Radiation for skull base meningiomas: review of the literature on the approach to radiotherapy

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Abstract: Skull base meningiomas (SBM) pose unique challenges for radiotherapy as these tumors are often in close proximity to a number of critical structures and may not be surgically addressed in many cases, leaving the question about the tumor grade and expected biological behaviour. External beam radiotherapy and radiosurgery are longstanding treatments for meningioma that are typically used as upfront primary therapy, for recurrent tumors and as adjuvant therapy following surgical resection. There is controversy regarding the optimal timing and approach for radiation therapy in various clinical settings such as the role of adjuvant radiotherapy for completely resected grade 2 tumours. Despite the use of radiotherapy for many decades, the evidence to guide optimal radiation treatment is limited largely to single institution series of EBRT, SRS and particle therapy. In this article, we review the published data to clarify the role of external beam radiotherapy, proton radiotherapy and single and multi-fraction radiosurgery for SBM. We also highlight the areas of potential research and need for clinical improvement, including the growing awareness and effort to improve cognitive function in this patient population, who typically have long life expectancy following their meningioma diagnosis.

Keywords: Meningioma; radiation therapy radiosurgery; proton; cognition

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Introduction

Meningiomas are indolent, slow growing tumours that generally arise from the arachnoid cap cells, which surround and adhere to the dura mater and so these tumors can arise from various anatomic regions within the central nervous system (CNS). Skull base meningiomas (SBM) are of particular challenge for radiotherapy due to their proximity to the brainstem, optic apparatus and a number of cranial nerves, posing risk of symptoms as the tumor progresses and greater risk of functional toxicities following local therapies such as surgery and radiation (1,2). SBM can be categorized as being from the anterior or middle cranial fossa (olfactory groove, tuberculum sellae, clinoid, sphenoid, wing and pure cavernous sinus) and from the posterior fossa (petrous, petroclival, jugular foramen, and foramen magnum) (3,4).

The main approaches for management of benign (WHO grade 1) and non-benign (WHO grade 2 and 3) meningiomas include active surveillance/observation, radical surgery, radical or partial surgery followed by radiotherapy, and radiotherapy alone (5). Definitive radiotherapy using conventionally fractionated external beam radiotherapy or
stereotactic radiosurgery (SRS) are generally considered as the primary therapy when the risks outweigh the benefits for surgical resection due to patient comorbidities or if gross total resection is not feasible due to location (proximity to important critical structures). Adjuvant radiotherapy following surgery is recommended for grade 3 tumours and selected cases of grade 1 or 2 tumours. The aim of radiation treatment is to stop or stabilize the growth of the tumor in order to minimize symptom progression. The introduction of intensity modulated radiotherapy (IMRT) and single fraction SRS approaches have played an important role in improving the therapeutic ratio of radiotherapy for SBM by enabling delivery of conformal doses of radiation to cover the tumor while sparing the surrounding normal tissues (6-12) (Figures 1,2).

In this article, we provide a review of the published literature around radiotherapy for SBM, to clarify the role of EBRT, proton radiotherapy, SRS and stereotactic radiotherapy (SRT).

**Fractionated radiotherapy**

Improvements in RT technology and imaging have allowed precise delivery of high dose radiation to CNS lesions. Conventional RT, which typically uses 1.8–2.0 Gy fractions over a 5- to 7-week course, has been dramatically improved with the use of intensity-modulated radiotherapy (IMRT) or volumetric arch therapy (VMAT). These new techniques have improved the conformity of radiation dose delivery so that high-dose coverage can be achieved for the tumor while simultaneously providing better dose sparing of the chiasm, cranial nerves, brainstem, and other adjacent critical organs (e.g., optics nerves, globes or lens) (13,14) (Figure 1).

Evidence to guide the appropriate utilization of radiotherapy in the management of meningiomas remains limited. In clinical practice a number of factors are considered in the decision to proceed with radiation treatment including tumor size, resectability, tumor grade and whether the tumor has recurred following surgery. Additionally patient comorbidities and patient preference is taken into account when deciding whether the initial treatment is with radiation or surgical resection, given the lack of data to suggest one treatment provides better outcomes over the other.

Fractionated radiotherapy is often delivered with SRT immobilization and/or image-guided radiotherapy (IGRT) approaches to optimize the precision of radiation delivery in combination with IMRT techniques to improve the dose shaping around complex targets in close vicinity to critical normal structures. Several studies have shown durable tumor control with 10-year local control (LC) rates of 80% or higher following treatment with fractionated radiotherapy as primary or adjuvant treatment (5,15). In Table 1 we summarize data from published articles on three-dimensional (3-D) conformal or IMRT outcomes for SBM of all grades (7,10,16-21).

Milker-Zabel et al. published outcomes in 94 patients treated with IMRT for SBM (WHO grade 1-3) (7). In this case series, 26 patients had IMRT as primary treatment, 14 patients as postoperative treatment for residual disease and 54 patients as salvage radiotherapy for recurrent disease after initial surgical resection. With a median follow-up of 4.4 years (range, 1.6–82.7 months), the overall LC was 93.6% [69 patients (73.4%) with stable; 19 (20.2%) with a reduction of tumor volume and 6 patients with local tumor progression on MRI]. Pre-existing neurological deficits improved in 39.8% of patients, and worsened in 7.4% of patients (7). Combs et al. reported the long-term outcomes for 507 patients with SBM (WHO grade 1–3) who were treated with high precision radiotherapy defined as radiation treatment delivered either in stereotactic set-up or using IGRT that allowed for planning target volume margins (PTV) of 1–2 mm. A median total dose of 57.6 Gy
(range, 25–68 Gy) was prescribed in median single doses of 1.8 Gy (range, 1.6–5 Gy). With a median follow-up time of 107 months, LC for the full cohort was 95% at 5 years and 88% at 10 years. Quality of life was unchanged or improved in 47.7% or 37.5% of the patients, respectively (10).

**WHO grade 1 (benign) SBM**

For benign SBM, fractionated radiotherapy is clinically most commonly used for large volume, growing and/or symptomatic tumours that are either unresectable or for

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**Figure 2** Representative axial image of a skull base meningioma that has slowly grown over several years, clinically and radiologically consistent with meningioma. It is delineated on a post-gadolinium T1-weighted MRI (left) and a Gamma Knife radiosurgery plan to deliver 18 Gy in a single fraction prescribed to the 50% isodose is demonstrated on the right. Note that NCCN guidelines for grade I meningioma recommend 12–16 Gy single fraction SRS with no confirmed role for SRS for grade II or III meningioma, but many of these small meningiomas never have histological confirmation prior to radiotherapy treatment.

**Table 1** Three-dimensional conformal or intensity modulated radiotherapy outcomes for skull base meningioma

<table>
<thead>
<tr>
<th>Study [year]</th>
<th>Sample (n)</th>
<th>Grade</th>
<th>Previous surgery (%)</th>
<th>RT technique</th>
<th>Median dose</th>
<th>Media follow-up (months)</th>
<th>Local Control (%)</th>
<th>Late toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debus et al. [2001] (16)</td>
<td>189</td>
<td>1 and 2</td>
<td>69</td>
<td>fSRT</td>
<td>56.8</td>
<td>35</td>
<td>Grade 1: 94% at 10 years; Grade 2: 78% at 8 years</td>
<td>12%</td>
</tr>
<tr>
<td>Pirzkall et al. [2003] (17)</td>
<td>20</td>
<td>1</td>
<td>80</td>
<td>IMRT</td>
<td>57</td>
<td>36</td>
<td>100% at 3 years</td>
<td>0</td>
</tr>
<tr>
<td>Selch et al. [2004] (18)</td>
<td>45</td>
<td>1</td>
<td>64</td>
<td>fSRT</td>
<td>50.4</td>
<td>36</td>
<td>97.4 at 3 years</td>
<td>0</td>
</tr>
<tr>
<td>Hamm et al. [2008] (19)</td>
<td>181</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>56</td>
<td>36</td>
<td>97% at 5 years</td>
<td>8.2%</td>
</tr>
<tr>
<td>Litré et al. [2009] (20)</td>
<td>100</td>
<td>NR</td>
<td>26</td>
<td>fSRT</td>
<td>45</td>
<td>33</td>
<td>93% at 3 years</td>
<td>0</td>
</tr>
<tr>
<td>Minniti et al. [2011] (21)</td>
<td>52</td>
<td>1</td>
<td>34</td>
<td>fSRT</td>
<td>50</td>
<td>72</td>
<td>93% at 5 years</td>
<td>5.5%</td>
</tr>
<tr>
<td>Combs et al. [2013] (10)</td>
<td>507</td>
<td>1–3</td>
<td>45.6</td>
<td>fSRT or IMRT</td>
<td>57.6</td>
<td>107</td>
<td>88% at 10 years; Grade 1: 91%; Grade 2/3: 53%</td>
<td>NR</td>
</tr>
<tr>
<td>Milker-Zabel et al. [2007] (7)</td>
<td>94</td>
<td>1–3</td>
<td>57.4</td>
<td>IMRT</td>
<td>57.6</td>
<td>52.8</td>
<td>93.6% at 4.4 years</td>
<td>7.4%</td>
</tr>
</tbody>
</table>
patients who are inoperable. Following surgical resection, there is controversy about early post-operative radiation versus delayed radiotherapy at the time of tumor recurrence. Data support that early adjuvant radiotherapy improves LC, particularly following partial resection (8). In contrast, delaying radiotherapy until tumor recurrence can help spare toxicities associated with radiation and may be the favored approach for patients at low risk for tumor recurrence following gross total resection (10). Factors associated with higher risk of postsurgical progression/recurrence include the incomplete resection, prior recurrence following surgical resection, mitotic index, and possibly presence of peritumoral edema (22-26).

For benign tumours (WHO grade I) that are planned for fractionated radiotherapy, the gross target volume (GTV) is typically the enhancing tumor and/or the surgical bed. There is typically no microscopic margin added to intact benign meningiomas and minimal margin added following surgical resection. The conventional radiation doses generally range between 50–54 Gy delivered in 1.8–2 Gy daily fractions (Figure 1).

**WHO grade 2–3 SBM**

For non-benign meningiomas (WHO grade II–III), with greater concern for brain invasion, the target volume usually includes additional margin for microscopic spread. Additionally, due to the more aggressive biology, higher doses of radiation ranging between 60–66 Gy are typically used (23,27,28). Although the literature is limited, retrospective studies suggested that the use of higher doses may result in better tumor control. Goldsmith et al. analyzed 140 patients with intracranial meningioma (23 non-benign meningioma) to assess the impact of postoperative radiotherapy after subtotal resection (STR). With a median follow-up of 40 months, 5-year PFS was 89% and 85%, for benign and non-benign meningioma, respectively. There was a significant improvement on PFS with radiation doses >53 Gy (63%) when compared to ≤52 Gy (17%) for malignant meningioma (P=0.01) (22).

In a series of 24 patients with non-benign (79% grade II) meningioma patients treated with combined proton and photon radiotherapy (mean total radiation dose of 65.01 CGE (range, 56–68 CGE) following STR (18/24 patients), the 5-year LC and OS for all patients was 46.7% and 53.2%, respectively. Authors also reported that combined proton and photons radiation dose >60 Gy significantly improved PFS (P=0.05) and OS (P=0.05) in their patients cohort (29).

Retrospective studies have demonstrated that early adjuvant radiotherapy for non-benign meningiomas results in mean improvement in 5-year PFS of 18% (range, 12–24%) (27,30-32). However, the majority of these studies have evaluated grade II and III meningiomas together, and the benefit may reflect selection bias of higher risk cases to receive adjuvant RT (23,24,33-36). Following STR of non-benign meningioma, patients are at high risk of further tumor progression and therefore are likely to have an improvement in LC with the addition of adjuvant radiotherapy. Aghi et al. reported the findings of 108 patients following STR for atypical grade II meningioma. Of 100 patients followed after STR alone, 41% experienced tumor progression at 5-years. This series reported that for the 8 patients who received adjuvant fractionated radiotherapy with a mean dose of 60.2 Gy to the resection bed plus a 1-cm margin, no recurrence was reported (23).

Mair et al. reported that of 114 consecutive patients who underwent first-time resection of WHO Grade II atypical meningiomas, the use of postoperative radiotherapy didn’t demonstrate significant difference in outcomes. However in a subgroup analysis, for patients who had undergone STR, postoperative RT provided a significant PFS benefit when excluding the 5 patients who had undergone postoperative radiosurgery for a tumor remnant but no radiotherapy (P=0.043) (34).

As the goals of treatment shift towards optimizing functional outcome and minimizing treatment-related toxicity, close observation may be more frequently considered if a GTR is achieved for a grade II meningioma. Mirimanoff et al. reported long-term follow up (median follow up was not reported) outcomes of 225 benign meningiomas patients who underwent surgery alone. The PFS after GTR at 10, and 15 years was 80%, and 68%, respectively. By contrast PFS after STR at 10, and 15 years only was 45%, and 9%, respectively (35). Other series have reported local recurrence rates following GTR ranging from 7–23% at 5 years and 20–39% at 10 years (24,29,35-38).

For atypical (WHO grade II) meningiomas, considerable controversy exists regarding the optimal timing of radiotherapy after a GTR (30). Currently, two ongoing Phase II trials (RTOG 0539: Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas—ClinicalTrials.gov identifier: NCT00895622 and EORTC 22042: Adjuvant Postoperative High-Dose Radiotherapy for Atypical and Malignant Meningioma: a Phase-II and Observation
Study—ClinicalTrials.gov identifier: NCT00626730) are assessing the role of radiotherapy in the management of patients with non-benign meningioma using either 3DCRT or IMRT. RTOG 0539 is an observational study for low risk meningioma (group 1) and a phase II trial for intermediate risk meningioma patient (groups 2) and high-risk meningioma patients (group 3). Group 1 is an observation arm (65 patients) and is composed by grade 1 post GTR or STR. Group 2 encompasses patients with grade 1 recurrent disease or grade 2 post-GTR to 3D conformal radiotherapy or IMRT or protons 54 Gy/30 fractions. Group 3 includes grade 2 recurrent disease or grade 2 post STR or any grade 3 to IMRT only 60 Gy/30 fractions. The study enrolment is complete (n=244) and it is currently awaiting the primary endpoint, which is progression-free survival at 3 years. Preliminary results of RTOG 0539 presented at the ASTRO annual meeting in 2015 reported on one of the 3 study arms, group 2, which included patients with recurrent grade 1 meningioma after GTR or STR or new WHO Grade 2 after GTR. In this study arm, the 3-years LC was 98.0%. (Median follow-up was not published) Among 44 patients receiving IMRT, 4 (9%) had developed grade 2 acute toxicity, and 11 (25%) grade 2 late toxicity. No acute or late toxicity ≥2 was reported. The EORTC 22042 is an observational (group 1) and phase II (group 2) with a primary outcome of progression free survival. Group 1 includes grade 2 and 3 meningioma post GTR to 60 Gy in 30 fractions and group 2 grade 2 and 3 post STR to 70 Gy in 35 fractions. The study has completed accrual (n=78).

Malignant or anaplastic grade III meningiomas are aggressive and carry considerably higher recurrence risk and lower survival than their benign counterparts. For these tumours, radiation treatment is generally recommended following surgical resection for improved tumor control. Dziuk et al. compared surgery alone to surgery plus RT in 38 patients with WHO grade III tumours. Nineteen (50%) received initial postoperative RT and presented with significant better 5-year PFS (80% vs. 15% for surgery alone (P=0.002) (27). Several publications have reported that radiotherapy can also shrink the remaining tumour burden in addition to preventing tumor recurrence or progression (5,26,33).

Similar to grade II meningiomas, additional margin is added for grade III meningiomas for microscopic tumor extension. The radiation doses have generally ranged between 54–60 Gy delivered in 1.8–2 Gy daily fractions with an optional boost to gross disease up to 66–70 Gy. DeVries et al. and Hug et al. found an improvement in LC and overall survival (OS) with radiation dose greater than 60 Gy (39,40). Similarly, Boskos et al. reported improved OS with doses exceeding 60 Gy and a trend toward further improvement beyond 65 Gy (41).

Katz et al. reported the results of radiotherapy delivered using accelerated fractionation with and without SRS in patients with atypical and malignant meningioma. The study assessed 36 patients in the following 3 groups: (I) accelerated fractionation group (n=22) treated with 60 Gy at 1.5 Gy twice per day with or without SRS; (II) SRS alone (n=3) treated with 10–17.5 Gy (mean 14 Gy, median 15 Gy) in a single fraction; and (III) conventional radiation (n=7) 50–64.8 Gy (mean 57 Gy) plus SRS (n=2, 10 Gy for both). The study revealed that patients treated with accelerated fractionation (group 1) had a higher rate of grade 3–5 toxicities when compared to conventional radiation (group 3) (grade 3–5: 55% vs. 0%; P<0.05) with no improvement in PFS (45 vs. 55%; P=0.99) (42).

Recurrent meningioma

Recurrent meningiomas, including those that remain WHO grade I, have a considerably higher rate of recurrence after surgery alone than do newly diagnosed tumours (42). Despite more aggressive biologic behaviour these tumours often retain their original histopathologic grade (43), therefore despite the grade of the recurrent tumor, postoperative RT is typically offered to improve LC of the tumor. One series reported that the 5-year LC with postoperative radiotherapy at the time of first recurrence was 88% vs. 30% without radiation (P=0.01) and this translated into a 5-year OS outcome of 90% vs. 45% (P= not reported) (24).

Radiosurgery

SRS typically delivers a highly conformal, high dose of radiation in a single fraction. SRS has been applied more frequently to the practice over the last 2–3 decades. It has been used after STR or at the time of recurrence and as a definitive primary treatment for presumed benign meningiomas (44-52). SRS is usually considered effective and safe for meningioma that is limited in size up to 3 cm in maximal diameter or 10 cc in volume and with sufficient distance from critical structures such as the optic chiasm, optics nerves, or brainstem. We present a summary of selected series on the use of SRS for skull base meningioma.
For mainly SBM and grade 1 meningiomas, 10 studies reported high LC rates with minor toxicities. With a median follow up of 46–86 months, PFS at 5 and 10 years was 89.7–99% and 79–83%, respectively. Treatment related toxicities, including radionecrosis, new onset or progression of cranial neuropathies, decline in cognition or memory, cerebellar deficits, alterations in body sensation, symptomatic edema, from SRS were largely under 10% (range, 1–17%). Based on retrospective series, high rates of LC have been achieved with a prescription dose of 12–16 Gy prescribed at the 50–80% isodose line, depending on the mode of SRS delivery (50,53-61). The largest series from Starke et al. analyzed 255 SBM and reported outcomes with a median follow-up of 78 months and median SRS prescribed doses of 14 Gy at mean prescription isodose line of 41% (range, 28–80%). Progression free survival at 5 and 10 years was 96% and 79%, respectively. Tumor regression and complication was reported in 49% and 10.6% of the cases, respectively. Treatment-related toxicities included new onset or progression of cranial neuropathies, which occurred in 22 patients (8.6%) and other neurological signs or symptoms occurred in an additional 6 patients (2%) (61).

Our review of the literature highlights 8 small series that focused on SRS for grade 2 meningiomas, mostly delivered after STR or at recurrence. With a median or mean follow up of 26–82 months, median or mean SRS dose of 12.4–18 Gy, PFS at 5 years was 58–83% based on 3 of the identified studies, respectively (46,62-68). These series suggested that lower prescription dose and tumor grade were the major predictors of recurrence following SRS (66,69). Kano et al. reported outcomes on 12 meningiomas (10 atypical and 2 anaplastic) with a median follow up of 43 months. Five year PFS was significantly higher for tumors treated with greater than 20 Gy compared with tumors treated with less than 20 Gy (P=0.0139) (64). By contrast, Stafford et al. found no dose correlation and reported a 5-year PFS of 68% with median SRS dose of 16 Gy (range, 12–36 Gy) and median follow-up of 47 months (46).

The role of SRS in the treatment of grade 3 meningioma is controversial (70). The largest series of SRS for patients with grade 3 meningioma reported the outcomes of 50 patients of which 40% patients had recurrent meningiomas (despite prior external beam radiation therapy to a median dose of 54.0 Gy). With a median follow up 38 months, the 5 years LC was 40% (71). Kondziolka et al. reported outcomes on 29 grade III meningioma patients managed with post-operative SRS. The mean SRS dose was 14 Gy.

### Table 2 Radiosurgery outcomes for skull base meningioma

<table>
<thead>
<tr>
<th>Study [year]</th>
<th>Sample (n)</th>
<th>Grade</th>
<th>Previous surgery (%)</th>
<th>SRS technique</th>
<th>Median dose</th>
<th>Median follow-up (months)</th>
<th>Local Control (%)</th>
<th>Late toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morita et al. [1999] (44)</td>
<td>88</td>
<td>SB</td>
<td>55</td>
<td>GK</td>
<td>16</td>
<td>35</td>
<td>95% at 5 years</td>
<td>14.8</td>
</tr>
<tr>
<td>Roche et al. [2000] (45)</td>
<td>80</td>
<td>SB</td>
<td>37</td>
<td>GK</td>
<td>14</td>
<td>30.5</td>
<td>92.8% at 5 years</td>
<td>5</td>
</tr>
<tr>
<td>Stafford et al. [2001] (46)</td>
<td>190 (80% SB)</td>
<td>88% grade 1</td>
<td>59</td>
<td>GK</td>
<td>16</td>
<td>47</td>
<td>93% at 5 years</td>
<td>13</td>
</tr>
<tr>
<td>Nicolato et al. [2002] (47)</td>
<td>156</td>
<td>Grade 1</td>
<td>52</td>
<td>GK</td>
<td>14.6</td>
<td>48.9</td>
<td>96.5% at 5 years</td>
<td>4</td>
</tr>
<tr>
<td>Kollová et al. [2007] (48)</td>
<td>368</td>
<td>Grade 1</td>
<td>30</td>
<td>GK</td>
<td>12.5</td>
<td>60</td>
<td>98% at 3 years</td>
<td>15.9</td>
</tr>
<tr>
<td>Feigl et al. [2007] (49)</td>
<td>214</td>
<td>Grade 1 and 2</td>
<td>43</td>
<td>GK</td>
<td>13.6</td>
<td>24</td>
<td>86.3% at 4 years</td>
<td>6.7</td>
</tr>
<tr>
<td>Chuang et al. [2004] (50)</td>
<td>43</td>
<td>Grade 1</td>
<td>–</td>
<td>LINAC</td>
<td>17</td>
<td>74.5</td>
<td>89.7% at 5 years</td>
<td>11</td>
</tr>
<tr>
<td>Dos Santos [2011] (51)</td>
<td>88</td>
<td>Grade 1</td>
<td>46.6</td>
<td>LINAC</td>
<td>14</td>
<td>87</td>
<td>92.5 at 5 years</td>
<td>19.3</td>
</tr>
<tr>
<td>Unger et al. [2012] (52)</td>
<td>173 (57.2% SB)</td>
<td>Grade 1</td>
<td>49</td>
<td>LINAC</td>
<td>15</td>
<td>21</td>
<td>89.3 % at 5 years</td>
<td>8.5</td>
</tr>
</tbody>
</table>
and found PFS rates of 17% at 15 months (72).

In summary, for benign and non-benign tumours that are planned for SRS, the GTV is typically the enhancing tumor (Figure 2). There is typically no microscopic margin added to GTV and inclusion of the dural tail is controversial. The SRS doses generally range between 12–24 Gy delivered in a single fraction. While this has shown good LC for benign SBM, there is limited data on the outcomes of SRS for grade 2 and 3 SBMs.

**Particle therapy**

Emerging treatment opportunities with protons and other heavy particle beams have the ability to potentially improve dose sparing of normal tissues through the exploitation of the Bragg peak phenomenon, which results in an extremely steep dose fall-off at the end of the beam. At the present time, the ability to generate an accurate highly conformal proton radiotherapy plan is dependent on the treating team and institution due to variability in accurate modeling of the physical properties of proton therapy. Ongoing studies to better model the linear energy transfer and estimate the true radiobiological effective dose of proton therapy for integration of this information into treatment planning systems will greatly improve our ability to optimize use of this treatment modality (73-75).

Thus far, published outcomes reported for proton therapy have been comparable to photon radiotherapy. There are now outcomes published for over 200 patients treated with protons, but these studies have generally mixed treatments of photon and proton treatment, inclusion of all tumor grades and a range of clinical scenarios including primary treatment, adjuvant treatment and salvage therapy for recurrence (60-62,76-81). Noël et al. reported on fifty-one patients with SBM treated with proton and photon radiation to a median total dose was 60.6 CGE (range, 54–64 CGE) delivered with photons once daily, 5 days a week, to a median dose of 30.6 Gy (25–54 Gy) in 1.8–2 Gy fractions and the proton component to a median dose of 30 CGE (10–31 CGE) with 1.8–2 CGE fractions. Median tumor volume was 17 mL (1 to 120 mL) and the CTV included the GTV plus 5–10 mm safety margin. With a mean follow-up of 25.4 months, 4-year LC and OS rates were, 98% and 100%, respectively. No severe toxicity was reported (82). Wenkel et al. assessed PFS and toxicity of combined proton and photon radiation treatment for incompletely resected or recurrent meningioma. Patients were treated with a median of 25 (range, 8–34) fractions for protons in 1.92 CGE fractions and a median of 6 (range, 0–23) fractions for photons in 1.8 Gy fractions. Median tumor gross volume was 34 cc (range, 2–243 cc) and the CTV included the possible microscopic disease. With a median follow-up of 53 months, OS at 5 and 10 years was 93 and 77%, respectively, and PFS at 5 and 10 years was 100% and 88%, respectively. Eight patients developed severe long-term toxicity, opthalmologic (4 patients), neurologic (4 patients), and otologic (2 patients) complications, which appeared to be dose related (receiving doses higher than those allowed) (80). Weber et al. reported the outcomes on 39 patients with histologically proven meningioma (34/39) treated with spot scanning proton radiotherapy to a median dose of 56.0 CGE (range, 52.2–66.6) at 1.8–2.0 CGE per fraction. Gross tumor volume ranged from 0.76 to 546.5 cc (median, 21.5) and CTV included the GTV plus regions of suspected microscopic spread (0–10 mm). With a mean follow-up time of 62.0 months, 5-year actuarial LC and OS rates were 84.8% and 81.8%, respectively, for the entire cohort (78).

Halasz et al. published on 50 patients treated with proton SRS [median dose 13 CGE (range, 10.0–15.5 Gy) (RBE) prescribed to the 90% isodose line] for benign meningioma. Median tumor volume was 2.1 cc (range, 0.3–9.7 cc). The median dose delivered was 13 CGE prescribed to the 90% isodose line. With a median follow-up of 32 months, 3-year LC rate was 94% and symptoms were improved in 47% (16/34) of patients (79). Gudjonsson et al. reported no signs of tumor progression after 36 months of follow-up following hypofractionated proton radiotherapy using doses between 14 Gy in 3 fractions to 24 Gy in 4 fractions, to the GTV plus 5 mm of margin, in 19 patients with partially-resected grade I (n=15) or unresectable (n=4) meningiomas (83).

There has been limited published data on heavy particle therapy. Combs et al. reported clinical outcome after a carbon ion boost in combination with high conformal photon radiation for high-risk meningioma, defined as atypical or anaplastic meningioma with ≥1 prior surgical resection. Carbon ion treatment was delivered with a median dose of 18 GyE, and photon radiation was applied with a median dose of 50.4 Gy. CTV including all macroscopic tumor, perifocal edema, as well as a safety margin of 2–3 cm. Median volume of the CTV was 217 mL. With a median follow-up of 77 months and 10 patients treated in this phase 1/2 trial actuarial LC rates after primary radiotherapy were 86% and 72% at 5 and 7 years (84,85).

In summary particle therapy shows promising results...
in patients with SBM in terms of local tumor control and treatment-related toxicities. In addition, it has been proposed that data supports that protons are associated with a lower risk of secondary malignancies (86).

**Cognitive functioning late toxicities in meningioma**

With the advances on treatment modalities that enable high dose coverage of the tumor while sparing surrounding tissues, the potential capability to lower the treatment related side effects has become an important focus of research. Cognitive toxicity can impact meningioma patients substantially due to their long expected life expectancy. While this is recognized in the clinical community, there is a paucity of literature on changes in cognitive function and its impact on health related quality of life in this population (87-89).

A recent systematic review on cognitive function in meningioma patients prior to and/or following surgery with or without radiotherapy identified 1,012 potential articles, 11 that met inclusion criteria. This review highlighted the limitations of analyzing this data due to various methodological differences across studies (e.g., lack of pre-treatment assessment or standard neurocognitive tests). Nonetheless, this review reported that meningioma patients frequently present with cognitive issues in multiple domains prior to any treatment. Following treatment (surgery with or without radiotherapy), the majority of patients appeared to show improvement in their cognitive functioning, although continuing to have mild impairments when compared to healthy controls (90).

**Suggestion for potential studies and research topics moving forward**

With the growing appreciation for variability in tumor behaviour despite similar histological classification, there are strong efforts to discover novel driver mutations that may predict for tumor behaviour and may be a treatment target (91,92). Advances in imaging, such as the use of novel PET tracers or functional MRI, are presenting an opportunity to non-invasively interrogate the tumor and surrounding tissues to improve our treatment selection and provide treatment guidance. For instance, including improved tumor delineation for radiation treatment. This is of particular value to skull-base meningiomas, as surgery may not be offered as initial therapy and therefore tissue is not always collected for diagnostic confirmation or tumor characterization.

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**Footnote**

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**References**


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