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CLINICAL INVESTIGATION

Consensus Radiation Treatment Planning Guidelines Using (68)Ga-DOTATATE PET/CT For Resected Meningiomas

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Purpose: Meningiomas are the most common primary intracranial tumor. Somatostatin receptor 2 is almost universally expressed in meningioma tissue. For patients who require adjuvant radiation, somatostatin receptor based (68)Ga-DOTATATE positron emission tomography (PET) imaging can detect additional or residual disease not discernible on magnetic resonance imaging. PET guided radiation treatments may improve local control, minimize toxicity by allowing for more precise radiation therapy plans, and allow for more precise dose-escalation to maximize local control. The aim of this study was to develop consensus PET guided treatment planning guidelines for common meningioma presentations.

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Methods and Materials: Five postoperative clinically relevant meningioma cases were selected from a prospective single-institutional registry of patients. Each patient had a preoperative and postoperative contrast-enhanced T1-weighted volumetric magnetic resonance imaging, and a postoperative (68)Ga-DOTATATE PET/CT, to assist with target delineation. The full treatment scenario including clinical history, histology, surgical history, and imaging were provided for each patient. Nineteen international experts who have published on the treatment and management of meningiomas, and who use (68)Ga-DOTATATE PET/CT in their practice, evaluated each case. Individual prescription recommendations were created, pooled, and discussed to create consensus recommendations.

Results: Consensus recommendations were created for each case. In most cases, PET-based contouring allowed for more precise dose-escalation to 66-70 Gy targeting residual disease. When compared to RTOG 0539 and modern clinical trial contouring guidelines, a smaller clinical target volume expansion from the surgical cavity was recommended using PET guided radiation plans in the absence of radiographic or pathologic evidence of brain or bone invasion.

Conclusions: This report provides consensus target volume delineation guidelines for meningiomas receiving postoperative radiation in common clinical situations. Integration of these guidelines into clinical practice may allow for more precise biomarker guided radiation treatments and standardize radiation therapy on future meningioma clinical trials.

Introduction

Meningiomas are the most common primary intracranial tumor.[1] Postoperative adjuvant therapy is focused on improving local control (LC) and progression free survival. For intermediate (recurrent grade 1 tumors, grade 2 tumors after gross total resection) and high-risk meningiomas (recurrent grade 2 tumors, grade 2 tumors after subtotal resection, any grade 3 tumor), RTOG 0539 supports the need for adjuvant radiation therapy.[2,3] The current standard of care after surgery is to obtain magnetic resonance imaging (MRI) with and without contrast to evaluate for residual disease and for assistance with radiation planning. Given the near-universal expression of somatostatin receptor 2 in meningioma tissue, somatostatin receptor based positron emission tomography (PET) imaging, including (68)Ga-DOTATATE PET/computed tomography (CT), can be used for imaging and workup of a meningioma.[4,5] Notably, multiple additional tracers including (68)Ga-DOTATOC, (68)Ga-DOTANOC, and (64)Cu-DOTATATE can also be used.[6] These tracers can be useful for radiation treatment planning, as PET imaging can detect additional or residual diseases not discernible on MRI in approximately 28% of patients.[7] PET guided radiation treatments for meningioma may improve LC through more accurate characterization of the extent of the disease and minimize toxicity by treating more focused radiation volumes.[8-10]

This study aimed to develop consensus radiation treatment planning guidelines for common resected meningioma presentations using (68)Ga-DOTATATE PET/CT from radiation oncologists with expertise in central nervous system tumors.

Methods and Materials

Five postoperative meningioma cases were selected from an IRB-approved prospective single-institutional registry of patients. The selected patients had surgery for a convexity or skull base meningioma, 2 common locations. Each case had a preoperative and postoperative contrast-enhanced T1-weighted volumetric MRI, and a postoperative (68)Ga-DOTATATE PET/CT, to assist with target delineation. Nineteen international experts who have published on the treatment and management of meningiomas were included in this study. For each case, the full treatment scenario—including clinical history, histology, surgical report, MRI, PET, and time from surgery—was provided. A modified Delphi method was used to create consensus decisions. Directed questions were sent out through anonymous surveys and responses were used to develop consensus recommendations for each patient, which were in turn used to create consensus guidelines that can be applied to similar scenarios. The following questions were asked for each case: (1) what dose would you deliver to the PET avid area; (2) would you offer dose-escalation to the PET avid area; (3) would you create a clinical target volume (CTV) margin around the PET avid area; (4) What dose would you deliver to the postoperative cavity based on MRI and CT; (5) would you create a CTV margin around the postoperative cavity; and (6) are there any other recommendations you would make for this case.

Results

Case 1 (grade 3 meningioma with residual disease on PET and brain invasion)

Case 1 is an 84-year-old female with a WHO grade 3 meningioma and invasion into the right parietal lobe who had an upfront surgical resection (Fig. 1). Initially, the surgeon believed that a gross total resection (GTR) was achieved. However, the postoperative MRI showed a small amount of nodular enhancement along the lateral aspect of the superior sagittal sinus. DOTATATE PET/CT showed a focus of increased radiotracer activity corresponding to MRI finding of nodular enhancement along the right lateral aspect of the superior sagittal sinus, suspicious for residual disease.

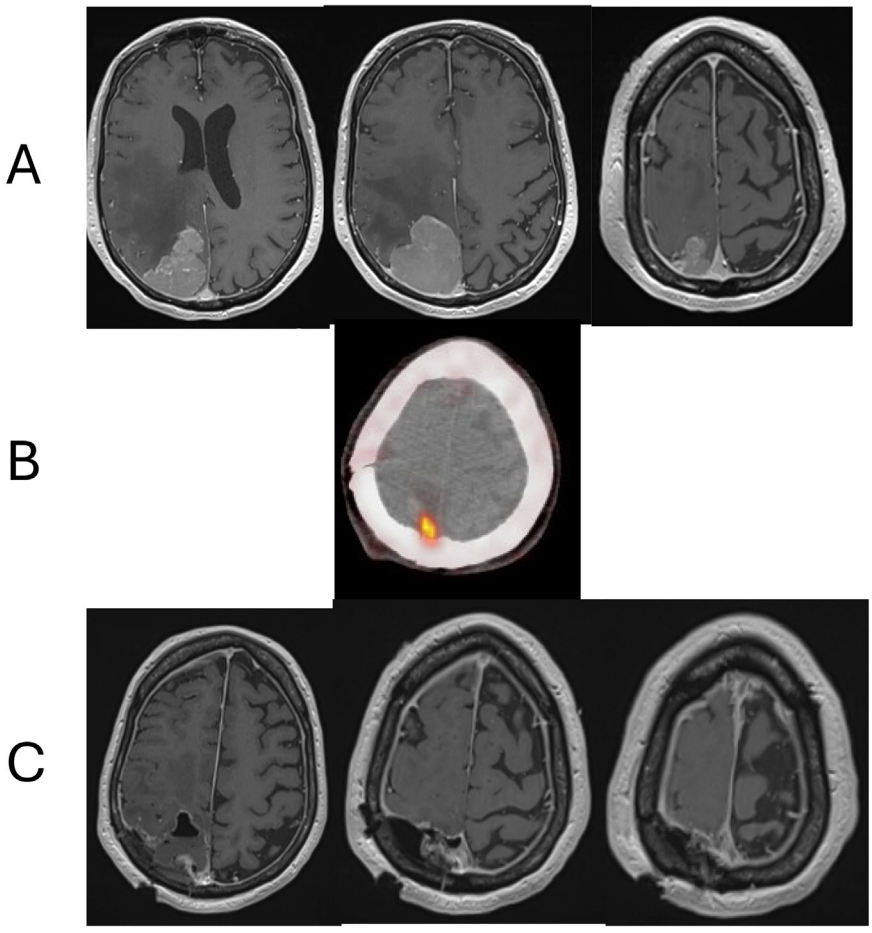

Fig. 1. Case 1-Grade 3 meningioma with residual disease on PET. (A) Preoperative MRI. (B) Postoperative PET. (C) Postoperative MRI. *Abbreviations:* MRI = magnetic resonance imaging; PET = positron emission tomography.

Consensus recommendation

60 Gy in 30 fractions with a sequential boost to PET avid disease gross tumor volume (GTV) to a total of 70 Gy in 35 fractions (GTV 70 Gy). The GTV 70 Gy to CTV 70 Gy expansion was recommended to be 0 mm with a 3 mm expansion from CTV 70 Gy to create the planning target volume (PTV) 70 Gy volume. There was pathologic and radiographic evidence of the brain; therefore, a 1 cm expansion from the postoperative cavity and residual tumor on MRI/PET along the dura with a 0.5-1 cm expansion into the brain will create the CTV 60 Gy volume. A 3 mm expansion from the CTV 60 Gy volume will create the PTV 60 Gy volume.

Discussion and alternative recommendations

This is an elderly patient with a high-risk meningioma and residual tumor after surgery. There was a unanimous decision to proceed with dose-escalation to the PET avid disease to 66-70 Gy. Dose-escalation to at least 66 Gy is associated with improved LC and progression free survival for grades 2 and 3 meningiomas with a low (4%) risk of symptomatic radiation necrosis.[11] Confining dose-escalation to PET avid disease may further minimize the risk of radiation necrosis. An alternative prescription for a patient with a good Karnofsky Performance Status is 60 Gy in 30 fractions to postoperative cavity with simultaneous integrated boost (SIB) to the PET avid disease to a total of 70 Gy in 30 fractions. If brain invasion is evident, a CTV 60 Gy expansion of at least 0.5-1 cm is recommended. To assist with contouring, a standardized uptake value (SUV) threshold of 2.3 is recommended as 1 method to differentiate meningioma from non-neoplastic tissue.[12] However, this technique has limitations, and using an SUV ratio to the superior sagittal sinus threshold of 3.2 has been shown to have robust sensitivity and specificity.[13] In addition, the benefit of boosting any avid disease that has not reached the threshold of frank positivity, or multifocal areas of low-level uptake in the 2-4 SUV range, can be considered to minimize the risk of a marginal recurrence.

Case 2 (grade 2 meningioma with residual disease on PET)

Case 2 is a 50-year-old woman with no prior radiation history and a right-sided tentorial WHO grade 2 meningioma exerting mass effect on the right temporal and occipital lobes (Fig. 2). This tumor was resected (with pathology exhibiting a Ki-67 of 2%) but residual disease was visible on DOTATATE PET/CT.

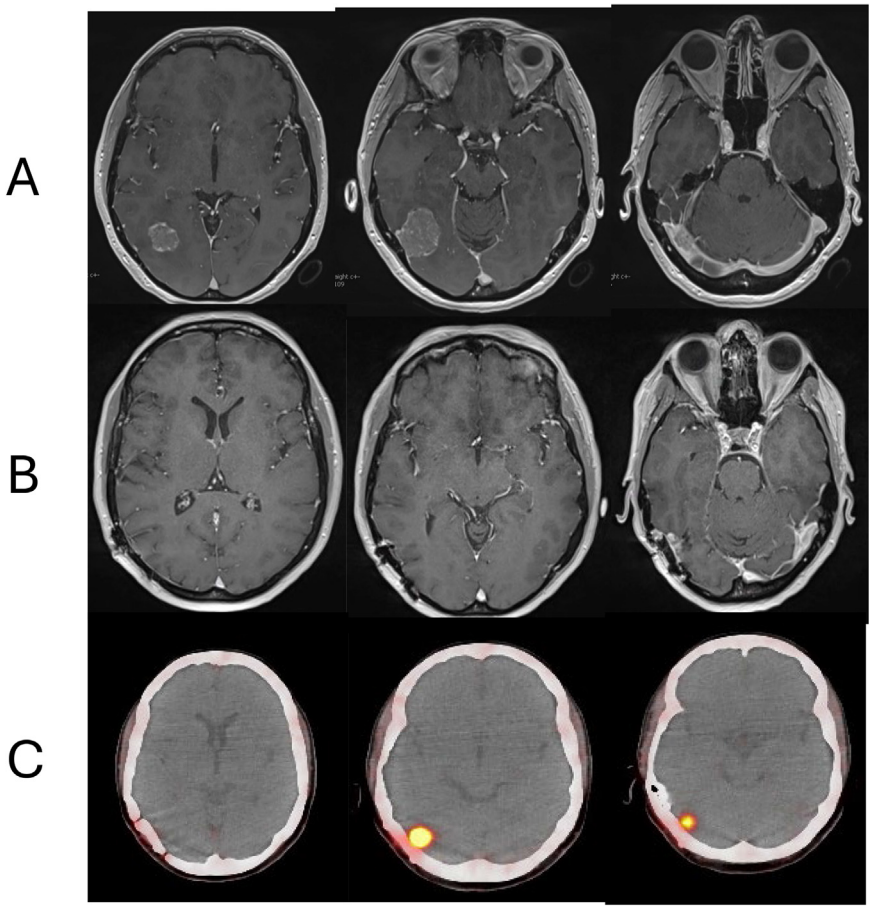

Fig. 2. Case 2-Grade 2 meningioma with residual disease on PET. (A) Preoperative MRI. (B) Postoperative MRI. (C) Postoperative PET. *Abbreviations:* MRI = magnetic resonance imaging; PET = positron emission tomography.

Consensus recommendation

A regimen of 60 Gy in 30 fractions to the postoperative cavity with a sequential boost to the PET avid disease GTV to a total of 66 Gy (GTV 66 Gy) in 33 fractions is recommended; escalating the dose up to 70 Gy in 35 fractions can be considered given the Zeng et al[11] data. The GTV 66 Gy to CTV 66 Gy expansion was recommended to be 0 mm with a 3 mm expansion from CTV 66 Gy to create the PTV 66 Gy. Since there is no pathologic or radiographic evidence of brain or bone invasion, a 0.5-1 cm expansion from the postoperative cavity along the dura without extension into the bone or brain is recommended to create the CTV 60 Gy volume. A 3 mm expansion from the CTV 60 Gy volume is recommended to create the PTV 60 Gy volume.

Discussion and alternative recommendations

This is a patient with a grade 2 meningioma and residual disease. As with case 1, an SIB, as opposed to a sequential boost, could be considered. This patient has a low Ki-67, although this might not be useful to stratify risk when grade is confirmed. Germline DNA sequencing and meningioma DNA sequencing to look for structural arrangement in NF2 might suggest radiation-induced meningioma if the patient has a past radiation history, and targeted gene expression profiling might be useful to risk stratify this tumor.[13,14] If the malignancy is confirmed to be low-risk, observation and radiosurgery as salvage or upfront radiosurgery/hypofractionated stereotactic radiation therapy (15-18 Gy in 1 fraction or 25-32.5 Gy in 5 fractions) could be an alternative prescription to treat the residual disease alone. There are multiple radiosurgery prescriptions that can be offered with a linear accelerator or gamma knife platform with institution and physician dependent margins, prescription doses, isodose lines, and fractionation regimens allowing for a wide range of acceptable treatments.

Case 3 (grade 1 with regrowth)

Case 3 is an 85-year-old woman with a left frontal WHO grade 1 meningioma, Ki-67 15%, status post-GTR. She has evidence of regrowth of the tumor on MRI and a PET scan 2.5 years after surgery (Fig. 3) but did not receive a second surgery.

Consensus recommendation

There are several options for this older patient with grade 1 disease and a >2-year interval from resection to recurrence.

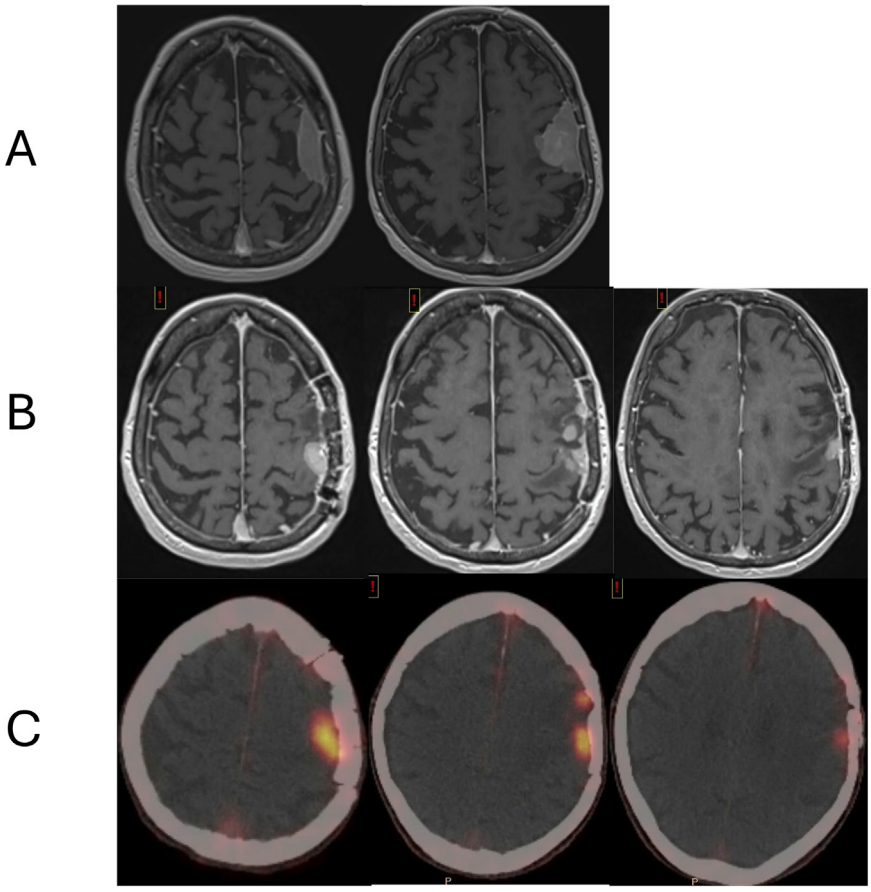

Fig. 3. Case 3-Grade 1 meningioma with regrowth. (A) Preoperative MRI. (B) Postoperative MRI. (C) Postoperative PET. *Abbreviations:* MRI = magnetic resonance imaging; PET = positron emission tomography.

A standard option is to assume that the WHO grade did not change (ie, no transformation to a higher grade), and to treat the recurrent disease to a dose of 54 Gy in 27-30 fractions. Targeting the surgical bed would be optional. However, if treating with single fraction stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiation therapy, targeting the GTV alone represents reasonable practice.

Discussion and further recommendations

This is a patient with a discordant grade and Ki-67. In some cases, it is possible that an incorrect grade was applied upfront, and a review of prior pathology would be beneficial if available. This patient would benefit from targeted gene expression profiling to determine the risk of tumor recurrence.[14,15] If, after genetic profiling, the tumor is confirmed to be a low-risk grade 1 meningioma, then the recommendation would remain to prescribe standard 54 Gy in 27-30 fractions to the PET avid disease (optionally including the postoperative cavity with no further CTV margin). If genetic profiling indicates a higher risk disease, we recommend treating the patient similarly to a WHO grade 2 meningioma. In such cases, it is reasonable to escalate the dose to 60 Gy in 30 fractions, including the postoperative cavity, followed by a sequential boost to the PET avid GTV, resulting in a total dose of 66 Gy (GTV 66 Gy) in 33 fractions. The GTV 66 Gy to CTV 66 Gy expansion is recommended to be 0 mm, with a 3 mm expansion from CTV 66 Gy to create the PTV 66 Gy. A 0.5-1 cm expansion from the postoperative cavity along the dura without extension into the bone or brain can be performed to create the CTV 60 Gy volume. A 3 mm expansion from the CTV 60 Gy volume will create the PTV 60 Gy volume. As with the previous cases, an SIB, as opposed to a sequential boost, can also be considered. Given the 2.5-year interval to recurrence, even if the tumor is a high-risk meningioma, it is reasonable to treat the GTV with radiosurgery (either single fraction or preferably hypofractionated stereotactic radiation therapy). 15 Gy (WHO grade 1) or 18 Gy (WHO grade 2 or higher) are acceptable single fraction stereotactic radiation therapy regimens. 25 Gy (WHO grade 1) or 30-32.5 Gy (WHO grade 2 or higher) are acceptable fractionated stereotactic radiation therapy regimens. As stated in case 2, there are multiple acceptable stereotactic radiation prescriptions.

Case 4 (grade 2 with residual disease on PET and bone involvement)

Case 4 is a 60-year-old woman who presented to the neurosurgical clinic with a right frontal bone lesion. An initial

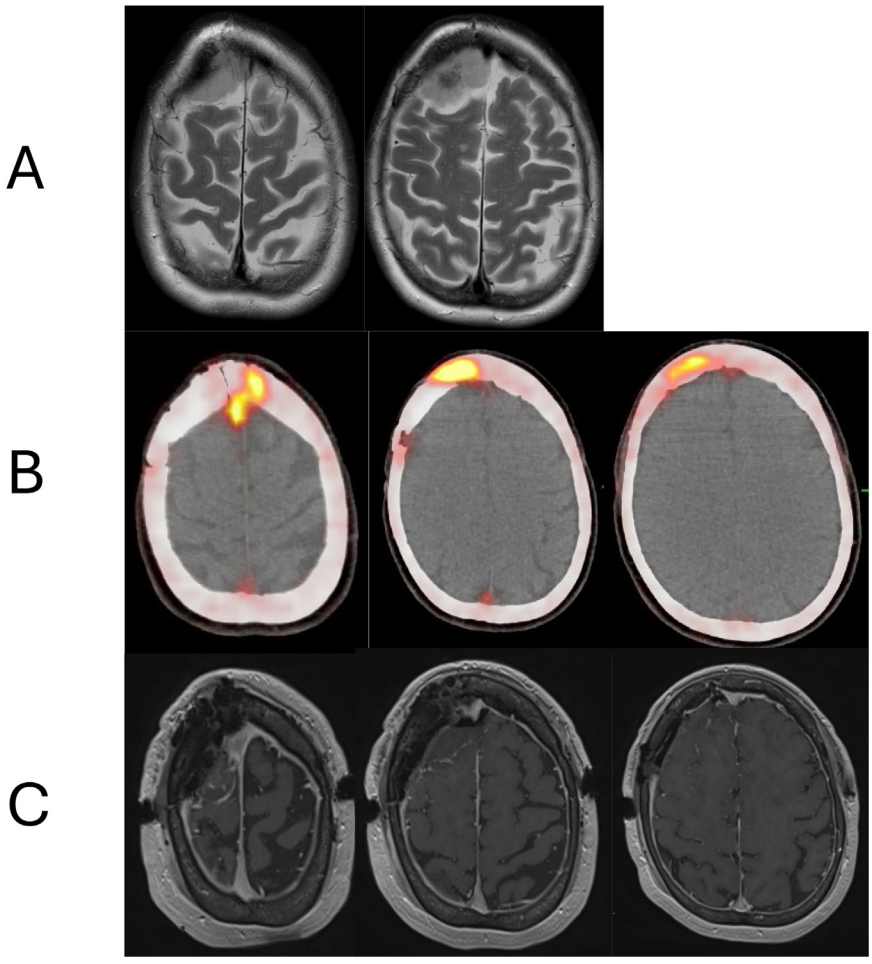

Fig. 4. Case 4-Grade 2 with residual disease on PET and bone involvement. (A) Preoperative MRI. (B) Postoperative PET. (C) Postoperative MRI. *Abbreviations:* MRI = magnetic resonance imaging; PET = positron emission tomography.

brain MRI showed a right superior frontal convexity mass with osseous involvement of the right frontal bone (Fig. 4). She was taken to the operating room for a resection of right frontal brain mass via craniotomy and was found to have a WHO grade 2 meningioma. A postoperative brain MRI showed resolution of the previously noted imaging postoperative change from resection of the right frontal lobe mass with soft tissue involving the anterior aspect of the superior sagittal sinus unchanged since the prior MRI related to chronic thrombus versus tumor involving the sinus.

Consensus recommendation

A regimen of 60 Gy in 30 fractions to postoperative cavity with a sequential boost to the PET avid disease GTV to a total of 66 Gy (GTV 66 Gy) in 33 fractions is recommended; escalating the dose up to 70 Gy in 35 fractions can be considered. The GTV 66 Gy to CTV 66 Gy expansion was recommended to be 0 mm with a 3 mm expansion from the CTV 66 Gy to create the PTV 66 Gy. Since there is evidence of bone invasion, a 5 mm expansion from the postoperative cavity into the bone, with the inclusion of the PET avid disease, will create the CTV 60 Gy volume. A 3 mm expansion from the CTV 60 Gy volume will create the PTV 60 Gy volume.

Discussion and alternative recommendations

For this patient with bone invasion, an expansion into the bone is warranted when planning radiation therapy. It is especially helpful to use PET imaging to assist with target volume delineation in cases of bone invasion. Given the residual disease in bone, multidisciplinary discussion of further resection to complete a GTR could be curative and allow for deferral of radiation, particularly if the superior sagittal sinus involvement on postoperative imaging was caused by thrombus and not tumor. Otherwise, all areas of bone and sinus involvement would need to be included in the radiation field. As with the previous cases, an SIB, as opposed to a sequential boost, can also be considered.

Case 5 (grade 2 in eloquent area)

Case 5 is a 66-year-old woman with a right cerebellopontine angle meningioma, WHO grade 2. She completed a right-sided retrosigmoid craniotomy and resection of tumor

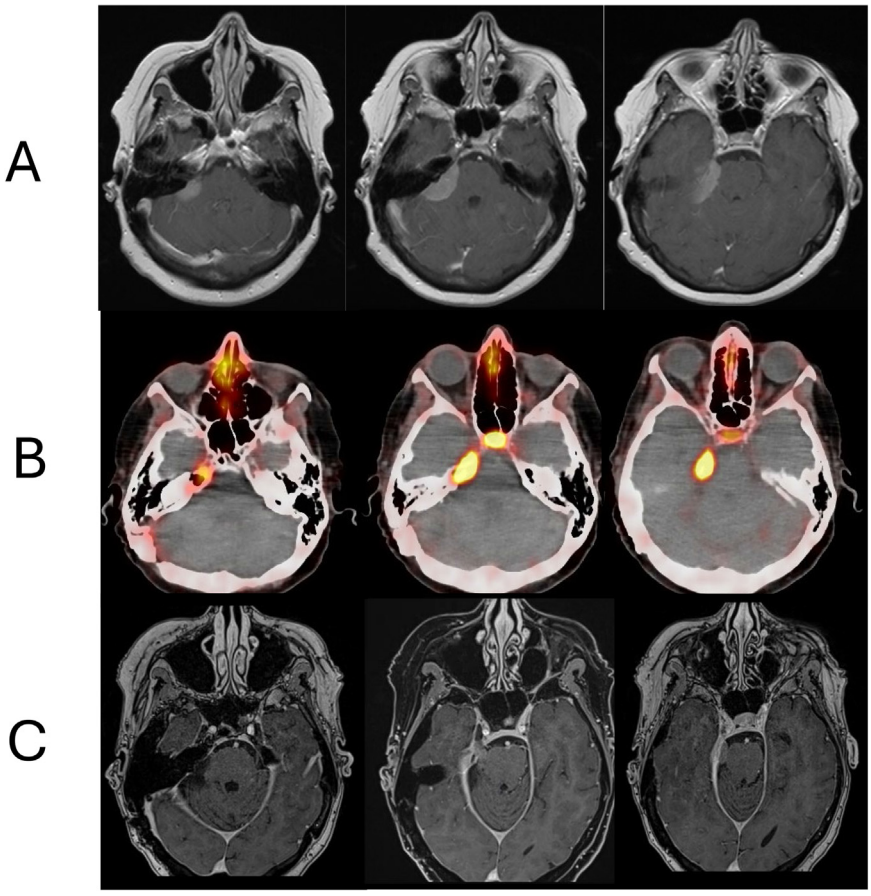

Fig. 5. Case 5-Grade 2 in eloquent area. (A) Preoperative MRI from several years ago. (B) Postoperative PET. (C) Postoperative MRI. *Abbreviations:* MRI = magnetic resonance imaging; PET = positron emission tomography.

performed 7 years ago. She has had slow but steady growth over the last several years (Fig. 5).

Consensus recommendation

A regimen of 59.4 Gy in 33 fractions to postoperative cavity, gross disease, and adjacent 5 mm of dura with a sequential boost to the PET avid disease to a total of 66 Gy (GTV 66 Gy) in 33 fractions is recommended; escalating the dose up to 70 Gy in 35 fractions can be considered. The GTV 66 Gy to CTV 66 Gy expansion was recommended to be 0 mm with a 3 mm expansion from CTV 66 Gy to PTV 66 Gy. A 3 mm expansion from the CTV 59.4 Gy volume will create the PTV 59.4 Gy volume. Undercovering the gross tumor to reach a brainstem D0.03 cc <60 Gy may be necessary in this case to minimize risk of toxicity. For tumors adjacent to or abutting the optic nerves or chiasm, a D0.03 cc <55 Gy with a small margin around the nerves allowed to receive 58 Gy can reduce risk of toxicity.

Discussion and alternative recommendations

This case is an excellent example showing the intrinsic PET activity of the pituitary gland when using DOTATATE PET imaging.[16,17] Careful imaging review is necessary to ensure that normal pituitary is not included in the radiation treatment field. In this eloquent location, preradiation audiometry and regular surveillance moving forward may be necessary. Single fraction SRS (18 Gy in 1 fraction) or fractionated stereotactic radiosurgery (30 Gy in 5 fractions) are both radiosurgery options with multiple other acceptable radiosurgery prescriptions as stated in cases 2 and 3. Conventional fractionation may be preferred because of brainstem proximity and higher grade diseases. An alternative conventional fractionation regimen is 54 Gy in 30 fractions to the PTV (3 mm expansion off gross disease) with an SIB of 60 Gy to PET avid gross disease given the eloquence and risk of late effects.

Discussion

Higher grade meningiomas require interdisciplinary management and often require radiation therapy. Novel imaging tools such as (68)Ga-DOTATATE PET/CT are becoming more widely adopted for target delineation and to increase radiation precision. As PET guided radiation becomes more common, consensus contouring guidelines are needed. RTOG 0539 informs modern meningioma radiation therapy management but recommends large expansion margins of up to 2 cm in normal brain tissue, even in the absence of brain invasion.[2,3] Volume adjustments around the dura and

Table 1 Consensus guidelines summary

Cases	Dose to PET avid area (Gy)	Consider dose-escalation	CTV margin around PET avid area (mm)	Dose to postoperative cavity (Gy)	CTV margin around postoperative cavity
Case 1 (grade 3 STR)	66-70	Yes	0-5	59.4-60	0-10 mm into brain (use 5-10 mm margin if brain invasion), 5-15 mm along dura
Case 2 (grade 2 STR)	60-70	Yes	0-5	59.4-60	0-10 mm into brain (use 5-10 mm margin if brain invasion), 0-10 mm along dura
Case 3 (grade 1 recurrence)	54-60, consider SRS alone	Yes	0-5	0-54	Consider 5 mm dural expansion
Case 4 (grade 2 STR, bone involvement)	60-70	Yes	0-5	59.4-60	5-10 mm into dura and bone
Case 5 (grade 2 eloquent area)	59.4-66, consider SRS alone	Yes	0-5	0-60	Consider 5 mm dural expansion

For PET guided volume, a 0-3 mm PTV expansion is recommended. For the postoperative cavity CTV, with a thermoplastic mask and daily image guided radiation therapy, a 3 mm PTV expansion is appropriate. Sequential boost is recommended for cases 1-5 but SIB is also appropriate.

Abbreviations: CTV = clinical target volume; PET = positron emission tomography; PTV = planning target volume; SIB = simultaneous integrated boost; SRS = stereotactic radiosurgery; STR = subtotal resection.

falx remain controversial topics. There have been competing studies suggesting that dural tail inclusion in radiation therapy plans may or may not affect recurrence patterns.[18,19]

These controversies show the urgent need for biomarker guided treatments to create more conformal radiation treatments. Anatomic boundaries that are informed by both preoperative MRI and PET imaging could become a new standard for meningioma patients treated with radiation. Standardization of contouring could allow more effective targeting of active disease, easier comparison of treatment outcomes between different institutions, and more effective integration of PET imaging into meningioma clinical trials. Two modern clinical trials, ROAM/EORTC-1308 and NRG-BN003, compared early adjuvant radiation versus observation after GTR of a grade 2 meningioma, but PET imaging was not required for trial inclusion and did not guide management.[20] Consensus contouring guidelines can guide future clinical trials for meningiomas.

Strengths of this study include inclusion of a diverse set of physicians with decades of experience treating meningioma patients. A comprehensive list of case examples covers most indications for adjuvant radiation therapy after surgical resection (Table 1). Alternative recommendations for each case are provided to account for variations in provider or institutional preference. Each grade of meningioma is included, with unique examples of tumors in eloquent areas, brain invasion, and bone invasion, offering guidance for more challenging situations. Recent guidelines, published after attaining consensus opinions for this current study, corroborate the benefits of using PET for meningioma planning.[21] One weakness of this study is a lack of randomized evidence comparing PET guided radiation to standard MRI guidance. Dose-escalation, albeit with promising results, is not yet recommended in NCCN guidelines for patients with grade 1 or 2 tumors.[22] Efficacy of PET guided radiation is limited to small single-institution trials and registries.[9,23] It is unclear whether targeting just PET avid disease without treatment of the postoperative cavity or dura, or with deescalated dose to the cavity and dura, increases the risk of local recurrence for patients for higher grade tumors, and this was not recommended in our guidelines; further evaluation is required to determine the benefits of deferring postoperative cavity treatment. The majority of DOTATATE PET data in meningioma has come from lower grade tumors, and the degree to which microscopic dural invasion under the detection limit for PET with higher grade tumors is unknown. Given the anatomic diversity of meningioma presentation and multiple contouring and technological approaches for treatment, it is challenging to provide a single generalizable consensus contour.

Conclusions

This is the first publication defining standardized meningioma contouring guidelines for PET guided radiation. These guidelines can serve as a template for radiation management of meningiomas and can allow for more standardized target definitions in meningioma protocols and clinical practice.

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