Efficacy and toxicity of particle radiotherapy in WHO grade II and grade III meningiomas: a systematic review

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OBJECTIVE Adjuvant radiotherapy has become a common addition to the management of high-grade meningiomas, as immediate treatment with radiation following resection has been associated with significantly improved outcomes. Recent investigations into particle therapy have expanded into the management of high-risk meningiomas. Here, the authors systematically review studies on the efficacy and utility of particle-based radiotherapy in the management of high-grade meningioma.

METHODS A literature search was developed by first defining the population, intervention, comparison, outcomes, and study design (PICOS). A search strategy was designed for each of three electronic databases: PubMed, Embase, and Scopus. Data extraction was conducted in accordance with the PRISMA guidelines. Outcomes of interest included local disease control, overall survival, and toxicity, which were compared with historical data on photon-based therapies.

RESULTS Eleven retrospective studies including 240 patients with atypical (WHO grade II) and anaplastic (WHO grade III) meningioma undergoing particle radiation therapy were identified. Five of the 11 studies included in this systematic review focused specifically on WHO grade II and III meningiomas; the others also included WHO grade I meningioma. Across all of the studies, the median follow-up ranged from 6 to 145 months. Local control rates for high-grade meningiomas ranged from 46.7% to 86% by the last follow-up or at 5 years. Overall survival rates ranged from 0% to 100% with better prognoses for atypical than for malignant meningiomas. Radiation necrosis was the most common adverse effect of treatment, occurring in 3.9% of specified cases.

CONCLUSIONS Despite the lack of randomized prospective trials, this review of existing retrospective studies suggests that particle therapy, whether an adjuvant or a stand-alone treatment, confers survival benefit with a relatively low risk for severe treatment-derived toxicity compared to standard photon-based therapy. However, additional controlled studies are needed.

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KEYWORDS meningioma; atypical; malignant; particle radiotherapy

Menigiomas are the most common primary brain tumor, accounting for approximately 33.8% of all central nervous system (CNS) tumors in the US.55 Based on the World Health Organization (WHO) classification, meningiomas are divided into benign (grade I), atypical (grade II), and anaplastic (grade III) subtypes.9,55 Atypical and anaplastic meningiomas are rare and account for 1%–25% of all meningiomas.27 Atypical meningiomas have high recurrence rates (28%–41%) following surgery without additional therapy.3,51 Malignant anaplastic meningiomas are the most aggressive, with recurrence rates ranging from 50% to 94% and significant risk for invasion and metastasis.62 The current standard of care for symptomatic or growing meningioma consists of maximal resection.62 Photon-based radiotherapy, including both stereotactic radiosurgery (SRS) and conventional stereotactic radiotherapy, is usually recommended as adjuvant therapy or as primary treatment for meningioma.63 However, alternative radiation techniques collectively known as “particle radiotherapy”
have emerged for treating meningiomas and other tumors of the CNS, including proton therapy, carbon ion therapy, or boron neutron capture therapy (BNCT). And although photon-based radiotherapy is used worldwide for the treatment of meningioma, particle radiation therapy could reduce the risk of the adverse radiation effects caused by photon-based radiotherapy.

In fact, particle-based therapies offer several tantalizing advantages. A primary concern associated with radiation therapy is inadvertent dose deposition in nontarget tissue. While acute deficits associated with radiation-induced brain injury are often transient, other impairments often result from permanent morphological alterations, such as hypoxic tissue damage (with subsequent cognitive decline)\(^{1,2}\) and radiation necrosis, caused by inflammatory responses to radiation damage.\(^{5,8}\) Tissue damage resulting from off-target radiation damage has been associated with numerous neurological deficiencies later in life, including losses in memory, attention, and executive decision-making.\(^{2,9}\) As well as high rates of dementia and a reduced long-term quality of life.\(^{3,6,9,9}\) In addition to concerns regarding neurological decline, brain irradiation is associated with increases in the incidence of secondary malignancies. Longitudinal monitoring of pediatric cancer patients has suggested that the receipt of conventionally fractionated radiation therapy is associated with an increased risk of secondary neoplasms later in life.\(^{4,3,4}\)

Particle-based radiotherapy could reduce unwanted tissue damage from off-target radiation. Dosimetry studies comparing the deposition pattern of protons to that of photons have shown that proton therapy reduces ionizing radiation exposure in normal tissue proximal to the radiation target.\(^{4,1}\) Photon-based methods deposit a significant fraction of their dosage before reaching the target. Conversely, particle-based radiation techniques, whose deposition pattern is characterized by a Bragg curve, deliver the bulk of the beam energy to the target, regardless of its depth, and minimize the unwanted damage to surrounding tissue.\(^{5,6}\) Moreover, particle radiation therapy minimizes unwanted exit dose, therefore reducing tissue damage to structures distal to the target.

While the efficacy and toxicity associated with particle-based radiation techniques have been explored in systematic reviews on low-grade primary brain tumors, few studies have explored the effect of particle radiotherapy in high-grade CNS malignancies.\(^{3,8,6}\) While the role of photon-based radiotherapy for high-grade meningioma has been investigated, additional studies are needed to elucidate the role of particle therapy in controlling these aggressive tumor histologies.\(^{1,5,2}\) The aim of the present analysis was to systematically review the studies addressing the safety and efficacy of particle radiotherapy for atypical and anaplastic meningiomas.

**Methods**

A systematic review on the efficacy of particle or combined photon and particle treatments in the management of WHO grade II and III meningiomas was performed according to PRISMA guidelines. Our literature search was developed by defining the population, intervention, comparison, outcomes, and study design (PICOS; Fig. 1). Inclusion criteria, outcome measures, and search strategy were defined in advance.

**Search Strategy**

Our review included studies on the use of particle-based radiotherapy in high-grade meningioma (WHO grades II and III) in the adult population (age > 18 years old), with 5 or more subjects, and written in the English language. Upfront exclusion criteria included review articles, book chapters, editorials, and articles in languages other than English. Other exclusion criteria were studies including pediatric patients, having fewer than 5 subjects, or reporting outcomes different from those detailed in Fig. 1. In order to ensure exhaustive canvassing of the published literature, we, in collaboration with a university librarian (H.N.W.), designed a comprehensive search strategy for each of three electronic databases (PubMed, Embase, and Scopus). Synonymous words for included search terms, such as “proton” and “carbon” for “particle” and “radiotherapy” for “radiation therapy,” were included to maintain high inclusivity for our initial search. Strategies also utilized medical subject headings (MeSH) and Boolean operators to capture all relevant publications.

Using a Boolean search scheme analogous to that applied in our literature search, we identified ongoing trials from clinicaltrials.gov, a database of clinical trials curated by the US National Library of Medicine at the National Institutes of Health. Only studies exploring particle-based radiotherapy in high-grade meningiomas were included.

**Data Extraction**

A comprehensive analysis of PubMed, Embase, and Scopus revealed 474 studies published between 1961 and 2019, and 189 of them were duplicates removed prior to screening. Eligibility, abstract, and full-text screening was performed independently in a standardized manner by reviewers (A.W. and M.C.J.). Disagreements were resolved by discussion between the two reviewers, with a third reviewer for cases in which no agreement could be reached (H.N.W.). Eleven studies, all of which were published between 2000 and 2018, explored the efficacy of particle or combined photon and particle treatments in the management of WHO grade II and III meningiomas and were included in our systematic review. Outcome variables included number of patients with a diagnosis of high-grade meningioma within each cohort, type of radiotherapy administered, median age, median dose, local control rate, overall survival rate, median length of follow-up, treatment planning details, and type and timing of toxicities. Two independent reviewers (A.W. and M.C.J.) assessed article quality according to the Oxford Centre for Evidence-based Medicine (OCEBM) guidelines. Metrics evaluated to ascertain levels of evidence included randomization, cohort size, and length of follow-up.

**Results**

Eleven studies with 240 patients were included in the final data extraction and analysis (Fig. 1 and Table 1). Of note, five of the studies included only patients with high-grade meningiomas (WHO grade II or grade III).\(^{10,12,13,2,42}\)
while the other studies also included patients with benign meningiomas (WHO grade I) and gliomas. None of the studies were randomized or prospective.

**Particle Radiotherapy Techniques and Treatment Plan Schema**

Seven of the studies investigated the effects of combination particle therapy (proton + photon, 50 Gy photon + 18 Gy median carbon boost).

In order to plan treatment, the gross tumor volume (GTV) was first mapped with an additional margin, ranging from 5 to 20 mm for high-grade meningiomas, and then creating a clinical target volume (CTV) based on pretherapy imaging. At minimum, the GTV comprises the tumor as well as any dural extension or hyperostotic change involved with the lesion. The margin added to high-grade meningioma is usually greater than the tumor edges because of the tumor's infiltrative pattern of growth. Typical imaging modalities used to characterize extent of the tumor include high-resolution contrast CT and MRI with some practitioners utilizing formats such as ⁶⁸Ga-DOTA-TOC-PET. Final treatment plans were then generated on 3D planning systems.

**Local Tumor Control**

In the five studies on high-grade meningioma only, local control rates at 5 years or at the end of the follow-up (median 145 months in Chan et al.) ranged from 46.7% to 86% (Table 1). Unfortunately, no data specific to grade II versus grade III meningioma local control rates were reported in the included studies.

**Overall Survival**

Overall survival rates ranged from 0% to 100% in studies focusing solely on high-grade meningioma, with a few studies reporting separate overall survival rates for WHO grade II and grade III meningiomas. Specifically, atypical meningiomas (WHO grade II) have better prognosis in terms of overall survival rates and median overall survival time as compared to malignant meningiomas (WHO grade III) in the studies by Chan et al. (100% vs 0%), Hug et al. (89% vs 51% at 5 years), and El Shafie et al. (median overall survival time 238.7 vs 173.6 months).

**Adverse Effects**

Radiation necrosis was the most commonly observed complication across the studies investigating particle therapy in high-risk meningiomas, affecting 3 patients across three study cohorts composed of 77 patients (3.9%; Table 2). Other less frequent adverse events included alopecia, skin irritation, and seizures. The vast majority of observed complications were categorized as grades 1 and 2, according to the Common Terminology Criteria for Adverse Events (CTCAE), whereas only one study reported the diagnosis of grade 3 toxicity (radiation necrosis). It is worth noting that the patient in this case had previously received pituitary radiation and was being treated for a radiation-induced meningioma; symptoms associated with radiation necrosis were resolved following treatment with pentoxifylline supplemented with vitamin E and hyperbaric oxygen. None of the included studies reported any secondary malignancies.

**Discussion**

**Adverse Events Following Particle Therapy**

Generally, the incidence of radiation-induced necrosis, which refers to the morphological changes in brain vascu-
## TABLE 1. Literature summary of 11 studies on WHO grade II and III meningiomas treated with particle therapy

| Authors & Year (tumors studied) | Cohort Size* | Type of Radiotherapy† | Median Cohort Age in yrs‡ | Median Dose | Local Control Rates | Overall Survival Rates | Median FU (mos) | Level of Evidence§ |
|---------------------------------|--------------|-----------------------|---------------------------|-------------|---------------------|-----------------------|-----------------|-------------------|
| Boskos et al., 2009 (Gr II–III meningiomas) | 24 | Proton + photon (24) | 52.5 | 34 CGE | 46.7% (5 yrs) | 53.2% (5 yr) | 32.2 | IV |
| Chan et al., 2012 (Gr II–III meningiomas) | 6 | Proton + photon (6) | 46 | 68.4 Gy (Gr II), 72 Gy (Gr III) | 83.3% (end of FU) | 100% (Gr II), 0% (Gr III) | 145 | IV |
| Combs et al., 2013 (multiple tumor types) | 36 | Photon + carbon boost (36); proton (176); carbon (84) | NA (48) | NA | 54% (1 yr) | NA | 12 | IV |
| Combs et al., 2013 (Gr I–III meningiomas) | 27 | Proton (38); carbon (17); photon + carbon (15) | NA (55) | 50 GyE + 18 Gy boost | 81.4% (end of FU) | 100% (end of FU) | 6 | IV |
| Combs et al., 2013 (Gr I–III meningiomas) | 10 | Photon + carbon (10) | 52 | 50.4 GyE + 18 Gy boost | 86% (5 yrs) | 90% (5 yrs) | 77 | IV |
| El Shafie et al., 2018 (Gr I–III meningiomas) | 22 | Proton (8); carbon (34) | NA (54) | 60 Gy (Gr II), 56 Gy (Gr III) | 71% (1 yr) | 238.7 mos (Gr II), 173.6 mos (Gr III) | NA | IV |
| El Shafie et al., 2018 (Gr I–III meningiomas) | 8 | Proton (2), photon + carbon (6) | NA (52) | Proton (NA), photon + carbon (50 Gy + 18 Gy) | 100% (3 yrs), 99.6% (5 yrs) | 96.2% (5 yrs), 92% (5 yrs) | 46.8 | IV |
| Hug et al., 2000 (Gr II–III meningiomas) | 31 | Photons + protons (16) | 49¶ | 160 MeV protons, 62 Gy photons¶ (Gr II), 58 Gy photons¶ (Gr III) | 80% (5 yrs) | 89% (5 yrs, Gr II), 51% (5 yrs, Gr III) | 59 | IV |
| McDonald et al., 2015 (Gr II–III meningiomas) | 22 | Proton (22) | 42 | 62 Gy (Gr II, III) | 71.1% (5 yrs) | 100% (end of FU) | 39 | IV |
| Murray et al., 2017 (Gr I–III meningiomas) | 35 | Proton (96) | NA (52.8) | NA | 86.4% (5 yrs) | 88.2% (5 yrs) | 56.9 | IV |
| Weber et al., 2012 (Gr I–III meningiomas) | 10 | Proton (39) | NA (48.3¶) | 56 Gy | 84.8% (5 yrs) | 81.8% (5 yrs) | 28.7 | IV |

CGE = Cobalt Gray equivalent; FU = follow-up; GR = grade; GyE = Gray equivalent; NA = not available.
* Number of patients in the study cohort who had a diagnosis of WHO grade II or III meningioma.
† Values in parentheses refer to the total number of patients treated with the indicated therapy regardless of whether they had WHO grade II or III meningioma.
‡ Values outside of parentheses represent the median age of the WHO grade II–III cohort, whereas values within parentheses represent the median age of patients with WHO grade I–III meningioma or multiple tumor types.
§ Evaluation of evidence level is in accordance with OCEBM guidelines.
¶ Mean value.
lature and cell composition following ionizing radiation, can range from 5.9% to 27% for patients undergoing cranial photon-based radiosurgery. A study investigating the effects of fractionated photon-based radiation therapy for intracranial low-grade neoplasms revealed that a total dose of more than 7.3 Gy in 2-Gy fractions to the bilateral hippocampus was associated with lasting deficits in list-learning delayed verbal recall. In comparative studies of radiation dosage to “organs at risk,” which include the hippocampi, cochlea, optical structures, and thalami, particle radiation therapy plans actually resulted in an overall dosing reduction in all locations as compared to plans for 3D conformal radiotherapy and intensity-modulated radiotherapy.

Furthermore, pediatric patients receiving conventional photon-based radiation to fields encompassing cerebral vasculature demonstrated a significant risk of vasculopathy, with nearly 20% of subjects experiencing either a transient ischemic attack or an infarction within 13 years following therapy. In the present review, the high-risk meningioma studies reported that the most common toxicity was radiation necrosis but at a rate lower than the radiation necrosis rates cited for photon-treated high-grade meningioma. Following therapy, nearly 20% of subjects experienced either alopecia and seizures. According to prior studies, transient ischemic attack or an infarction within 13 years following various radiation modalities in benign meningioma, the symptoms associated with tissue radiation damage appear to correlate with target location, with patients presenting with posterior fossa tumors especially at risk for proton-induced complications. The limited number of studies and patients in which particle-based therapies have been applied to grade II and III meningiomas hinders meaningful correlative analyses between target location and treatment-induced complications; however, future trials of particle therapy for high-risk meningiomas could shed further light on the factors influencing the incidence of side effects of such treatment.

The risk of secondary malignancies induced by ionizing radiation is also of great concern. In a retrospective study on the incidence rate of secondary malignancies following various radiation modalities in benign meningioma, proton therapy was found to be associated with a lower risk of radiation-induced cancers (1.3 vs 2.8 cases per 10,000 patient-years). Additionally, dosimetric studies have shown that reduced proton therapies are associated with reduced in-field dosages, where the majority of secondary malignancies occur. None of the studies included in our review reported any secondary malignancies. However, it should be noted that the longest median follow-up was 145 months in a limited cohort of 6 patients (Table 1). Additional studies with longer follow-ups are necessary to better understand the risk of radiation-induced cancers following proton-based radiotherapy.

### Prognostic Factors for Local Tumor Control and Overall Survival

Treatment with proton or carbon radiation leads to relatively high rates of local control (46.7%–86%) and overall survival (53.2%–100%) in atypical and anaplastic meningioma. Otherwise, rates of local control for grade II meningioma range from 41.7% to 95% following photon-based SRS. Survival rates are especially poor for grade III meningioma treated with photon therapy, ranging from 40% to 44% at 5 years.

Local control (72%–82.6%) and freedom from recurrence have been favorable but variable for atypical meningioma treated with any form of radiation therapy. Chen et al. found several significant prognostic factors for local control in grade II meningiomas treated with surgery and adjuvant therapy, for example, achieving gross-total resection, using adjuvant radiation therapy, and even having a history of previous cranial radiation therapy. On the other hand, a study on Gamma Knife treatment for grade II and III meningiomas found that patient sex and a margin dose below 13 Gy were significant factors associated with local control.

A high histopathological tumor grade generally correlates with poor survival because of poor local tumor control and a high risk of recurrence and metastasis. As a result, overall survival rates at 5 years for WHO grade II (75.9%) and grade III (55.4%) meningiomas remain much lower than the rate for their benign grade I counterpart (85.5%), according to a comprehensive national database study. Rates of progression-free survival (0% by the end of follow-up and 43% at 10 years) and overall survival (20% by the end of follow-up) were poor for grade III meningioma treated with nonparticle SRS. In our cohorts, some of the significant tumor-related prognostic factors for survival were histological grade at diagnosis and prior local control. With regard to treatment selection, combined photon and proton radiation therapy as well as whether proton therapy was administered for primary versus recurrent tumor also had a significant association.
TABLE 3. Ongoing clinical trials exploring particle therapy in high-grade meningioma

| Study ID      | Study Name                                                                 | Phase | Enrollment (no. of patients) | Intervention                          | Primary Outcome       | Secondary Outcome | Completion Date  | Associated Publications |
|---------------|----------------------------------------------------------------------------|-------|------------------------------|---------------------------------------|-----------------------|-------------------|-----------------|----------------------|
| NCT01166321   | Carbon Ion Radiotherapy for Atypical Meningiomas (MARCIE)                   | II    | 40                           | Carbon boost                         | PFS (3 yrs)           | OS (3 yrs)        | 12/2020         | Combs et al., 2010   |
| NCT01795300   | Comparison of Proton and Carbon Ion Radiotheraphy With Advanced Photon Radiotherapy in Skull Base Meningiomas: The PINOCCHIO Trial | NA    | 80                           | Carbon RT, proton RT, HF photon RT, photon RT | Toxicity (1 yr)       | OS (3 yrs)        | 5/2022          | NA                   |
| NCT02693990   | A Trial of Increased Dose Intensity Modulated Proton Therapy (IMPT) for High-Grade Meningiomas | VII   | 60                           | IMPT                                  | Toxicity (2 yrs)      | Local control (5 yrs), OS (2 yrs), linear energy transfer | 2/2024          | NA                   |
| NCT03267836   | Neoadjuvant Avelumab and Hypofractionated Proton Radiation Therapy Followed by Surgery for Recurrent Radiation-refractory Meningioma | I     | 12                           | Avelumab + proton RT                  | Immunogenicity (2 yrs) | Toxicity (7 mos), radiological & pathological response (3 mos), PFS (2 yrs), OS (2 yrs) | 7/2020          | NA                   |
| NCT02978677   | Proton Dose Escalation for Patients With Atypical or Anaplastic Meningiomas (PANAMA) | NA    | 90                           | Photon/proton RT/boost                | PFS (5 yrs)           | Toxicity (late/acute; 5 yrs), OS (5 yrs), recurrence (5 yrs), QOL (5 yrs) | 12/2028         | NA                   |

HF = hypofractionated; IMPT = intensity-modulated proton therapy; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RT = radiotherapy.

A total of five ongoing clinical studies investigating the utility of particle therapy in atypical and anaplastic meningioma were identified. Toxicity is measured according to the Common Terminology Criteria for Adverse Events (CTCAE). Quality of life is graded according to the European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients (EORTC-QLQ-C30) and Brain Cancer Patients (EORTC-QLQ-BN20) criteria.
with survival outcome. Further studies are necessary to characterize the efficacy and utility of radiation therapy for aggressive subtypes of meningioma.

**Ongoing Investigations Into Particle Therapy in High-Risk Meningiomas**

Particle radiotherapy is a field of active investigation to define its use and outcomes in the clinical setting, to develop new and highly precise delivery strategies, and to define the radiobiological effects of these techniques in a laboratory setting. The majority of studies in our review identified the use of protons in combination with conformal photon therapy; however, investigations into alternative delivery methods, such as proton-based SRS and intensity-modulated proton therapy (IMPT), have shown promise. Photon-based SRS involves the administration of a radioablative dose to the target in either a single fraction or a hypofractionated scheme and has been a mainstay of meningioma radiotherapy for decades. While comprehensive investigations are yet to be completed in the setting of atypical and anaplastic meningiomas, a comparison of proton SRS and photon SRS in the management of brain metastases has suggested that protons have minimal treatment-related toxicity and reduce the integral normal tissue radiation dose. IMPT, as compared to the more common scattered proton therapy, offers increased modulation of radiation deposition proximal to the target and improved conformality of dosage application. Moreover, IMPT administration in small patient cohorts has shown promising results. One case series (15 patients) examined short-term disease control and toxicity profiles in patients with skull base malignancies treated with IMPT. During the 27-month follow-up, none of the patients reported grade 3–5 adverse events, although two patients developed either local or distant disease recurrence. Meningiomas, which often form near the delicate structures easily damaged by ionizing radiation, such as the brainstem and cranial nerves, could be ideal candidates for IMPT use in the future.

In addition to investigations focusing on the development and refinement of radiotherapeutic technology, recent and ongoing clinical studies seek to determine the effectiveness of particle therapy for brain tumors. While particle therapy is well established for the treatment of a number of tumor types, efficacy has not been established in high-grade meningioma. Our review identified 11 studies analyzing outcomes and toxicity associated with particle-based radiotherapy in the setting of high-grade meningioma. However, all of the studies were retrospective analyses, and our analysis of the strength of evidence per OCEBM guidelines revealed a lack of definitive evidence supporting the use of particle therapy in atypical and anaplastic meningioma (Table 1). We also identified five phase I and II clinical trials actively exploring the efficacy and toxicity associated with the use of ions in the management of grade II and III meningiomas; however, results are not expected until 2020 at the earliest (Table 3). The primary outcome evaluated in the majority of the ongoing trials (3/5 studies) is treatment-related complications; the other two studies are assessing toxicity as a secondary outcome. Overall survival is either a primary or secondary endpoint in all five trials, and three of the five trials are also collecting data on progression-free survival. The studied interventions are diverse, with two trials exploring carbon-based radiotherapy and one evaluating proton radiotherapy in combination with immunotherapy. Results from these studies, in combination with future phase III trials, are critical for improving our understanding of the role of particle therapy in the setting of high-grade meningioma.

**Considering the Cost-Effectiveness of Particle Therapy**

Ongoing concerns regarding particle therapy are centered around patient access and treatment cost. While the US has yet to construct a clinically operational heavy ion therapy center, the number of proton centers has expanded from six 10 years ago to thirty-one as of February 2019 (https://www.ptcog.ch/index.php/facilities-in-operation). However, insurance approval for proton radiotherapy remains challenging and could pose significant hurdles to the timely delivery of this treatment. Other logistical hurdles to particle radiotherapy, such as upfront treatment cost, could also pose formidable barriers. Statistical modeling of the expected lifetime costs associated with proton therapy for pediatric medulloblastoma offers optimism, with some studies suggesting an eightfold reduction in costs given the reduced incidence of treatment-related adverse events. However, upfront costs for proton radiotherapy remain high. Furthermore, cost-effectiveness studies of proton therapy in CNS malignancies have been largely limited to pediatric medulloblastoma with no cost-effectiveness studies published on the treatment of grade II and III meningiomas specifically.

**Limitations and Future Directions for Study**

Our systematic review on particle radiation therapy for grade II and III meningiomas included eleven studies with various cohort sizes, five of which were specific for high-grade meningiomas. Selection bias and confounding factors related to patient inclusion and treatment selection are inherent to retrospective studies, particularly those on uncommon diseases or treatment modalities without standardization of care. Furthermore, our systematic review is limited to the type of analyses each study included, making it potentially difficult to make generalizable conclusions regarding local control and overall survival without future prospective and randomized studies. The strengths of our review include its focus on describing particle radiation therapy as an alternative treatment option for high-risk meningiomas, which are more difficult to manage than their benign counterpart.

**Conclusions**

In summary, our systematic review about particle radiotherapy for grade II and III meningiomas suggests that particle radiation, whether as proton or carbon ions in combination with photons or as stand-alone therapy, is an acceptable alternative to photon therapy in terms of survival benefit and risk profile. High-grade meningiomas are difficult to manage, and the addition of proton or carbon radiation results in relatively high rates of local control.
and overall survival specifically in atypical and anaplastic meningioma cohorts. More data need to be collected to inform the optimal dosing strategy given the variability (operator dependent) in the median doses administered. Overall, particle radiotherapy carries benefit and is safe for patients with aggressive forms of meningioma. Given the current limits of few studies with small cohorts, additional studies, especially pending prospective trials, are certainly warranted to investigate the utility of particle radiotherapy as an additional treatment option for grade II and III meningiomas.

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References

1. Adeberg S, Harrabi SB, Bougaf N, Bernhardt D, Rieber J, Koerber SA, et al: Intensity-modulated proton therapy, volumetric-modulated arc therapy, and 3D conformal radiotherapy in anaplastic astrocytoma and glioblastoma: a dosimetric comparison. *Strahlenther Onkol* 192:770–779, 2016
2. Adeberg S, Harrabi SB, Bougaf N, Verma V, Windisch P, Bernhardt D, et al: Dosimetric comparison of proton radiation therapy, volumetric modulated arc therapy, and three-dimensional conformal radiotherapy based on intracranial tumor location. *Cancers (Basel)* 10:10, 2018
3. Aghi MK, Carter BS, Cosgrove GR, Ojemann RG, Amin-Strahlenther Onkol 192:770–779, 2016
4. Aizer AA, Arvold ND, Catalano P, Claus EB, Golby AJ, Johnson MD, et al: Adjuvant radiation therapy, local recurrence, and the need for salvage therapy in atypical meningioma. *Neuro Oncol* 16:1547–1553, 2014
5. Arvold ND, Niemierko A, Broussard GP, Adams J, Fullerton B, Loefller JS, et al: Projected second tumor risk and dose to neurocognitive structures after proton versus photon radiotherapy for benign meningioma. *Int J Radiat Oncol Biol Phys* 83:e495–e500, 2012
6. Athar BS, Paganetti H: Comparison of second cancer risk due to out-of-field doses from 6-MV IMRT and proton therapy based on 6 pediatric patient treatment plans. *Radiother Oncol* 98:87–92, 2011
7. Atkins KM, Pashtan IM, Bussière MR, Kang KH, Niemierko A, Daly JE, et al: Proton stereotactic radiosurgery for brain metastases: a single-institution analysis of 370 patients. *Int J Radiat Oncol Biol Phys* 101:820–829, 2018
8. Attia A, Chan MD, Mott RT, Russell GB, Seif D, Daniel Bourland J, et al: Patterns of failure after treatment of atypical meningioma with gamma knife radiosurgery. *J Neurooncol* 108:179–185, 2012
9. Backer-Gröndahl T, Moen BH, Torp SH: The histopathological spectrum of human meningiomas. *Int J Clin Exp Pathol* 5:231–242, 2012
10. Boskos C, Feuvret L, Noel G, Habrand JL, Pommier P, Alapetite C, et al: Combined proton and photon conformal radiotherapy for intracranial atypical and malignant meningioma. *Int J Radiat Oncol Biol Phys* 75:399–406, 2009
11. Brown WR, Thore CR, Moody DM, Robbins ME, Wheeler KT: Vascular damage after fractionated whole-brain irradiation in rats. *Radiat Res* 164:662–668, 2005
12. Chan AW, Bernstein KD, Adams JA, Parambi RJ, Loefller JS: Dose escalation with proton radiation therapy for high-grade meningiomas. *Technol Cancer Res Treat* 11:607–614, 2012
13. Chen WC, Magill ST, Wu A, Vasudevan HN, Morin O, Aghi MK, et al: Histopathological features predictive of local control of atypical meningioma after surgery and adjuvant radiotherapy. *J Neurosurg* 130:443–450, 2018
14. Cho M, Joo JD, Kim IA, Han JH, Oh CW, Kim CY: The role of adjuvant treatment in patients with high-grade meningioma. *J Korean Neurosurg Soc* 60:527–533, 2017
15. Coke CC, Corn BW, Werner-Wasik M, Xie Y, Curran WJ Jr: Atypical and malignant meningiomas: an outcome report of seventeen cases. *J Neurooncol* 39:65–70, 1998
16. Combs SE, Edler L, Burkholder I, Rieken S, Habermehl D, Jäkel O, et al: Treatment of patients with atypical meningiomas Simpson grade 4 and 5 with a carbon ion boost in combination with postoperative photon radiotherapy: the MARCIE trial. *BMC Cancer* 10:615, 2010
17. Combs SE, Hartmann C, Nikoghosyan A, Jäkel O, Karger CP, Haberer T, et al: Carbon ion radiation therapy for high-risk meningiomas. *Radiother Oncol* 95:54–59, 2010
18. Combs SE, Kessel K, Habermehl D, Haberer T, Jäkel O, Debus J: Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base. *Acta Oncol* 52:1504–1509, 2013
19. Combs SE, Welzel T, Habermehl D, Rieken S, Dittmar JO, Kessel K, et al: Prospective evaluation of early treatment outcome in patients with meningiomas treated with particle therapy based on target volume definition with MRI and 68Ga-DOTATOC-PET. *Acta Oncol* 52:514–520, 2013
20. Ding X, Zhou J, Li X, Blas K, Liu G, Wang Y, et al: Improving dosimetric outcome for hippocampus and cochlea sparing whole brain radiotherapy using spot-scanning proton arc therapy. *Acta Oncol* 58:483–490, 2019
21. El-Khatib M, El Majdoub F, Hoevels M, Kocher M, Müller RP, Steiger HJ, et al: Stereotactic LINAC radiosurgery for incompletely resected or recurrent atypical and anaplastic meningiomas. *Acta Neurochir (Wien)* 153:1761–1767, 2011
22. El Shafie RA, Czech M, Kessel KA, Habermehl D, Weber D, Rieken S, et al: Clinical outcome after particle therapy for meningiomas of the skull base: toxicity and local control in patients treated with active rasterscanning. *Radiat Oncol* 13:554, 2018
23. El Shafie RA, Czech M, Kessel KA, Habermehl D, Weber D, Rieken S, et al: Evaluation of particle radiotherapy for the re-irradiation of recurrent intracranial meningioma. *Radiat Oncol* 13:86, 2018
24. Fang P, Jiang W, Allen P, Glitza I, Guha N, Hwu P, et al: Radiation necrosis with stereotactic radiosurgery combined with CTLA-4 blockade and PD-1 inhibition for treatment of intracranial disease in metastatic melanoma. *J Neurooncol* 133:595–602, 2017
25. Fetcko K, Lukas RV, Watson GA, Zhang L, Dey M: Survival and complications of stereotactic radiosurgery: A systematic review of stereotactic radiosurgery for newly diagnosed and recurrent high-grade gliomas. *Medicine (Baltimore)* 96:e2839, 2017
26. Frytak S, Shaw JN, O’Neill BP, Lee RE, Eagan RT, Shaw EG, et al: Leukoencephalopathy in small cell lung cancer patients receiving prophylactic cranial irradiation. *Am J Clin Oncol* 12:27–33, 1989
27. Fuller GN: The WHO Classification of Tumours of the Adult Central Nervous System, 4th edition. *Arch Pathol Lab Med* 132:906, 2008
28. Gondi V, Hermann BP, Mehta MP, Tomé WA: Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *Int J Radiat Oncol Biol Phys* 85:348–354, 2013
et al: World Health Organization grade III (nonanaplastic) meningioma: experience in a series of 23 cases. World Neurosurg 112:e754–e762, 2018
67. Zhang M, Ho AL, D’Astous M, Pehdharkar AV, Choi CY, Thompson PA, et al: CyberKnife stereotactic radiosurgery for atypical and malignant meningiomas. World Neurosurg 91:574–581, 581.e1, 2016

Disclosures
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Author Contributions
Conception and design: Wu, Jin, Meola, Chang. Acquisition of data: Wu, Jin, Wong. Analysis and interpretation of data: Wu, Jin. Drafting the article: Wu, Jin. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Wu. Study supervision: Chang.

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