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Efficacy and toxicity of bimodal radiotherapy in WHO grade 2 meningiomas following subtotal resection with carbon ion boost: Prospective phase 2 MARCIE trial

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Abstract

Background. Novel radiotherapeutic modalities using carbon ions provide an increased relative biological effectiveness (RBE) compared to photons, delivering a higher biological dose while reducing radiation exposure for adjacent organs. This prospective phase 2 trial investigated bimodal radiotherapy using photons with carbon-ion (C12)-boost in patients with WHO grade 2 meningiomas following subtotal resection (Simpson grade 4 or 5).

Methods. A total of 33 patients were enrolled from July 2012 until July 2020. The study treatment comprised a C12-boost (18 Gy [RBE] in 6 fractions) applied to the macroscopic tumor in combination with photon radiotherapy (50 Gy in 25 fractions). The primary endpoint was the 3-year progression-free survival (PFS), and the secondary endpoints included overall survival, safety and treatment toxicities.

Results. With a median follow-up of 42 months, the 3-year estimates of PFS, local PFS and overall survival were 80.3%, 86.7%, and 89.8%, respectively. Radiation-induced contrast enhancement (RICE) was encountered in 45%, particularly in patients with periventricularly located meningiomas. Patients exhibiting RICE were mostly either asymptomatic (40%) or presented immediate neurological and radiological improvement (47%) after the administration of corticosteroids or bevacizumab in case of radiation necrosis (3/33). Treatment-associated complications occurred in 1 patient with radiation necrosis who died due to postoperative complications after resection of radiation necrosis. The study was prematurely terminated after recruiting 33 of the planned 40 patients.

Conclusions. Our study demonstrates a bimodal approach utilizing photons with C12-boost may achieve a superior local PFS to conventional photon RT, but must be balanced against the potential risks of toxicities.

Key Points

1. Bimodal radiotherapy with a C12-boost can achieve excellent local tumor control in WHO grade 2 meningiomas after subtotal resection.
2. Radiation-induced contrast enhancement (RICE) and/or necrosis was frequently encountered, particularly in periventricular regions.

Graphical Abstract

Phase 2 - MARCIE trial

Radiotherapy with carbon-ion boost in subtotally resected WHO grade 2 meningiomas

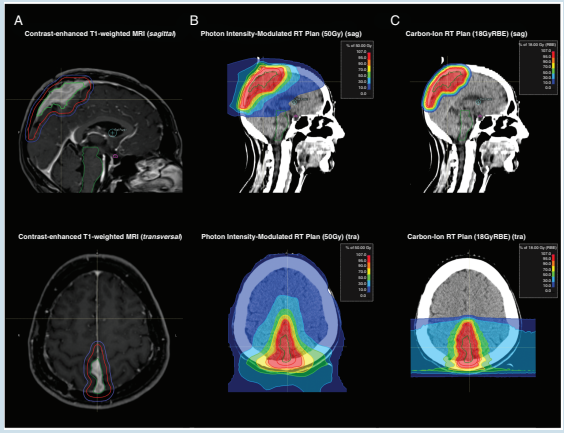
TREATMENT DESIGN

Combination of

Carbon-ion boost:
- 18 Gy [RBE] in 6 fractions

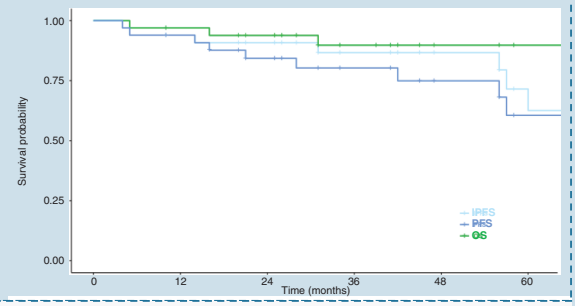
photon radiotherapy
- 50 Gy in 25 fractions

TREATMENT PLAN AND OUTCOME (n = 33)

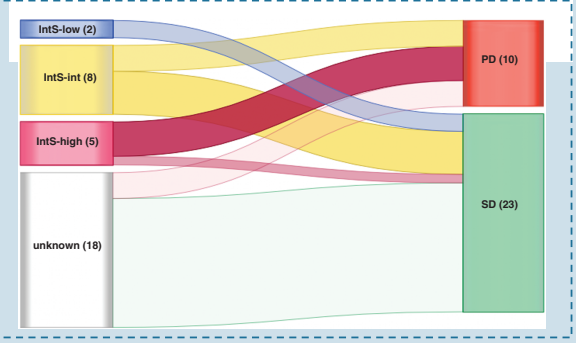


[PANEL ABOVE].
Exemplary **photon and carbon-ion treatment plan** for study patient MARCIE-33.

[RIGHT PANEL].
Integrated Morphologic-Molecular Scoring (Int-low, -int, -high) (Maas et al. 2021) predicts risk of tumor progression following study treatment.



3-year estimates of **PFS: 80.3%**, **local PFS: 86.7%** and **OS: 89.8%.**



Deng et al.

Importance of the Study

Novel radiotherapeutic modalities including protons and carbon ions provide a physical dose superiority and increased relative biological effectiveness (RBE)—as compared to conventional photon RT—enabling a reduction in the integral radiation dose exposure of the surrounding organs at risk.

Our study demonstrates that bimodal RT with a dose of 50 Gy photons and 18 Gy (RBE) C12-boost can achieve an excellent local PFS with a 3-year local progression-free survival of 86.7% in WHO grade 2 meningiomas following subtotal resection. Radiation-induced contrast enhancement (RICE) was encountered in 45% of patients, particularly in periventricular regions. However, patients exhibiting RICE were mostly either asymptomatic or presented immediate neurological and radiological improvement after the administration of corticosteroids.

Our study indicates that bimodal therapy may be considered for well-selected patients with molecularly confirmed, higher-risk meningiomas, a sufficient distance (>5 mm) from the cerebral ventricles to seek improved local tumor control.

Meningiomas represent the most common primary brain tumor type, comprising approximately 15–26% of all i.c., neoplasms.[1–3] While 80% of meningiomas display a benign clinical behavior and can generally be cured by resection alone, around 20% of meningiomas recur after resection. For this aggressive subset, additional treatment is often recommended, including further surgery, radiotherapy and/or chemotherapy.[4] The current WHO classification of CNS tumors recognizes 3 grades in meningiomas, which generally correspond to the degree of malignant behavior, ranging from WHO grades 1 to 3.[1–3] Historically, meningioma grading has been largely based on histological criteria (eg mitotic count and brain invasion).

However, a subset of WHO grade 1 meningioma demonstrate tumor progression after initial treatment which cannot be predicted by histological features alone, while some histological grade 2 or 3 meningiomas display unexpectedly favorable local tumor control. In the latest update of the CNS5 WHO classification in 2021, additional molecular alterations were introduced into meningioma grading, reflecting an increasing understanding of the molecular landscape.[2,4,5] Various molecular classification systems have been established on the basis of DNA methylation profiling, recurring somatic short variants, copy-number variants (CNV), and differentially expressed genes—or a combination of both molecular and histological parameters.[6–13] For instance, the integrated meningioma score (IntS) comprises histological grading, CNVs, and DNA methylation family,[10] while other systems amalgamate CDKN2A/B status, histological grading and CNVs,[9] or CNVs, DNA methylation profiling, RNA, and DNA sequencing.[8,11] While the identification of molecular risk factors was generally retrospective in design, independent testing in validation cohorts will be required to further advance the adoption of molecularly-based risk prediction in meningiomas, as implemented for the EORTC 22042–26042 trial on WHO grades 2 and 3 meningiomas undergoing adjuvant high-dose radiotherapy.[5] In the context of postoperative radiotherapy response prediction, a recent publication from Chen et al. has demonstrated the utility of a targeted gene expression biomarker in discriminating meningioma outcomes.[7]

Historically, high-risk meningiomas were reported to display a local control range between 40% and 70% following primary tumor resection.[1,14–17] Patients having undergone nonradical resection show significantly worse outcomes relative to patients who underwent radical neurosurgical resection.[18] The extent of tumor resection can be assessed after neurosurgical intervention with postoperative MRIs and is categorized by the Simpson grading system, with Simpson grade 4 or 5 exhibiting a significantly worse outcome compared to patients with radical neurosurgical resection (Simpson grades 1–3).[18–20] Radiotherapy represents an integral component in the therapeutic armamentarium for the management of patients with meningiomas either not safely amenable to surgery or after incomplete surgical resection.[4] Current EANO guidelines provide class 3 evidence on the use of fractionated RT (postoperatively) in atypical meningiomas.[4] At the time of study initiation, patients of nonradical resection (Simpson grades 4 and 5) were reported to show significantly worse outcomes than patients with nonbenign meningiomas after radical neurosurgical resection: treated with surgery alone, local recurrence rates were reported to be approximately 50% for subtotal excised, and 90% for completely resected patients at 3 years.[17]

Novel radiotherapeutic modalities including protons and carbon ions represent an auspicious alternative.[21,22] Radiotherapy (RT) with charged particles provides a higher absorbed dose in the tumor via the Bragg Peak while reducing the integral radiation dose exposure of normal tissue, including adjacent organs at risk. Furthermore, heavy charged particles (eg carbon ions, C12) display an increased relative biological effectiveness (RBE) relative to photons and therefore offer higher efficacy which is particularly advantageous in radioresistant tumors.[23–25] Our previous phase I/II trial performed at the GSI Helmholtz Centre for Heavy Ion Research analyzed the efficacy of a bimodal radiotherapy in 10 patients with high-risk meningiomas. In this study, a C12-boost with 18 Gy (RBE) in single doses of 3 Gy (RBE) to the macroscopic tumor was used in combination with precision photon radiotherapy delivered as intensity-modulated radiotherapy (IMRT) or fractionated stereotactic radiotherapy (FSRT) with a total dose of 50.4 Gy in 28 fractions.[26] With a 5-year progression-free survival rate of 86%, the study displayed a favorable clinical outcome, particularly in light of the presence of macroscopic residual tumor at the time of RT.[26] Further studies analyzing the role of proton and C12-RT for the treatment of atypical and anaplastic meningiomas are listed in Supplementary Table 1.

Based on the aforementioned results, the phase II MARCIE trial was conducted to investigate the effectiveness of a C12-boost in combination with photon RT in patients with atypical meningiomas.[26] Moreover, integrated molecular-morphologic risk scoring was performed to contextualize the clinical outcome by molecular subgroup.[10,13]

Methods

Study Design and Patient Selection[26]

The primary endpoint of this study was 3-year progression-free survival. Secondary endpoints include overall survival, toxicity, and safety. The study was performed as a single institution single-armed phase II trial. Detailed inclusion and exclusion criteria can be reviewed from the initial publication of the study protocol.[26] In brief, patients with histologically confirmed, WHO grade 2 meningiomas with macroscopic tumor following subtotal resection, defined as Simpson grade 4 or 5, were included. The study was designed to demonstrate that carbon ion boost in combination with postoperative photon radiotherapy can improve the progression-free survival rate after 3 years by 20%. The benchmark for the largest 3-year PFS which, if true, implies that the efficacy of study treatment is too low is assumed to be 50% according to literature data with a comparable patient population which was available in 2012 during study initiation.[17] The study treatment was initially envisaged to start <12 weeks following surgical resection as early adjuvant treatment ($n = 13$), but time-to-study-treatment was subsequently broadened to include

late adjuvant treatment ($n = 20$), with the aim of reflecting clinical real-world data in meningioma management, as the timing of radiotherapy following surgery still remains controversial.[27] GTV prior to radiotherapy was compared to the initial tumor volume visible on the first postoperative MRI to assess growth dynamics during latency time. Patients fulfilling the inclusion criteria received a carbon ion boost of 18Gy (RBE) in single doses of 3 Gy (RBE) to the macroscopic tumor, in combination with photon radiotherapy delivered as intensity-modulated (IMRT) or 3D-conformal (3DCRT) radiotherapy with a dose of 50 Gy in 25 fractions. All patients received the same treatment regimen in this study. The enrollment of 40 patients fulfilling the aforementioned criteria was initially proposed. The study was prematurely terminated in July 2020 after recruiting 33 of the initially planned 40 patients due to 1 treatment-associated death. An interruption exceeding 4 days between the end of photon RT and the C12-boost was not allowed in this trial.

Following RT, the patients were initially scheduled for follow-up visits every 3 months (or earlier depending on their clinical condition), which included a contrast-enhanced MRI and clinical-neurological assessment.

Treatment Planning and Dose Prescription

Treatment planning was performed using contrast-enhanced CT- and MR-imaging for target delineation. While the GTV solely consisted of the visible macroscopic tumor, defined by the nodular contrast enhancement in MR imaging, the clinical target volume (CTV) comprised the pre and/or postoperative tumor bed, peritumoral edema, hyperostotic changes with possible bone infiltration, and the adjacent dural enhancement or thickening (eg dura tail) identified on CT/MRI. An additional margin of up to 1 cm on the GTV was added to define CTV1. Finally, an isotropic margin of 3–5 mm was added to the CTV1 to form the (photon) planning target volume (PTV1). Radiotherapy with photons was delivered as 3DCRT or with IMRT. The carbon ion boost was delivered to the GTV including the area of contrast enhancement on T1-weighted MR-imaging. The CTV2 for the C12-boost was defined by adding a safety margin of up to 6 mm to the GTV plus an additional isotropic 2–3 mm to create the planning target volume (PTV2) (Figure 1). Margins were adapted respecting anatomical borders with respect to the brain parenchyma and/or organs at risk. The photon RT was planned with the systems available at that time (including HELAX-Masterplan/Nucletron and RayStation). Treatment plans for the C12-boost were generated using Syngo PT-Planning (Siemens) and Raystation with biological plan optimization. Biological plan optimization was calculated using the LEM I model.[28] The Heidelberg Ion Therapy Beam Center (HIT) uses digital X-ray technology, which provides 2 orthogonal images of the skull, referenced to the treatment plan. The robotic treatment table allows a translation in 6 directions, including translational and rotational movements which facilitates an optimal positioning with less than 1mm positioning uncertainties possible. Image guidance for photon radiotherapy was performed using conventional 3D-cone beam CT.

Follow-up and Survival Analysis

After completion of treatment, no further adjuvant therapy was scheduled. In case of tumor progression, subsequent treatment options (eg neurosurgical resection, chemotherapy, reirradiation, etc.) were explored individually and discussed in an interdisciplinary setting. Clinical neurological examination and neuroimaging (MRI or CT scans) were regularly performed, according to the study protocol. The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used to assess treatment toxicity and adverse events. PFS was determined from the start date of radiotherapy until tumor progression or death. Progression was determined according to the guidelines by the Response Assessment in Neuro-Oncology Working Group (RANO).[29] Furthermore, local progression-free survival (l-PFS) was defined as tumor progression within the PTV of the C12-boost with an additional margin of 5 mm. Overall survival (OS) was defined from the start date of radiotherapy until the last follow-up or death. Radiation-induced contrast enhancement (RICE) was classified as new posttreatment contrast enhancement on MRI in surrounding brain tissue within the 80% isodose line analogous to RANO criteria during the follow-up period. Cases were evaluated using all available MRIs, radiation treatment plans, and medical records that reflect time course and concurrent therapies.[30] Radiation necrosis was defined as the subset of symptomatic corticosteroid-refractory RICE, which required subsequent therapy (eg bevacizumab), according to the national DEGRO practical guideline for CNS radiation necrosis part 1: Classification and a multi-step approach for diagnosis[31] and part 2: Treatment of the German Society for radiation oncology.[32]

Statistics

Overall survival (OS) and progression-free survival (PFS) were evaluated by Kaplan–Meier analysis. A P-value < .05 was considered significant. Safety and treatment tolerability were assessed according to the clinical criteria presented in the NCI CTCAE Version 4.0. Binary and categorical patient characteristics between subgroups were compared via a 2-sided Fisher's exact test. The study was designed to demonstrate that carbon ion boosts in combination with postoperative photon radiotherapy may improve the PFS rate after 3 years (PFS-3yR) by 20%, as compared to the available data in 2012, where patients with nonbenign meningiomas treated with surgery alone, local recurrence rates are 50% for subtotal excised, and 90% for completely resected patients at 3 years.[17]

Further statistical considerations and sample size calculations were listed in the Supplements and in the initial study protocol in Combs et al.[33]

DNA Methylation Profiling and Molecular Risk Scoring

The Illumina Infinium HumanMethylation450 (450k) or MethylationEPIC (EPIC) arrays were applied to generate genome-wide DNA methylation profiles, as previously described.[5,13,34] Meningioma methylation class families were determined by the highest scoring family score as obtained

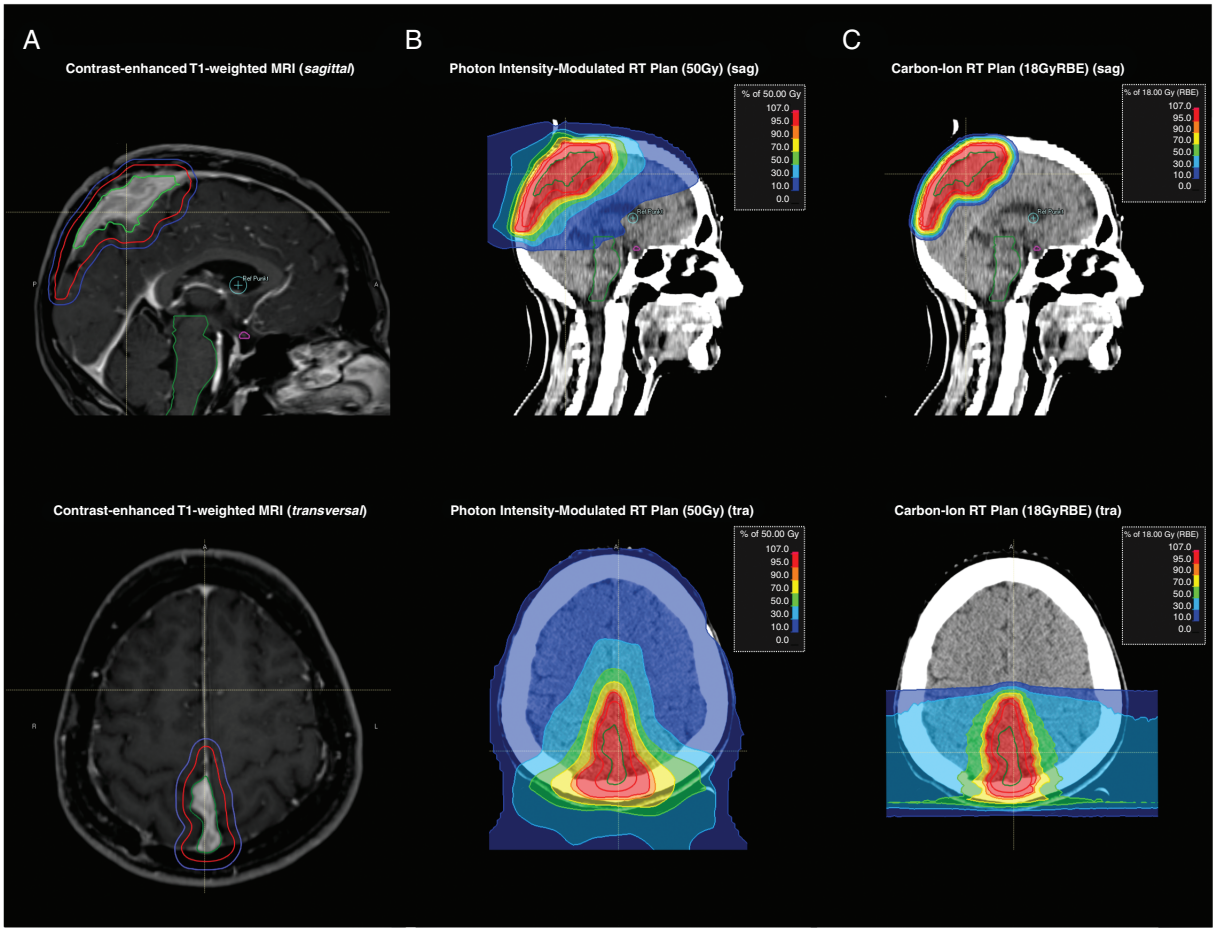


Figure 1. Exemplary photon and carbon-ion treatment plan for study patient MARCIE-33. (A) Visible macroscopic residual tumor parafalcine on contrast-enhanced T1-weighted MRI. The circled lines represent gross total volume (GTV) in green, clinical target volume (CTV2) in red, and the planning target volume in blue (PTV2) for the carbon ion boost. The dose distribution of the photon treatment plan (total dose of 50 Gy in 25 fractions) (B) and the carbon-ion boost (total dose of 18 Gy RBE in 6 fractions) (C) are shown with colored zones indicating the dose range in the surrounding brain parenchyma and skull.

from the v12.5 DKFZ brain tumor classifier[34] at www.molecularneuropathology.org. Copy-number variation (CNV) analysis from 450k and EPIC methylation array data was performed using the consumer Bioconductor package version 1.12.0. Further, Integrated Model Scores (IMS) were calculated by summarizing the respective scores of methylation family (range: 0–4), WHO grading (range: 0–2) and chromosomal losses of 1p, 6q, and/or 14q (range: 0–3) and defined as low (0–2), intermediate (3–5), and high (>5), as previously described.[10] Additional assignment using independent methylation-based classification systems, as previously described by Choudhury et al. (2022)[8] and Driver et al. (2022),[9] was performed using publicly available platforms, by investigators who developed these systems or by applying the grading score listed in the publication.

Ethical Considerations

All participants provided written informed consent. The study complied with the Declaration of Helsinki and the Ethics Committee of the University Clinic Center Heidelberg approved the protocol (S-444/2009). The study was registered in the ClinicalTrials Registry (EuduratCT No. 2009-016683-36).

Results

Clinical Patient and Tumor Characteristics

Study recruitment was initiated in July 2012 and prematurely terminated in July 2020 after enrolling 33 of the initially planned 40 patients due to treatment-associated death in 1 case. Median KPS was 90% (range: 70–100%) in the study cohort. The majority of meningiomas (66.7%) emerged along the meninges of the cerebral hemispheres. A subset of meningiomas were at the sphenoid wing (15.2%), the cerebellum (12.1%) and the skull base (3.0%). The location was considered periventricular (maximum distance of 5 mm to the cerebral ventricles) in 51.5% (17/33)

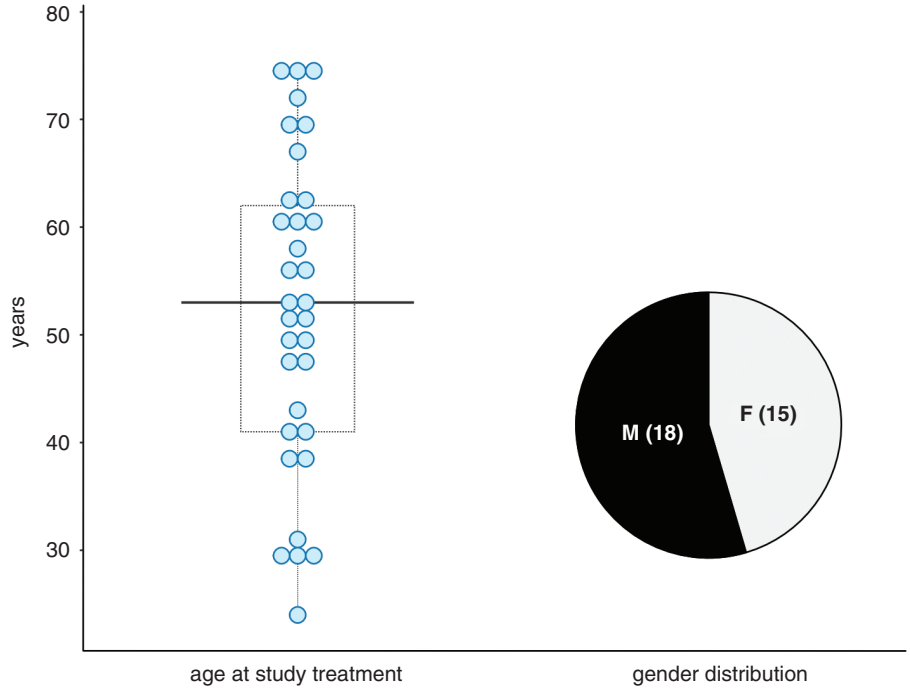


Figure 2. Clinical patient characteristics in the MARCIE study cohort. Clinical parameters including age at study treatment and gender distribution are illustrated, with numbers in circles indicating group sizes.

cases. The median age at the time of treatment initiation was 53 years (range: 29–75 years), and 54.5% of all study patients were male (Figure 2). According to the study protocol, all patients were diagnosed with a WHO 2 meningioma, according to WHO 2016 or 2007 guidelines. Median time-to-study-treatment was 6 months (range: 1–45 months) following surgical resection. According to RANO criteria,[29] all patients ($n = 13$) in the early adjuvant group (<12 weeks) and 12/20 late adjuvant patients showed stable disease between postoperative baseline-MRI and the start of RT, measured in the RT-planning MRI. In the late adjuvant group ($n = 20$), stable disease on MRI was further reported in 3/20 additional patients, however, with worsening clinical status during the time period—thus formally qualifying as progressive disease. The median time from surgery to the start of radiotherapy was 13 months (range: 4–46 months) in the late adjuvant group. Progressive disease on imaging was encountered in 5/20 patients prior to the start of RT after 27, 27, 36, 39, and 46 months, respectively. Median GTV prior to radiotherapy was 11 mL (range: 1.31–144.89 mL). Further clinical and histopathological characteristics and residual GTVs are listed in Supplementary Table 3.

Treatment Toxicities

There were no acute toxicities exceeding CTCAE grade 3 observed during radiotherapy or within 3 months after completion of the study treatment. Frequently encountered acute symptoms are illustrated in Table 1.

Regarding late toxicities, seizures were reported in 4 patients during follow-up, which were adequately managed by anticonvulsant treatment adjustment. Anticonvulsant treatment was administered perioperatively in 42.4% of patients. Motor (12%) and sensory deficits (27%) were encountered as late or chronic toxicity, often simultaneously with the occurrence of RICE. In fact, the first sign of radiation injury was typically presented as an increase in the T2-FLAIR signal corresponding to edema prior to RICE. However, all of our study patients—with or without RICE—displayed T2-FLAIR signals in the high-dose region. The median latency period between the end of study treatment and RICE was 12.5 months (range: 4–45 months) (Table 2).

Patients with periventricular lesions ($n = 17$) (maximum distance of 5 mm between PTV-margin and ventricles) were at a particularly elevated risk, with RICE observed in 11/17 (65%) cases following study treatment. In comparison, only 4 patients (4/16, 25%) with non periventricular located meningiomas were affected by RICE (Supplementary Table 2, $P < .05$). There was no clear correlation between the boost volume (PTV) and the likelihood of RICE (Supplementary Figure 1). Therapeutic management of RICE was dictated by the severity of symptoms. Asymptomatic patients ($n = 6$) were observed and subjected to close clinical and radiological monitoring every 6–12 weeks. An oral corticosteroid therapy (eg dexamethasone) was administered in 9 patients with RICE presenting neurological symptoms (eg headache, dizziness, sensory or motoric deficits, etc.), typically with 8–16 mg/day with a gradual dose reduction. A clinical and radiological improvement was observed in 56% (5/9) of patients following oral corticoid therapy. However, a subsequent VEGF inhibition with bevacizumab (7.5 mg/kg, every 2 weeks) was

Table 1. Acute Toxicities Following Study Treatment

Symptoms	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3	CTCAE Grade > 3
Headache	6% (2/33)	6% (2/33)	3% (1/33)	–
Dizziness	1% (1/33)	6% (2/33)	–	–
Nausea	9% (3/33)	6% (2/33)	–	–
Seizures	–	–	3% (1/33)	
Fatigue	12% (4/33)	6% (2/33)	6% (2/33)	–

Table 2. Late Toxicities Following Study Treatment

Symptoms	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3	CTCAE Grade 4	CTCAE Grade 5
Headache	3% (1/33)	–	–	–	–
Dizziness	6% (2/33)	–	–	–	–
Nausea	–	–	–	–	–
Motoric deficits	3% (1/33)	6% (2/33)	3% (1/33)	–	–
Sensory deficits	6% (2/33)	12% (4/33)	9% (3/33)	–	–
Seizures	–	–	9% (3/33)	3% (1/33)	–
Fatigue	9% (3/33)	3% (3/33)	3% (1/33)	–	–
RICE/RN	18% (6/33)	15% (5/33)	6% (2/33)	3% (1/33)	3% (1/33)

required in 33% (3/9) of the subcohort of patients with steroid-refractory RICE—qualifying as radiation necrosis. Two patients presented a neurological and radiological recovery after 2 and 4 cycles of bevacizumab. However, 1 patient received 21 cycles of bevacizumab following study treatment, with limited success in containing the progression of the radiation necrosis. Furthermore, 1 patient (MARCIE-31) died 5 months following study treatment due to the rapid progression of RN and its subsequent complications (Supplementary Figure 2), without prior administration of oral corticosteroids or VEGF inhibition. Ultimately, this event led to an early termination of the trial in July 2020.

Survival Outcome

The median follow-up time was 42 months (range: 5–109 months). Tumor progression during follow-up was observed in 10 of 33 patients (30.3%), with local progression in 8/10 cases. The remaining 2 patients presented an isolated distant i.c., recurrence, as defined as a new lesion outside the 80%-isodose line. Further distant i.c., recurrences were encountered in the course of the disease in 4 out of 8 patients who presented a local progression beforehand. No intraspinal dissemination was reported.

The 3-year estimates of PFS and IPFS were 80.3% (95% CI 67.2–95.9%) and 86.7% (95% CI 75.2–99.9%), respectively. The 3-year overall survival was 89.8% (95% CI 79.3–100%), with 3 cases of death after 5, 16, and 31 months following study treatment (Figure 3). There was no significant difference in survival outcome between the early adjuvant (with RT < 12 weeks following resection), and late adjuvant (>12 weeks) cohort. Two deaths were the consequence of tumor progression, while 1 death after 5 months was attributed to complications from treatment-induced radiation necrosis (MARCIE-31). After the occurrence of the radiation necrosis, neurosurgical resection at an external center was performed due to a suspected tumor progression, however, upon pathological examination, necrotic brain tissue in the subsequent evaluation was identified. Unfortunately, postoperative complications resulted in a fatal outcome. Consequently, the study recruitment was terminated as a precautionary measure after recruiting 33 of the initially planned 40 patients. To note, RICE-specific treatment with bevacizumab during follow-up was administered in 2 patients chronologically after tumor progression, while 1 patient (MARCIE-27) received bevacizumab 12 months prior to progression, with a potential additional antineoplastic effect in this case.

Molecular-based stratification identified patients at risk for progression[10]

For a subset of cases (15/33) with sufficient tumor tissue, post hoc epigenetic analysis was performed to determine the DNA methylation family and copy-number variations (CNV), according to Maas et al.[10] In brief, IMS were calculated by summarizing the respective scores of methylation family (range: 0–4), WHO grading (range: 0–2) and chromosomal losses of 1p, 6q, and/or 14q (range: 0–3). IMS were defined as low (0–2), intermediate (3–5), and high (>5).[10] DNA methylation profiling revealed that the largest subset (9/15) was assigned to the intermediate-A (int-A) methylation family. Two cases were classified as intermediate-B

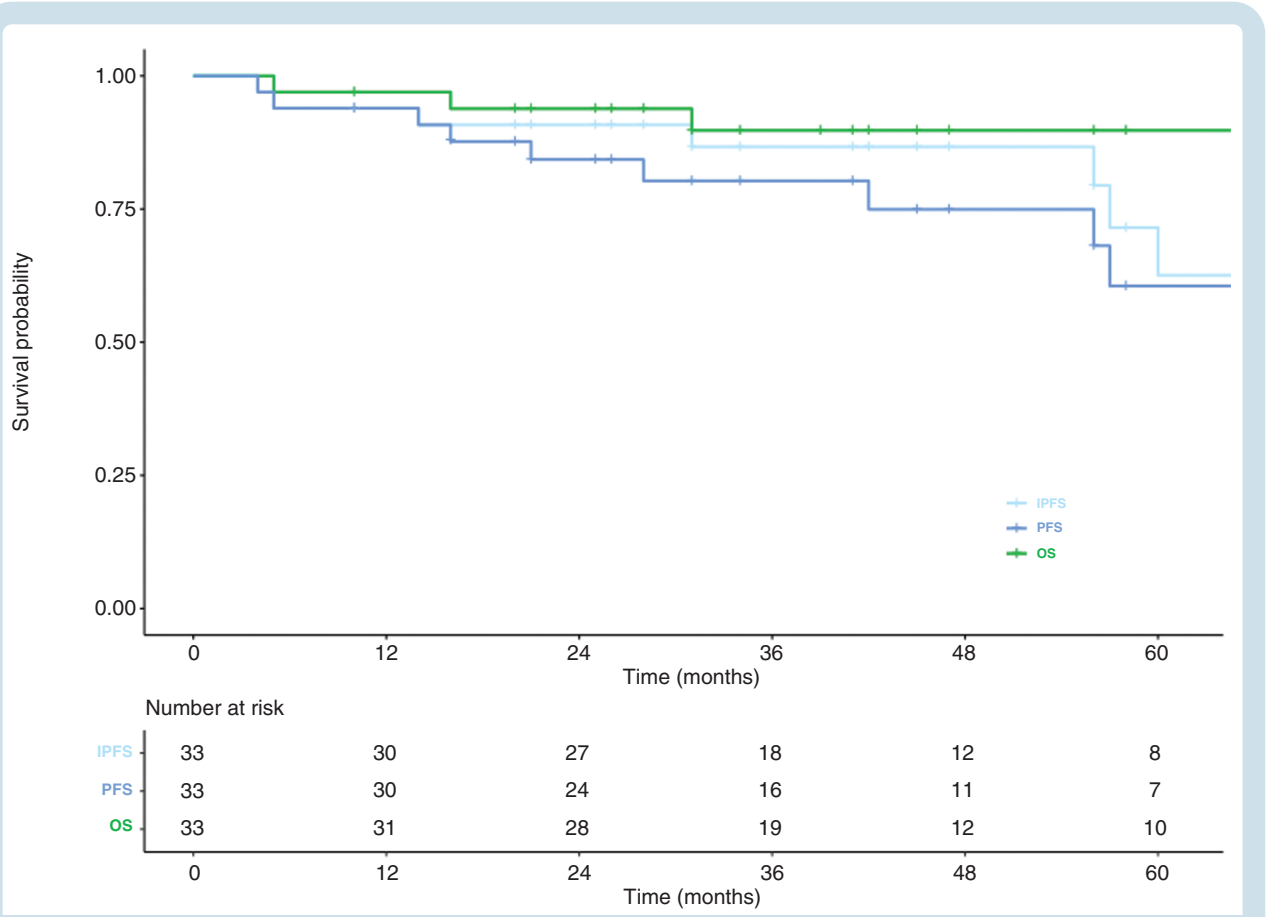


Figure 3. Local progression-free (lPFS), progression-free (PFS), and overall survival (OS) following bimodal radiotherapy. Survival probability was calculated by Kaplan–Meier analysis: 3-year estimates of progression-free survival (PFS) and lPFS were 80.3% (95% CI 67.2–95.9%) and 86.7% (95% CI 75.2–99.9%), respectively. Distant, out-of-field recurrences were excluded in determining lPFS.

(int-B) and 1 case as malignant (mal). Three meningiomas were categorized as benign (ben) based on their methylation profiles. Moreover, CNV-based risk prediction allotted 11/15 meningiomas at a high-, and 4/15 at an intermediate-risk score. Integrated molecular-morphological scores (IMS) were generated by aggregating the WHO grading, CNV score and methylation family (Supplementary Table 3). In total, 5/15 meningiomas were classified as *high*-risk and 8/15 as *intermediate*-risk based on their 3-tiered scores. Notably, 2 WHO grade 2 meningiomas were assigned an integrated score of 1, suggesting a *lower* risk of progression.

The clinical outcome was subsequently contextualized in light of the molecular risk scoring: 2/5 molecular *high*-risk meningiomas demonstrated a local tumor progression exclusively after 87- and 89-months following study treatment. A combination of both local and distant i.c., tumor progression was encountered in 1 *high*-risk case (MARCIE-01), respectively. Another *high*-risk patient (MARCIE-30) demonstrated a distant multifocal i.c., tumor occurrence exclusively after 16 months, with no sign of local progression. For the *intermediate*-risk meningiomas, local tumor control was achieved in 5/8, while tumor progression was observed in 3/8 cases after 4, 57, and 60 months. Tumor progression was not encountered in molecular low-risk meningiomas (0/2) during the follow-up period. In summary, the molecular high-risk meningiomas demonstrated local *or* distant tumor progression in 80% (4/5), the intermediate-risk in 37.5% (3/8), and the low-risk group in 0% of analyzed cases (Figure 4). Molecular data was unavailable in the only patient (MARCIE-27) who received bevacizumab 12 months prior to progression.

Additional comparative analyses using the UCSF (Choudhury et al., 2022[8]) and Boston classifier (Driver et al., 2022[9]) have demonstrated a substantial overlap in identifying patients at risk of progression: all IntS-*high-risk* patients ($n = 5$) were classified as grade 3 (Driver et al., 2022[8]) or hypermitotic (Choudhury et al., 2022[9])—both representing the most aggressive molecular subgroup within their respective classification systems. On the contrary, all IntS-*low-risk* cases corresponded to grade 1 or the immune-enriched subgroup, suggesting a largely congruent evaluation at both ends of the spectrum (Supplementary Table 3).

Discussion

The study cohort, comprising patients with WHO grade 2 meningiomas following subtotal resection and postoperative bimodal radiotherapy, demonstrated a 3-year PFS

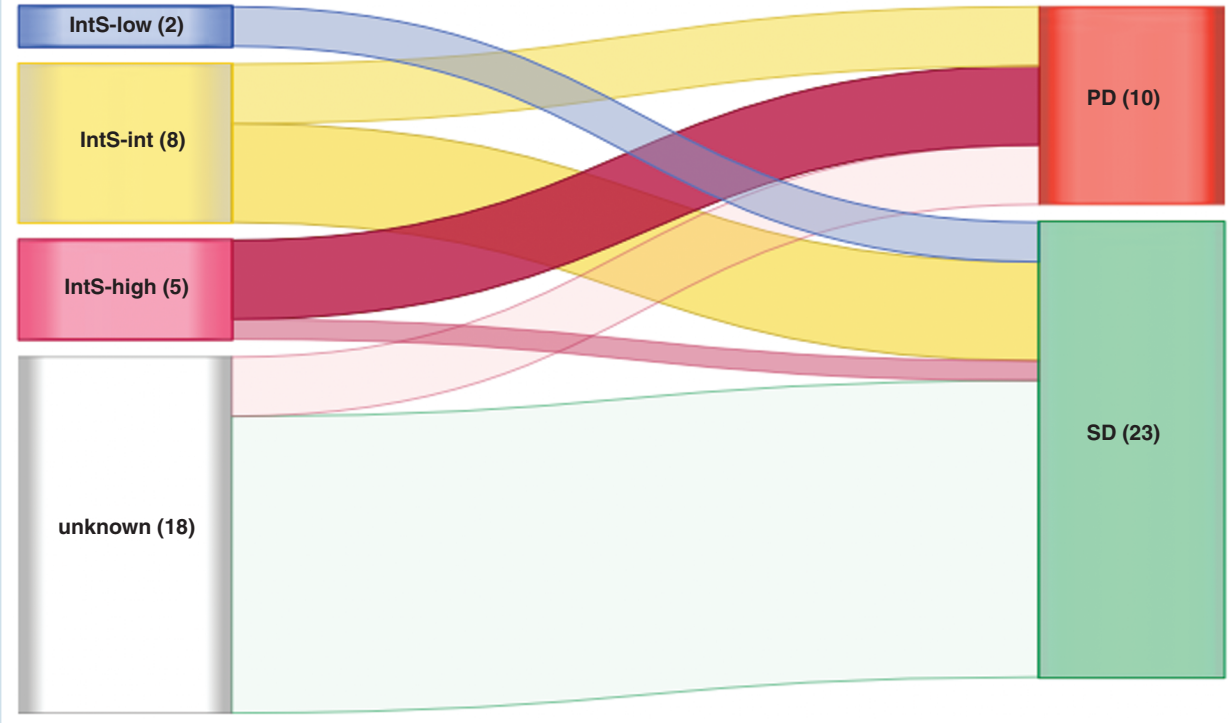


Figure 4. Integrated morphologic-molecular scoring[10] (Int-*low, -int, -high*) predicts risk of tumor progression following study treatment.

and I PFS of 80.3% (95% CI 67.2–95.9%) and 86.7% (95% CI 75.2–99.9%), respectively. The 3-year overall survival was estimated at 89.8% (95% CI 79.3–100%). While study treatment was initially envisaged to start <12 weeks following surgical resection, the time-to-study-treatment was subsequently broadened to reflect clinical real-world data in meningioma management, as the timing of radiotherapy following surgery still remains controversial, as treatment decisions are largely driven by providers and patients.[4,29] At the time of study initiation in 2012, patients of nonradical resection (Simpson grades 4 and 5) were reported to show significantly worse outcomes than patients with nonbenign meningiomas after radical neurosurgical resection: with surgery alone, local recurrence rates were estimated at 50% for subtotal excised, and 90% for completely resected patients at 3 years.[17] Since then, several publications have shown an increase in local tumor control which may be attributed to the technical advancement in surgical and radiotherapeutic management. For high-risk meningiomas comprising recurrent or subtotal resected WHO grade 2, or WHO grade 3 tumors ($n = 53$), the radiation therapy oncology group phase 2 trial (RTOG 0539) has estimated a 3-year local control rate of 68.9%, and an overall 3-year PFS and OS of 58.5% and 78.6%, respectively, following IMRT with 60 Gy in 30 fractions.[15] Of note, the subset of patients with either a subtotal resection WHO grade 2 meningioma ($n = 11$) experienced a 72.7% 3-year PFS in the RTOG 0539 trial, as compared to the improved 3-year local PFS of 86.7% in the current MARCIE trial, which may be regarded with the inherent limitations of a cross-trial comparison.[15] Future volumetric assessments of the high-risk RTOG 0539 patients in question (WHO grade 2, STR)[15] are required to allow an amended comparison between the 2 cohorts.

As to the timing of RT, a multicentered, retrospective Canadian study by Wang et al. comprising 404 meningiomas, has illustrated that meningiomas which received adjuvant RT showed significantly improved local tumor control compared to those that received salvage RT, particularly for WHO grade 2 cases ($n_{\text{WHO grade 2}} = 189$).[27] This observation may be attributed to the enrichment of inherently aggressive meningiomas in the salvage RT group, as opposed to the cohort with immediate adjuvant RT that will likely capture some meningiomas that would not have progressed even without RT. To note, 5/20 patients in the late adjuvant group (>3 months between surgery and RT, $n = 20$) showed tumor progression on MRI prior to radiotherapy, compared to the first postoperative MRI—thus, study treatment may technically be regarded as salvage radiotherapy in these cases. However, in our MARCIE cohort, no difference in survival outcome was reported between the early ($n = 13$) and late adjuvant (or salvage) group, which may—however—be attributed to the small cohort size. Overall, no conclusions can be drawn in regard to the preferable timing of our study treatment (eg immediate vs. late adjuvant) due to the wide range (1–45 months) after resection.

In our study cohort, chronic side effects (eg motor and sensory deficits) were often encountered simultaneously with the occurrence of RICE. A substantial fraction of patients (45%) presented with RICE following study treatment. The administration of RICE-specific therapy using corticosteroids led to a neurological and radiological improvement in 56% of all symptomatic patients. Subsequent treatment escalation

with bevacizumab was required in 3 steroid-refractory patients, formally qualifying as radiation necrosis, resulting in a rapid recovery in 2/3 patients after 2 and 4 cycles. To note, 1 patient (MARCIE-27) received bevacizumab 12 months prior to progression which may represent a confounder in PFS for this particular case due to the additional antineoplastic effect of bevacizumab on meningiomas.[35,36] The clinical response to RICE and radiation necrosis-specific therapy (eg corticosteroids or bevacizumab) was in accordance with recent reports for glioma patients following photon and proton radiotherapy, where clinical regression was encountered in 62% of cases.[30] Interestingly, the wide latency period between radiotherapy and the occurrence of RICE (median: 12.5 months, range: 4-45 months) necessitates a close clinical and radiological follow-up in these patients. While the first sign of radiation injury was generally presented as an increase in the T2-FLAIR signal corresponding to edema, which occurred before the emergence of RICE.[31] However, all of our study patients—with or without subsequent RICE—presented T2-FLAIR signals in the high-dose region, hampering the identification of patients at risk of subsequent RICE based on the T2-FLAIR signal alone.[31,32] Late-occurring RICE were observed after a latency period of up to 45 months following study treatment—a timeframe which could falsely allow the extension of clinical follow-up intervals. Patients with meningiomas located in the periventricular region were at a particularly elevated risk of developing an RICE following study treatment. An association between the risk of RICE and periventricular tumor site was previously described in patients with low-grade glioma following proton radiotherapy: an increased risk of RICE was encountered if the irradiated tumor was located in proximity to the ventricular systems.[37,38] Our data further highlight that caution should be exercised if attempting dose escalation in patients with periventricular located brain tumors, which should be appropriately taken into consideration during treatment planning and clinical follow-up.[37] In summary, we hypothesize the high total biologically effective dose and equivalent dose (EQD2) of 72.5 Gy may be a key element in explaining the frequent occurrence of RICE: with 50 Gy in 2 Gy single dose (photons) and 18 Gy (RBE) in 3 Gy (RBE) single dose (C12) based on an $\alpha/\beta = 2$ for brain tissue.[39]

In general, as RICE presents an immediate response to corticosteroids, radiation necrosis is—per definition—irreversible, if left untreated.[31] Thus, consensus guidelines have suggested considering RICE and radiation necrosis as a continuous spectrum with the risk of a fluent transition from RICE to radiation necrosis in the high-dose-treated region.[31,32] Thus, a differentiation is often only possible with the benefit of hindsight. The inherent diagnostic impreciseness in distinguishing RICE from radiation necrosis may also represent a limitation to our study.

To optimize treatment outcomes and follow-up management, we wish to emphasize that consultation with the primary treatment center may be indispensable in cases of radiation-induced side effects. One fatal event was reported in a study patient (MARCIE-31) due to postoperative complications after neurosurgical resection at an external center in the case of misdiagnosed tumor progression. No radiation necrosis-specific treatment (eg bevacizumab) was initiated before neurosurgical resection. Considering this tragic event, we hope to motivate efforts to foster collaborative approaches to improve patient care in light of the complex therapeutic interventions and nuanced follow-up in the case of radiation-induced side effects.

Current advances in RT methods (Image guidance via Cone beam CT, 6D-table, and IMRT) enable superior image guidance, facilitating a reduction of the CTV2 margin of 6 mm applied in our study, which may be advisable in the future to minimize radiation-induced side effects (eg RICE). Further considerations pertain to the estimation of the RBE of carbon ions: carbon ions typically demonstrate an RBE of 3–5 in the target volume and lower values in the entrance channel. This allows a highly conformal dose delivery with an increase of the RBE-weighted dose in the tumor relative to the surrounding organs at risk.[21,30,40,41] However, recent studies on selected malignancies (eg prostate cancer) have shown that nominally equivalent RBE-weighted doses of carbon ions may result in varying clinical responses, depending on the underlying RBE calculation.[30] Thus, future studies are planned to explore the influence of biological dose calculation in meningiomas, paving the way to a personalized RBE-weighted dose prescription in meningioma patients.

Post hoc DNA methylation-based meningioma classification has identified patients at risk of progression after radiotherapy—an observation which is largely in accordance with previous reports on single institutional cohorts or the multicentered EORTC 22042–26042 trial on WHO grades 2 and 3 meningiomas undergoing adjuvant high-dose radiotherapy.[5] Two study patients classified as IntS-*low-risk* showed no signs of progression, while IntS-*intermediate-* and *high-risk* meningiomas displayed less favorable clinical outcomes, which was largely consistent across the distinct methylation-based classifiers developed in Heidelberg, Boston,[9] and UCSF[8] (Supplementary Table 3). Beyond the DNA methylation-based systems, a recent study by Chen et al. (2023) has demonstrated the predictive power of a targeted gene expression biomarker in identifying primary WHO grade 2 meningiomas, which may display an inherently favorable prognosis where postoperative radiotherapy could be safely omitted in favor of close surveillance.[7] Overall, molecular meningioma classification and integrated risk scoring will be increasingly relevant for the interpretation of current and the design of future clinical trials by enabling the contextualization of trial outcomes according to meningioma biology.[4–12,42]

In conclusion, our study tentatively suggests that dose escalation using bimodal RT with a dose of 50 Gy photons and 18 Gy (RBE) C12-boost may achieve an improved local PFS in patients with WHO grade 2 meningiomas and Simpson grades 4 and 5 with a 3-year local PFS of 86.7%, as compared to 72.7% in the RTOG 0539 trial for sub totally resected WHO grade 2 meningiomas. Thus, a bimodal therapy may be considered for well-selected patients with molecularly confirmed, intermediate- and high-risk meningiomas, a sufficient distance (>5mm) from the cerebral ventricles to seek improved local tumor control.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

carbon ion radiotherapy | meningioma | particle radiotherapy | postoperative radiotherapy | WHO grade 2

Conflict of interest statement

C.K. received honoraria for lectures and editing from the Heidelberg University and Karlsruhe Institute of Technology, Thieme, and Springer. P.H.S. received honoraria from Novocure for participation in the Advisory Board. A.v.D. has licenses and patents for the VE1 (Roche Ventana) and H09 (Dianova) antibodies, and patent pending for the methylation-based tumor classification. A.v.D. is a founder and shareholder of Heidelberg Epignostix GmbH. J.D. received honorary from RaySearch Laboratories, Vision RT Limited, Merck Serono, Siemens Healthcare, PTW-Freiburg Dr. Pychlau and Accuray Incorporated. J.D. is the CEO of the Heidelberg Ion Beam Therapy Center (HIT), and a member of the Board of Directors at the Heidelberg University Hospital.

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Authorship statement

Conceived the strategy: M.D., F.S. S.C., K.H., J.D., L.K.; supervised the project: M.D., S.C., K.H., J.D., L.K.; performed the analysis: M.D., F.H., S.N.M., P.S., F.S. L.K.; provided material, clinical and methodological expertise: C.P.K., P.S., T.E., E.M., J.H.-R., J.L., P.H.-S, K.S., D.B., C.J., A.U., A.W., W.W., A.v.D., F.S., S.C.; wrote the manuscript: M.D., L.K. All authors have seen and approved the manuscript.

Data availability

All code used R 4.1.0 and publicly available packages cited in the paper. Additional data used and/or analyzed will be made available upon reasonable request.

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