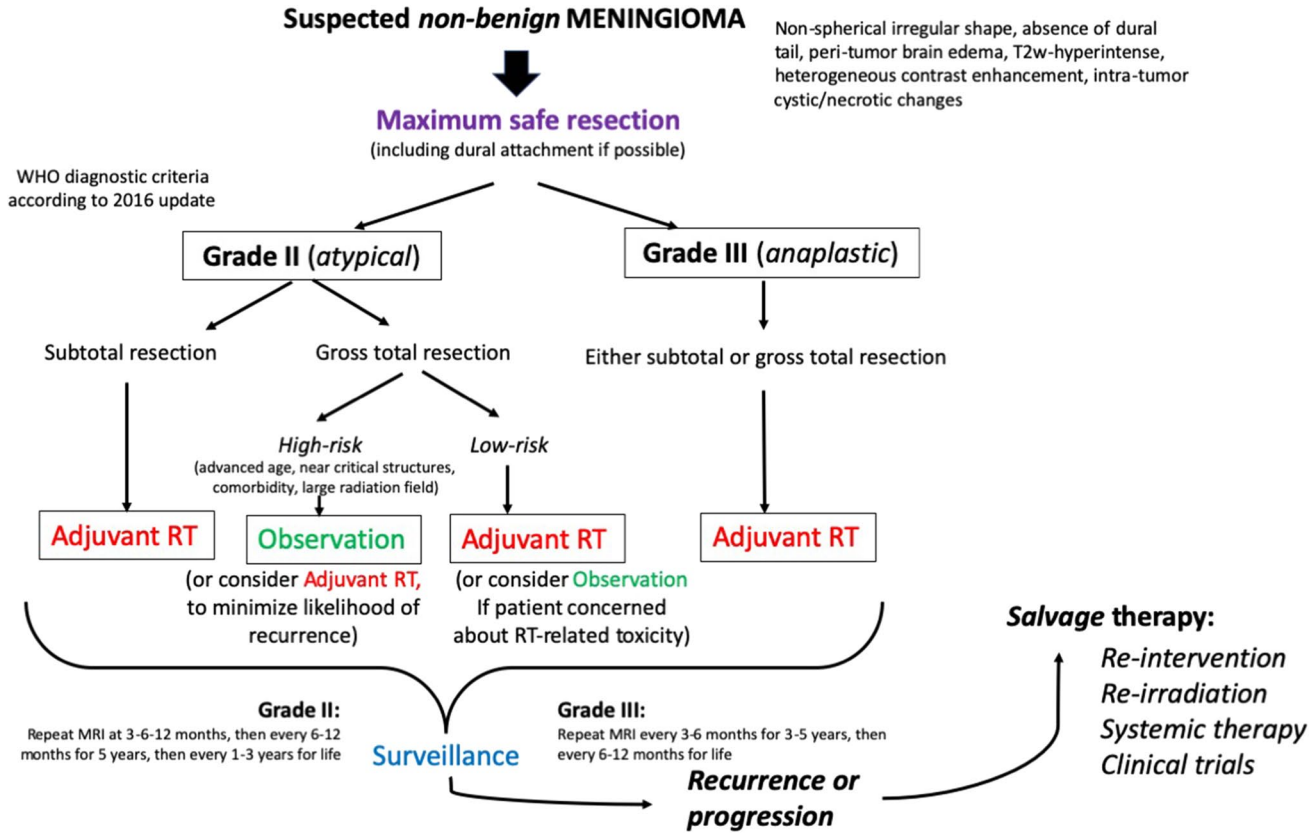

Fig. 2 Recommended indications of radiotherapy in atypical and anaplastic meningiomas

conflicting evidence provided by many heterogeneous studies. Such studies commonly included a limited number of patients, the definition of atypical/anaplastic tumors evolved over time, many studies analyzed grade II and III lesions together, the definition of GTR also changed over time, and a certain selection bias (tendency to preferentially irradiate patients with poorer expected prognosis) was present in the majority of retrospective series [13, 69]. Likewise, radiation-related issues were not systematically reported in studies, like technique, dosage, scheme, field, target volume, and margins. In the recent review by Bagshaw et al. [12], adjuvant radiotherapy was offered to all atypical tumors irrespective of extent of resection upon recognizing that salvage treatments, either re-intervention or re-irradiation, do not seem to impact on survival significantly. They recommend relatively high doses of fractionated radiotherapy, at 59.4 Gy and 54 Gy, for STR and GTR, respectively, and single-dose 18–20 Gy if stereotactic radiosurgery is used.

In 2016, the European Association of Neuro-Oncology (EANO) issued guidelines for the diagnosis and treatment of meningiomas [70]. These were in concordance with previous recommendations, in which grade II tumors undergoing GTR could be observed, whereas grade II with STR and grade III should receive fractionated radiotherapy (54–60 Gy). For both grade II and III meningiomas, fractionated radiotherapy is generally preferred over stereotactic radiosurgery, which in turn might be better suited for primary treatment of small benign meningiomas or for small and deep-seated postoperative remnants. Surveillance of non-benign meningiomas require shorter control intervals compared to regular grade I lesions, therefore, repeating MRI every 3–6 months instead of annually. EANO guidelines adopted the definition of GTR as Simpson's grades I, II, and III. Given the quality of studies supporting the use of adjuvant radiotherapy, all recommendations provided in the EANO guidelines statements were based on evidence level B, C, and good practice points.

In this view, the main issue to elucidate when confronting a high-grade meningioma is whether adjuvant therapy (primarily radiotherapy) should be proposed upfront or reserved for recurrence. Given that the extent of resection is a key prognostic factor, efforts should be made to achieve resections as complete as possible in the first surgery. Yet, it is common practice to observe grade I subtotally resected meningiomas, given that many residues remain unchanged over long periods of time, if not for life. In contrast, subtotally resected high-grade variants, generally due to involvement of vital structures or deeply located, tend to grow locally over time at a much higher speed, making further resections

more complicated. These cases are commonly offered adjuvant therapy in the belief that local control is improved, and subsequently PFS and OS.

However, studies have yet failed to demonstrate a sound impact of adjuvant radiotherapy on OS likely attributable to the lack of randomized controlled trials on the matter [12, 13, 70]. It is striking that no such trials had been conducted so far given the enormous amount of eligible patients available worldwide and the conflicting evidence regarding its effectiveness among subgroups of meningiomas, stratified by prognostic factors, like age, grade, extent of resection, location, and histopathological subtypes. The latest WHO classification of meningiomas has transformed many previously considered grade I tumors into higher grades, merely upon histopathologic criteria [9]. In addition, historical surgical aggressiveness directed to deep-seated meningiomas, like cavernous sinus or petroclival region, has been revised given the intolerable surgical morbidity (especially cranial neuropathies) reported in some modern series [71–73]. These two factors have significantly increased the number of patients eligible for adjuvant radiation.

Only two prospective non-randomized trials have studied the effect of radiotherapy on non-benign meningiomas. The RTOG 0539 phase II trial [37] analyzed cohorts of intermediate risk (new grade II undergoing GTR or recurrent grade I) and high risk (grade III or new grade II undergoing STR or recurrent grade II). All patients received 54 Gy as adjuvant therapy. They reported a remarkable 3-year PFS of 93.8%. Interestingly, both subgroups within the intermediate risk achieved statistically similar PFS rates. Among high-risk patients, 3-year PFS, LC, and OS were 59.2%, 68.9%, and 78.6%, respectively. The EORTC 22,042–26,042 phase II trial included grade II and III meningiomas. Atypical lesions undergoing GTR and adjuvant radiotherapy (60 Gy) achieved a 3-year PFS and OS of 88.7% and 98.2%, respectively. However, none of these studies compared adjuvant radiotherapy against observation nor randomized patients to treatment and control arms.

The currently ongoing ROAM/EORTC 1308 phase III multi-center trial [69] was designed to randomize GTR atypical meningioma patients to either radiation (60 Gy in 30 fractions) or observation. This trial was intended to determine whether early adjuvant radiotherapy reduced the risk of tumor recurrence following GTR of atypical meningiomas. Embedded within this trial and pre-randomization, a qualitative study was performed [74], in which specific researchers examined how information about the trial is exchanged between physicians and patients during recruitment interviews and its influence on consent obtention. In a sub-sample of patients, they compared discussions during recruitment consultations with clinicians' and patients' interpretations of such consultations. This has been shown to be effective to improve patient and doctor acceptability and maximize recruitment [75]. In fact, this analysis identified several challenges that practitioners face in conveying equipoise, addressing difficulties with communication, and exploring patient treatment preferences, with potential impact on improving informed consent and recruitment. A second trial is also underway (phase III NRG-BN-003 trial or NCT 03,180,268), comparing radiation (59.4 Gy) versus observation in GTR patients [13]. Table 4 shows the main characteristics of both trials and the estimated completion date. These trials address a simple but important question about meningioma management, and their preliminary results, likely available in a few years from now, have the potential for changing the current neuro-oncologic practice worldwide. Other clinical trials have been recently activated or are currently recruiting patients in order to test the efficacy of carbon ion radiotherapy in atypical meningioma (NCT01166321), proton dose escalation in atypical and anaplastic meningiomas (NCT02978677), and the efficacy of postoperative radiotherapy for atypical meningiomas without venous sinus invasion after GTR (NCT04127760).

Radiation therapy modalities have not been compared between them in well-designed studies as to provide evidence of one treatment modality over the others. In general, higher doses (at least 54 Gy) seem to provide better overall outcomes [70]. According to the review by Hwang et al. [76], PFS was significantly higher when 60 Gy were given compared to lower doses, and when combined proton and photon irradiation was used [77]. Conventional fractionated external beam radiotherapy (typically using 1.8–2.0 Gy/fraction over 5- to 7-week course) benefits from the conformality of radiation dose delivery provided by intensity-modulated RT (IMRT) and volumetric arch therapy [78]. For grade II and III meningiomas, doses ranging between 60 and 66 Gy are typically used [21, 79]. Applied to skull base meningiomas, stereotactic radiotherapy with IMRT provides 3- and 5-year local control rates over 93%, although this technique is generally viewed as a second-tier option once surgery and/or conventional RT have failed [80]. Single fraction stereotactic radiosurgery (SRS) is an effective option for lesions < 10 cc, a maximum diameter less than 3–4 cm, and sufficient distance from critical structures [76]. According to Kano et al. [81], a marginal dose of 16–20 Gy associates a 5-year local control rate of 60–75%. Interestingly, the inclusion of the dural tail in the treatment volume has proven beneficial in benign meningioma but has not been yet studied in high-grade meningioma [76]. Likewise, hypofractionated stereotactic radiotherapy (five fractions or less), indicated for larger lesions, have yielded good results in benign meningioma but has not been studied in aggressive meningiomas [82, 83]. Interstitial brachytherapy has been reported to be an effective adjunct to surgery and external beam radiotherapy, especially for malignant, recurrent, and large meningiomas, yet associating over 25% rate of wound complications and

Table 4 Main characteristics of the ongoing ROAM/EORTC 1308 and NRG-BN-003 trials on the effect of adjuvant radiotherapy following total surgical removal of atypical meningiomas

	ROAM/EORTC 1308	NRG-BN-003
Official title, trial designation, sponsor, website	Radiation versus Observation following surgical resection of Atypical Meningioma: a randomized controlled trial (the ROAM trial)	Phase III Trial of Observation Versus Irradiation for a Gross Totally Resected Grade II Meningioma
	HTA 12/173/14	NCT03180268
	The Walton Centre NHS Foundation Trust (UK), EORTC, NIHR, TROG	NRG Oncology, National Cancer Institute
	https://www.isrctn.com/ISRCTN71502099; https://www.roam-trial.org.uk	https://www.clinicaltrials.gov/ct2/show/NCT03180268?term=NCT+03180268&draw=2&rank=1
Principal Investigator, participating countries	Michael Jenkinson, MD (UK) Australia, Austria, Belgium, France, Germany, Ireland, Italy, New Zealand, Spain, Switzerland, United Kingdom	C. Leland Rogers, MD (USA) USA, Canada, Japan, Saudi Arabia (159 centers, mostly in the USA)
Design	Phase III, two-arm multi-center randomized controlled trial. Currently recruiting	Phase III, open-label multi-center randomized controlled trial. Currently recruiting
Study hypothesis	To determine whether early adjuvant fractionated radiotherapy reduces the risk of tumor recurrence or death due to any cause compared to active monitoring in newly diagnosed atypical meningioma	This randomized phase III trial studies how well radiation therapy works compared with observation in treating patients with newly diagnosed grade II meningioma that has been completely removed by surgery
Treatment arm	Patients will be randomized in a 1:1 ratio to early adjuvant radiotherapy (60 Gy in 30 fractions) for 6 weeks (intervention) Web-based randomization	Patients undergo radiation therapy 5 days a week over 6.5–7 weeks for a total of 33 fractions after gross total resection (59.4 Gy in 33 daily fractions of 1.8 Gy each)
Control arm	Active monitoring with MRI	Patients undergo observation after gross total resection
Follow-up	Patients will be followed up for 60 months post randomization	Patients are followed up at 3, 6, and 12 months, every 6 months for year 2 and 3, then yearly for 10 years
Study start date	September 1, 2014	June 14, 2017
Estimated enrollment	190 participants (115 already randomized)	148 participants
Primary endpoint	Time to MRI evidence of tumor recurrence or death due to any cause [disease free survival (DFS)]. (DFS will be counted from the date of surgery until the date of MRI evidence of tumor recurrence or death due to any cause. Only clear dural thickening as identified by the investigator is to be considered tumor.)	To determine, in terms of progression-free survival (PFS), the extent of clinical benefit of the addition of adjuvant radiotherapy (RT) to gross total resection (GTR) for patients with newly diagnosed World Health Organization (WHO) grade II meningioma
Secondary endpoints	(1) Toxicity of radiotherapy assessed by CTCAE (Common Terminology Criteria for Adverse Events), (2) Quality of life, (3) Neurocognitive function (UK sites only), (4) Time to second line (salvage) treatment (surgery, radiotherapy, radiosurgery), (5) Time to death (overall survival [OS]), (6) Health economic analysis (incremental cost per QALY gained) (UK sites only)	(1) Overall survival (OS). (2) Disease-specific survival (DSS). (3). Toxicity (grade 3+, exclusive of expected alopecia). (4) Neurocognitive function (NCF). (5) Outcomes and patient reported outcomes (PRO) measurements. (6) Adherence to protocol-specific target and normal tissue parameters. (7) Concordance measurements of central versus parent-institution pathology. (8) Tissue microarray construction, and assessment of pHH3 mitotic index and molecular correlates to OS
Inclusion criteria	Sixteen years or older. Histologically confirmed newly diagnosed solitary atypical meningioma (WHO grade II) based on the 2016 WHO criteria. Complete resection (Simpson 1, 2 or 3) as assessed by the surgeon	Eighteen years or older. Newly diagnosed unifocal intracranial meningioma, gross totally resected (Simpson grades 1–3, upon postop MRI), and histologically confirmed as WHO grade II based upon pathology findings at the enrolling institution; WHO grade will be assigned according to WHO 2016 criteria

Table 4 (continued)

	ROAM/EORTC 1308	NRG-BN-003
Exclusion criteria	Neurofibromatosis type II (NF-2), Optic nerve sheath tumors, multiple meningiomas, radiation-induced meningioma, clinical evidence of second malignancy, except for cervix carcinoma in situ or basal cell carcinoma, and history of invasive malignancy unless treated with curative intent and the patient has not been disease free for the last five years. Previous intracranial tumor, pregnant or lactating women	Optic nerve sheath meningioma, spinal or other extracranial meningioma, multiple meningiomas, hemangiopericytoma, metastatic meningioma, prior radiation to scalp, prior invasive malignancy. Pregnancy or major medical illnesses or psychiatric impairments
Estimated completion date	September 30, 2025	August 31, 2027
Expected date for publication of results	March 31, 2026	–
Preliminary publication	Jenkinson MD, Javadpour M, Haylock BJ, et al. The ROAM/EORTC-1308 trial: Radiation versus Observation following surgical resection of Atypical Meningioma: study protocol for a randomised controlled trial. Trials. 2015;16:519. Published 2015 Nov 14. 10.1186/s13063-015-1040-3	–

radiation necrosis, many of which needed further surgery [84]. Salvage brachytherapy with I-125 or Cs-131 seeds, occasionally used in recurrent grade II–III meningiomas already re-operated and irradiated, has yielded a 40% need for reoperation due to wound complications [57]. Finally, heavy particle therapy with carbon ion radiotherapy offers the advantages of highly localized deposition of energy as in proton therapy, reduced cell cycle-dependent radiosensitivity, and increased efficacy for cancer stem-like cells [76]. The NCT01166321 phase II open-label trial (expected to be completed by December 2020) is currently recruiting patients with atypical meningiomas undergoing partial resection (Simpson 4 and 5) treated with carbon ion boost in combination photon radiotherapy.

As already standardized for glioma [9] or ependymoma [84], the eventual upcoming genetic- and molecular-based classification of meningiomas will likely introduce a new way of stratifying risk in meningioma, and may provide a surrogate prognostic factor of survival and recurrence.

Advances on the immunogenetic landscape of meningioma have been recently reviewed [85]. Using unsupervised clustering of DNA methylation data, Sahm et al. [86] were able to identify two major epigenetic patterns across the three grades of meningioma: group A, including four methylation classes (three benign and one intermediate), and group B which included two additional classes (one intermediate and one malignant). Interestingly, the majority of NF2 (Neurofibromatosis-2) gene-mutated tumors gathered in group A, and most TERT mutations in group B. This 6-methylation class subdivision predicted PFS better than the current WHO 15-histology variants and 3-grade classification [86]. Additionally, a meningioma recurrence score has been proposed, based on methylation status, extent of resection, and WHO grade which can be used in the clinical setting to inform choices for follow-up and to decide about adjuvant therapy [87]. However, meningioma is characterized by a relatively low mutational burden compared to other brain tumors; therefore, identification of prognostic biomarkers has yet provided modest clinical impact for decision making. In general, TERT promoter and BAP1 mutations are linked to poorer prognosis [85]. This molecular subgrouping may eventually simplify meningioma stratification and will necessarily need to be acknowledged when designing future trials.

Among unresectable meningiomas, in which tumor growth is confirmed, especially if suspicious of being high grade, upfront radiation or systemic therapy is mandatory [70]. A detailed description on the effectiveness of chemotherapy and other systemic therapies in non-benign meningioma is beyond the scope of this review and can be found elsewhere [88–90]. At the time of recurrence, if feasible, re-intervention is the first-choice irrespective of grade or previous extent of resection [12, 13, 24, 70]. Irradiation is

the preferred modality when re-intervention is deemed not possible and for small deep tumor remnants. Salvage re-irradiation can also be an option. Studies show that PFS and OS are improved the longer the interval between prior radiotherapy and re-irradiation [13]. Although metastasis is rare and can occur throughout the natural course of any type of meningioma, including grade I lesions [91], it is much more common among higher-grade tumors [13, 70]. Anecdotally, the recent paper by Golub et al. [92] reports on a possible abscopal effect after IMRT treatment of an intracranial meningioma, with radiographically significant response of another untreated second intracranial lesion, distant to the radiation field, also suggestive of meningioma.

Conclusions

According to the recently updated WHO classification of central nervous system tumors, grade II and III meningiomas comprise a larger proportion of all meningiomas. Maximum safe resection including the dural attachment is the recommended first treatment option for all types of meningiomas. Atypical and anaplastic meningiomas carry a significantly increased recurrence rate compared to benign meningiomas, which negatively impacts survival. Adjuvant radiation is currently advised for subtotally resected grade II and for all grade III meningiomas. In the case of grade II meningiomas undergoing gross total resection, close radiologic and clinical observation is feasible. The potential benefit of adjuvant radiation in this subset of patients is currently being tested in ongoing clinical trials.

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Compliance with ethical standards

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