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[^{68}Ga]-DOTATATE PET/MRI as an adjunct imaging modality for radiation treatment planning of meningiomas

Sean S. Mahase[†], Diana A. Roth O'Brien[†], Diana No, Michelle Roytman, Myrto E. Skafida, Eaton Lin, Nicolas A. Karakatsanis, Joseph R. Osborne, Andrew Brandmaier, Susan C. Pannullo, Rohan Ramakrishna, Philip E. Stieg, Jonathan P. S. Knisely[†], and Jana Ivanidze[†]

Department of Radiation Oncology, Weill Cornell Medicine, New York, New York, USA (S.S.M., D.A.R., D.N., A.B., J.P.S.K.); Department of Radiology, Weill Cornell Medicine, New York, New York, USA (M.R., M.E.S., E.L., N.A.K., J.R.O., J.I.); Department of Neurological Surgery, Weill Cornell Medicine, New York, New York, USA (S.C.P., R.R., P.E.S.)

Corresponding Author: Jana Ivanidze, MD, PhD, Department of Radiology, Weill Cornell Medicine, New York, NY, USA (jai9018@med.cornell.edu).

[†]*These authors contributed equally to this work.*

Abstract

Background. Meningiomas express high levels of somatostatin receptor 2 (SSTR2). SSTR2-targeted PET imaging with [^{68}Ga]-DOTATATE can aid with distinguishing residual meningioma from reactive changes in the postoperative setting. We present initial dosimetric analyses, acute events, and local control data utilizing [^{68}Ga]-DOTATATE PET/MRI-assisted target delineation for prospectively-treated intermediate-risk meningiomas.

Methods. Twenty-nine patients underwent DOTATATE PET/MRI meningioma evaluation in 2019. Eight patients with 9 postoperative meningiomas met RTOG 0539 intermediate-risk criteria (recurrent WHO grade I, 1/9; WHO grade II, 8/9). Target volumes were created using DOTATATE PET/MRI to determine residual disease and received a nominal dose of 35.0 Gy over 5 fractions. For comparison, cases were recontoured and planned with MRI alone per RTOG 0539 guidelines. Mean and maximum equivalent 2 Gy doses were generated for target volumes and organs at risk (OAR) within 1 cm of the PTV and compared using Wilcoxon matched pairs signed rank test.

Results. DOTATATE PET/MRI-guided planning significantly reduced mean PTV (11.12 cm^3 compared to 71.39 cm^3 based on MRI alone, $P < .05$) and mean and max dose to the whole brain, optic nerves, and scalp. PET/MRI plans resulted in at least 50% reduction of mean and max doses to the lens, eyes, chiasm, cochlea, brainstem, and hippocampi. One patient experienced focal alopecia. There were no local recurrences at 6 months.

Conclusion. Incorporating DOTATATE-PET/MRI for postoperative target delineation in patients with intermediate-risk intracranial meningiomas results in PTV reduction and decreased OAR dose. Our findings warrant larger studies evaluating DOTATATE-PET/MRI in the radiotherapeutic planning of postoperative meningiomas.

Key Points

- [^{68}Ga]-DOTATATE PET/MRI significantly reduces radiation treatment volumes.
- Reduced target volumes allowed safe delivery of hypofractionated radiotherapy.

Importance of the Study

Imaging with [68Ga]-DOTATATE, which targets somatostatin receptor 2A (SSTR2A), has demonstrated clinical utility in delineating residual meningioma in the postoperative setting. In this study, patients with intermediate-risk meningiomas necessitating postoperative radiotherapy underwent dosimetric analyses comparing DOTATATE PET/MRI-assisted target delineation to standard-of-care MRI-based planning. DOTATATE-PET/MRI significantly reduced target volumes and the dose received by organs at risk. Among patients treated with DOTATATE-based planning, 1 experienced focal alopecia, and no local recurrences were observed at 6 months. This pilot prospective study provides initial validation incorporating [68Ga]-DOTATATE PET/MRI in the radiotherapeutic management of postoperative intermediate-risk meningiomas. These findings warrant larger trials evaluating its application in the postoperative setting, as well as comparing its efficacy to that of other SSTR2-targeted agents.

Meningiomas are the most common intracranial neoplasms, comprising 36.1% of primary brain tumors.[1] Pathological grading is prognostic of patient outcomes[2–4] and will become increasingly vital to guiding treatment as atypical meningioma diagnoses rise with successive changes in WHO classification criteria.[2,4,5] The multidisciplinary approach to meningioma management traditionally centers on clinical judgment and institutional guidelines. Control rates following surgery are dependent on both tumor grade and the extent of resection. Simpson grade I-III resections are often considered definitive for WHO grade I meningiomas, while grade II and III meningiomas frequently recur following even an apparent gross total resection.[6,7] Similarly, recurrent meningiomas of any grade exhibit a more aggressive clinical course and can recur years after treatment.[7,8]

Adjunct external beam radiotherapy (EBRT) or stereotactic radiosurgery/fractionated stereotactic radiosurgery (SRS/fSRS) can improve outcomes in select meningioma subsets at higher risk of recurrence, such as subtotally resected and locally recurrent meningiomas.[6,8,9] Radiotherapy for intermediate-risk group recurrent WHO grade I meningiomas or totally resected grade II meningiomas was prospectively evaluated in the Radiation Therapy Oncology Group (RTOG) 0539 study. They demonstrated superior 3-year-progression-free survival rates in intermediate-risk meningiomas treated with adjuvant radiotherapy compared with historical data.[10]

Accurate delineation of the tumor volume and/or resection cavity is crucial to optimizing treatment delivery while minimizing radiotherapy-related sequelae. The implementation of 3D-based planning with incorporating MRI improved local control.[11] Nevertheless, MRI-based postoperative delineation of residual disease extent can be challenging in the setting of infiltrative "en plaque" lesions, parenchymal invasion, and postoperative scarring.[10] Approaches increasing the irradiated volume to avoid a marginal miss will thus increase the probability of radiation-related morbidity.

Somatostatin receptor 2A (SSTR2A) is expressed with high sensitivity and specificity in meningiomas, supporting its use as a pathologic biomarker.[12–14] [68Ga]-DOTATOC hybrid PET/MRI provides precise morphological visualization of meningiomas, enabling reductions in the irradiated target volume.[15] A recent report demonstrated the utility of [68Ga]-DOTATATE to accurately assess the extent of disease in patients with recurrent meningiomas and differentiate residual/recurrent meningiomas from post-treatment change.[16] Building on these findings, we present initial volumetric and dosimetric analyses utilizing [68Ga]-DOTATATE PET/MRI as an adjunct imaging modality in the planning of radiation volumes for prospectively treated meningiomas. As secondary aims, we report acute adverse events and 6-month outcomes.

Methods

Study Design

The cohort entails all patients who underwent [68Ga]-DOTATATE PET/MRI prior to fSRS at New York Presbyterian - Weill Cornell Medicine in 2019. Each patient's demographic data, tumor characteristics, prior treatments, and clinical response were obtained from querying electronic medical records. This study was approved by the Weill Cornell Medicine Institutional Review Board. All patients were referred for radiotherapy consultation following discussion in our multidisciplinary neuro-oncology tumor board either immediately after surgical resection or upon disease progression. Options discussed with patients included continued observation, EBRT and participation as study subjects in NRG-BN003 (which would entail randomization between observation and partial brain radiotherapy), and the possibility of fSRS based upon [68Ga]-DOTATATE PET/MRI. The decision to perform fSRS was made in consensus between patient, referring neurosurgeon, and radiation oncologist.

[68Ga]-DOTATATE PET/MRI

PET/MRI was performed on a Biograph mMR scanner (Siemens Healthineers, Erlangen, Germany) according to

our previously described institutional protocol.[17] Briefly, PET imaging started at 5–15 min postinjection of approximately 5 millicuries of [^{68}Ga]-DOTATATE. PET data were acquired in 3D List Mode for a total of 50 min, to allow for subsequent static and dynamic PET data analysis. MRI was performed during the same period as previously described,[15,18] including pre- and post-contrast sagittal 3D T2 FLAIR (TR/TE 6300–8500 ms/394–446 ms, 120 degree flip, 1 mm slice thickness) and 3D T1 SPACE (TR/TE 600–700 ms/11–19 ms, 120 degree flip, 1 mm slice thickness). MR-based attenuation correction was performed according to the manufacturer's standard-of-care specifications for brain PET/MR exams. For reference purposes, maximum standardized uptake values (SUVmax) were obtained for the pituitary gland (the only intracranial site of high physiologic SSTR2 expression) as a positive reference and the superior sagittal sinus (SSS) as a negative reference given lack of SSTR2 expression and its function as cranial blood pool.[17]

Meningioma Detection With [^{68}Ga]-DOTATATE PET/MRI

We previously evaluated the utility of differentiating meningioma from post-treatment change using the SSS as a background reference region and demonstrated marked, statistically significant differences in mean SUV_{max} ratio of meningioma/SSS versus post-treatment change/SSS.[17] Based on this previous work, we considered lesions with greater than 3-fold increase in SUV_{max} compared to SSS to be suspicious for tumor, and lesions with less than 3-fold increase versus SSS SUVmax were favored to represent postsurgical change.

Radiotherapy Planning and Delivery

Radiotherapy planning volumes were contoured by an attending radiation oncologist in conjunction with a neurosurgeon, and in consultation with the radiologist (dual trained in neuroradiology and nuclear medicine). For treatment planning, high-resolution thin-slice (1.25 mm) CT scans were rigidly fused with [^{68}Ga]-DOTATATE PET/MRI data sets. Clinical target volumes (CTV) were derived using gross disease identified on MRI and regions of increased SSTR2 avidity[17] on the [^{68}Ga]-DOTATATE PET/MRI, employing the appropriate PET SUV windowing as per the radiologist's recommendation and based on previously published studies.[10,17] All CTV were given an isometric 3.0 mm expansion to generate the planning target volume (PTV).

Ascribing an α/β=6 for atypical meningiomas allows the calculation of a biologically equivalent dose of 70.2 Gray (Gy) for a patient receiving 54.0 Gy over 30 fractions based on RTOG 0539. Our patients received a course of hypofractionated radiotherapy to a nominal dose of 35.0 Gy over 5 fractions, yielding a similar biologically effective dose of 75.83 Gy. All patients were treated using noncoplanar volumetric modulated arc therapy (VMAT) using 3–4 arcs and either 6× or 10× flattening filter-free beams that maintained a minimum coverage of 95% of the PTV receiving 100% of the prescription dose. The treatment plans were generated using Eclipse v15.6 (Varian Medical Systems) with either AAA or AcurosXB calculation algorithms. All dose constraints for hypofractionated radiotherapy plans were evaluated using TG101 guidelines. Patients were treated on a Novalis (BrainLab) Truebeam STX linac (Varian Medical Systems), with MLC leaf width of 2.5 mm. Departmental guidelines for hypofractionated treatments were followed, including Exactrac (BrainLab) kV imaging at each couch angle prior to delivery of a VMAT arc to ensure accurate stereotactic treatment delivery.

Patients were followed clinically with standard of care (SOC) MRI and clinic visits at 3-month intervals by their treating radiation oncologist and neurosurgeon. Per protocol, patients underwent follow-up [^{68}Ga]-DOTATATE PET/MRI 6 months after completion of fSRS to monitor for disease progression. Acute and chronic adverse events (AE) were tabulated using Common Terminology Criteria for Adverse Events (CTCAE version 5.0). Incidence rates of grade ≥2 acute (≤90 days from start of radiation) and late (>90 days) AEs for dermatology, neurology, and ocular/visual were reported for all eligible patients who received protocol treatment. Local control was measured to date of progression or last follow-up.

Creation of Comparative Standard of Care Volumes

Each patient was re-contoured per guidelines delineated for the intermediate-risk group cohort in RTOG 0539 (defined as patients with a newly diagnosed gross totally resected WHO grade II meningioma, or a recurrent WHO grade I meningioma irrespective of the resection extent)[12] using only preoperative and postoperative MRIs and the radiotherapy simulation scan to create the SOC CTV. The gross tumor volume (GTV) is defined by the tumor bed and any residual nodular enhancement on the postoperative MRI with contrast. Cerebral edema and the dural tail were not specifically included within the GTV. The GTV was isometrically expanded by 1.0 cm to create the CTV. The CTV margin was reduced to 0.5 cm around natural barriers to tumor growth such as the skull. However, in the presence of hyperostotic or directly infiltrated bone, the involved bone was included within the GTV, and thus encompassed by the CTV. A 3.0 mm isometric CTV expansion was used to create the SOC PTV for comparison for each patient. VMAT plans using 6 or 10 MV photons were generated using the SOC volumes prescribed to a dose of 54.0 Gy in 30 fractions. All target volumes and organs at risk (OARs) constraints were based on RTOG 0539 planning guidelines.[19]

Statistical Analyses

CTVs and PTVs developed from the [^{68}Ga]-DOTATATE PET/MRI assisted and SOC MRI-assisted plans were compared. All treatment-related data were converted to EQD2 for dosimetric analyses. In addition, the shortest distances of the target volumes to relevant organs at risk were investigated. All lesions with a distance ≤ 1.0 cm from these critical structures were analyzed. Mean and maximum

equivalent doses were generated for target volumes, and organs at risk within 1.0 cm of the PTV and compared using Wilcoxon matched pairs signed rank test. All statistical analyses were performed using Graphpad Prism version 8 (Graphpad Software).

Results

Study Population

Twenty-nine patients underwent DOTATATE PET/MRI for evaluation of their meningiomas from January 1, 2019 to December 31, 2019. Fourteen patients were treated with plans incorporating DOTATATE PET/MRI data, of which 8 patients with 9 postoperative meningiomas met intermediate-risk criteria per RTOG 0539 (recurrent WHO grade I, 1/9; WHO grade II, 8/9). Clinical and demographic characteristics of the study population are outlined in Table 1 and Supplementary Table 1. One patient received adjuvant radiotherapy for a residual meningioma, and later underwent a second course of fSRS for a spatially distinct new meningioma that was initially resected. Three patients were part of our prospective pilot cohort[17] and 5 patients were enrolled prospectively as part of our ongoing clinical trial, *DOMINO-START* (https://clinicaltrials.gov/ct2/show/NCT04081701).

Table 1. Demographic and Clinical Characteristics ($n = 8$; $m = 9$)[a]

Patient Characteristics	
Gender (*n*)	
Female	6
Male	2
Race (*n*)	
Caucasian	4
African American	2
Other	2
Age (years)	
Mean; Range	56; 28–76
KPS (*n*)	
≥70	8
<70	0
Residual or Recurrent (*m*)	
Residual	6
Recurrent	3
WHO grade (*m*)	
Grade I	1
Grade II	8
Time from surgery to radiotherapy (months)	
Average; range	16.4; 2–56

n = number of patients; *m* = number of meningiomas.
[a]One patient treated at 2 different time points for a spatially distinct recurrent meningioma and a residual meningioma.

Impact of [68Ga]-DOTATATE PET/MRI on Radiotherapy Planning

Employing [68Ga]-DOTATATE PET/MRI for radiotherapy planning resulted in GTV reductions in 5 patients (Table 2). Conversely, [68Ga]-DOTATATE PET/MRI detected previously unidentified subclinical disease in 3 patients. [68Ga]-DOTATATE PET/MRI-assisted radiotherapy planning resulted in significantly reduced PTVs compared to conventional MRI alone (mean 11.1 ± 4.1 cm^3, compared to 71.4 ± 49 cm^3; Figure 1). The BED_{max} (73.3 ± 11.0 Gy, compared to 62.5 ± 4.3 Gy) and the BED_{mean} (62.5 ± 4.6 Gy, compared to 55.3 ± 1.3 Gy) received by the PTVs were higher among DOTATATE-PET/MRI-guided plans, respectively. Dosimetric evaluation of organs at risk within 1.0 cm of the PTV demonstrated that [68Ga]-DOTATATE PET/MRI-assisted radiotherapy planning significantly reduced the mean and max doses received by the whole brain, scalp, and optic nerves (Table 3). Additionally, [68Ga]-DOTATATE PET/MRI-guided plans reduced mean and max doses to the lens, eyes, chiasm, cochlea, brainstem, and hippocampi by at least 50%, but these reductions did not meet statistical significance (Figure 2). Acute side effects were limited to one instance of acute grade one alopecia. No recurrences were detected at 6-month post-treatment imaging follow-up (Figure 3).

Discussion

This pilot study validates implementing [68Ga]-DOTATATE PET/MRI as an adjunct imaging modality for radiotherapy planning and delivery for meningiomas. Meningiomas comprise a heterogeneous group of benign neoplasms whose post-resection control rates are dependent on several factors, including grade, resection extent, tumor location, and recurrent disease.[3,4,6–8,20] Thus, physicians must be cognizant of factors potentially compounding a patient's recurrence risk, such that an appropriate consideration for radiotherapy can be made to improve local control in the adjuvant or recurrent setting.[7,8,11,18–21] Despite overwhelming data in favor of radiotherapy in meningioma management, there are concerns about potential AEs. However, technological advancements, in parallel with improvements in treatment planning software, enable more conformal EBRT planning, resulting in higher cumulative dose delivery while minimizing toxicities. The incorporation of [68Ga]-DOTATATE PET/MRI, entailing the use of a highly specific tumor-specific marker to precisely guide treatment, may herald the next step in radiotherapy planning for meningiomas.

Using SSTR-targeted molecular imaging in radiotherapy planning is an active area of investigative interest, with [68Ga]-DOTATOC, [68Ga]-DOTATATE, and [68Ga]-DOTANOC among the most commonly used ligands.[22] In prior studies, [68Ga]-DOTATOC avidity provided complementary information particularly in skull-base lesions,[23] with improved delineation of tumor extension affecting the CTV,[24] and GTV.[25] [68Ga]-DOTATOC PET resulted in significant PTV modifications in patients undergoing EBRT, with no evidence of recurrence at 1-year follow-up in a patient who had no PET-avid disease following resection, suggesting

Table 2. Individual Patient and Tumor Characteristics

Patient Number	Age	Gender	Race	KPS	Tumor Location	Residual/ Recurrent	Simpson Grade	Ki-67 (%)	WHO Grade	Time From Surgery to Radiotherapy (months)
1	36	F	Caucasian	100	Superior sagittal sinus	Residual	4	3	II	6
2	73	M	Caucasian	90	Superior sagittal sinus	Residual	2	9	II	2
3A[a]	66	F	Asian	80	Post-central gyrus	Residual	1	8	II	5
3B[a]	66	F	Asian	80	Frontal convexity and anterior falx	Recurrent	1	8	II	11
4	76	F	Caucasian	90	Parasagittal	Recurrent	1	8	II	56
5	28	M	Other	90	Frontal	Residual	1	2	II	15.5
6	44	F	African American	100	Cerebellopontine angle	Residual	4	15	II	5.3
7	51	F	Caucasian	100	Parietal convexity	Residual	2	Not available	II	7
8	64	F	African American	100	Olfactory groove	Recurrent	1	<5	I	40

[a]One patient treated at 2 different time points for a spatially distinct recurrent meningioma and a residual meningioma.

Figure 1. DOTATATE PET/MRI reduces radiotherapy planning target volumes. Comparative PTVs for patient 1 (see Table 2 for clinical information and Table 3 for dosimetric data). (A) sagittal and (B) coronal images rendered using iPlan software (BrainLab) demonstrating PTV drawn based on DOTATATE PET/MRI fusion: 15.4 cm^3. (C) sagittal and (D) coronal images demonstrating SOC PTV based on RTOG 0539 using only preoperative and postoperative MRIs: 105.0 cm^3. A 3.0 mm CTV expansion was used to create the PTV in both plans. CTV = clinical target volume; PTVs = planning target volumes; RTOG = radiation therapy oncology group; SOC = standard of care.

SSTR-targeted PET can be used to select patients who may be spared adjuvant radiotherapy.[26] These findings culminated in the National Comprehensive Cancer Network guidelines permitting SSTR-based imaging to aid in delineating tumor extent in the initial treatment setting, and to distinguish residual/recurrent disease from postoperative scar tissue.[27] Furthermore, feasibility of PET-based radiotherapy planning in high-grade meningioma has recently been demonstrated in a retrospective study.[28]

[^{68}Ga]-DOTATATE-PET shares binding homology with [^{68}Ga]-DOTATOC-PET but possesses a 10-fold higher receptor affinity.[10] [^{68}Ga]-DOTATATE-PET avidity has been shown to correlate with SSTR expression, with a higher sensitivity (90% vs 79%) than MRI for detecting meningiomas, with similar specificity.[16] We recently reported using [^{68}Ga]-DOTATATE-PET in a cohort of 20 patients, showing [^{68}Ga]-DOTATATE-PET successfully confirmed the presence of recurrent meningioma in 17 cases. [^{68}Ga]-DOTATATE-PET was also able to distinguish post-treatment change or chronic reactive dural thickening from recurrence, and aided in evaluating disease extent regarding base of skull lesions, as well as ascertaining osseous invasion and detecting the presence of previously undiagnosed meningiomas.[17]

Novel imaging modalities that accurately identify residual meningioma in a postoperative bed may improve

Table 3. Dosimetry of Contoured Organs at Risk ≤ 10 mm From Planning Target Volume

Organ at Risk	Mean Dose SOC – Plan (Gy)	Mean Dose DOTATATE - Assisted Plan (Gy)	*P*-value	Max Dose SOC – Plan (Gy)	Max Dose DOTATATE - Assisted Plan (Gy)	*P*-value
Whole brain	6.582	1.611	<.05	60.97	71.41	<.05
Scalp	8.726	1.723	<.05	54.29	18.85	<.05
Optic nerves	17.44	4.86	<.05	41.36	17.29	<.05
Brainstem	15.84	6.7	>.05	46.34	48.26	>.05
Chiasm	28.08	12.9	>.05	30.64	25.44	>.05
Cochlea	53	28.1	>.05	57.59	46.58	>.05
Eyes	9.933	3.967	>.05	28.5	23.28	>.05
Lens	6.55	2.92	>.05	19.73	5.54	>.05
Hippocampi	19.02	6.94	>.05	57.17	56.98	>.05
Lacrimal gland	37.58	24.04	>.05	53.72	57.87	>.05

Gy = gray; SOC = standard of care.

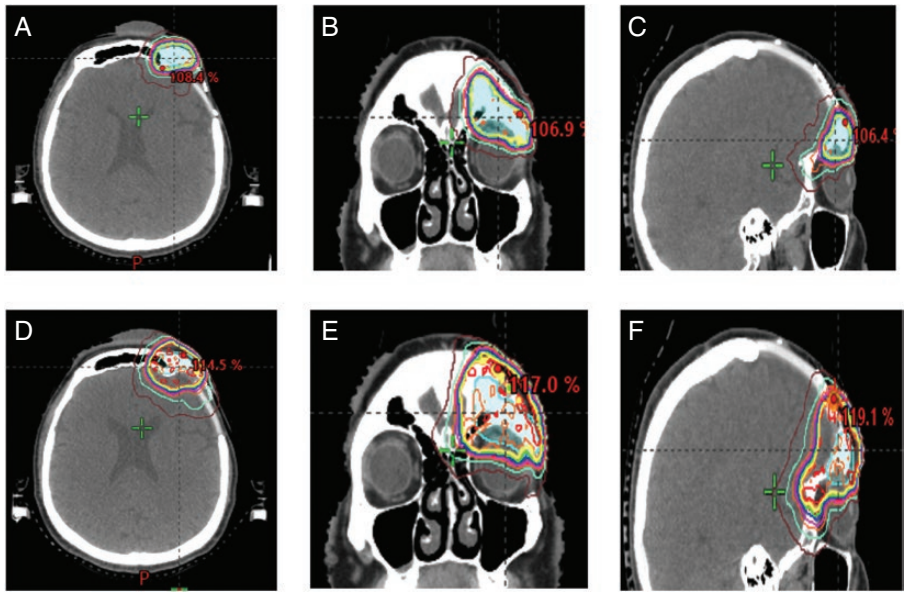

Figure 2. DOTATATE PET/MRI-guided radiotherapy reduces dose to adjacent organs at risk. Comparative isodose plans for patient 6 (see Table 2 for clinical information and Table 3 for dosimetric data) generated using Eclipse v15.6 (Varian Medical Systems) with both AAA and AcurosXB calculation algorithms. (A) axial (B) coronal and (C) sagittal representative images for treated plan using DOTATATE PET/MRI guided fusion. (D) axial (E) coronal and (F) sagittal representative images for SOC plan based on RTOG 0539 using only preoperative and postoperative MRIs. A 3.0 mm CTV expansion was used to create the PTV in both plans. *Isodose lines:* Red = 110%; orange = 105%; yellow = 100%; green = 95%; blue =90%; magenta = 80%; teal = 50%; brown = 30%. CTV = clinical target volume; PTVs = planning target volumes; RTOG = radiation therapy oncology group; SOC = standard of care.

radiotherapy targeting. The potential clinical benefit of integrating molecular imaging information to refine radiotherapy treatment volumes is an emerging concept with favorable results in other disease sites.[29] Thus, the FDA recently approved [68Ga]-PSMA-11, the first drug for PET imaging in patients with prostate cancer which allows highly specific assessment for primary diagnosis, evaluation for local soft tissue recurrence, and quantification of metastatic disease burden.[30] In lymphoma, [18F]FDG PET/CT has demonstrated improved clinical outcomes when incorporated in radiotherapy planning in a large multicenter study.[31]

SRS is a promising method to minimize AEs by virtue of conformally delivering high radiotherapy doses to meningiomas[32] with comparable local control outcomes to EBRT.[33] Normal tissue complications will be lower when normal tissues can be accurately excluded from the high-dose volume, but the effectiveness of the irradiation is

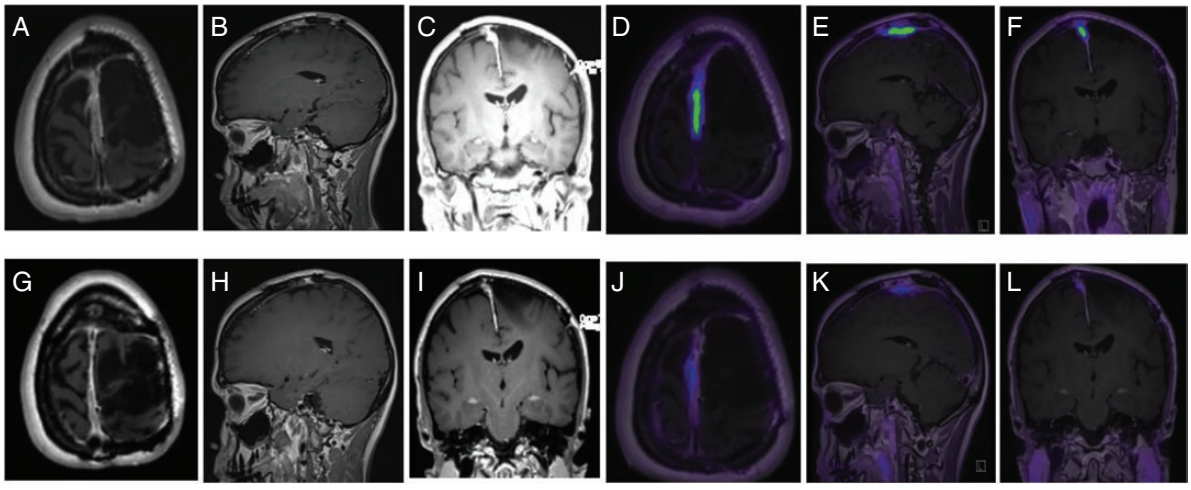

Figure 3. Pre- and postradiotherapy imaging of treated patient. Top row: (A) axial (B) sagittal and (C) coronal MRI T1 post-contrast and (D) axial (E) sagittal and (F) coronal PET fused representative images for patient 1 prior to radiotherapy (see Table 2 for clinical information and Table 3 for dosimetric data). Bottom row: (G) axial (H) sagittal (I) coronal MRI T1 post-contrast and (J) axial (K) sagittal and (L) coronal PET fused representative images for patient 1 at 6 months postradiotherapy.

reliant on accurately targeting neoplastic cells to avoid marginal misses and the need for salvage treatments. The inability to correctly delineate and treat subclinical disease with SRS was a major factor for excluding its use in RTOG 0539, which accounted for remaining postoperative microscopic disease through treatment of the entire resection cavity with an additional 0.5–1.0 cm CTV expansion.[19] While there has been no standardized approach for partial brain irradiation for WHO-II meningiomas and there is no recognized standard of management, the standardized contouring guidelines of RTOG-0539 provide useful information about local control and toxicity. Utilizing [^{68}Ga]-DOTATATE-PET to precisely locate and delineate residual postoperative disease reduces radiotherapy CTVs to an extent enabling safe SRS delivery. A recent meta-analysis of 12 retrospective studies reported an increased use of fractionated regimens correlated with escalating tumor size, with median tumor volumes of 2.84, 5.45, and 12.75 cm^3 being treated with SRS, fSRT, and conventionally fractionated EBRT, respectively. Furthermore, SRS as a radiation modality was associated with worse tumor control and high rates of AEs.[34] These findings may be dependent on the ability to precisely define the location and volume of residual meningioma cells, which also impacts the dose delivered to adjacent normal tissues.

The implementation of DOTATATE-PET/MRI helps discern subclinical disease in the postoperative setting, where residual/recurrent meningioma may be difficult to differentiate from postoperative scar tissue. This is particularly relevant in the setting of subtotal resections (Simpson Grade II and higher) necessitated because of critical neurovascular structure involvement, where the residual, unresected tumor is the most likely site for continued progression of tumor growth. The ability to accurately delineate neoplastic cells using DOTATATE-PET/MRI enables reducing the CTV for SRS/fSRS, and promotes feasible dose escalation. Suggested EBRT doses historically range between 50 and 60 Gy,[19,21] with doses above 52 Gy conferring improved control.[19] While grade I meningiomas have a low α/β (reported as 3.28 by Shrieve et al.) characteristic of late-responding tissues, atypical meningioma growth rate is reflective of a higher α/β.[35,36] Ascribing an α/β=6 for atypical meningiomas produced a biologically equivalent dose of 70.20 Gy and an equivalent 2 Gy per fraction (EQD2) of 52.65 Gy if a patient received 54.0 Gy over 30 fractions. To maintain similar effective dosing, patients undergoing fSRS in our cohort received a nominal dose of 35 Gy over 5 fractions, yielding a biologically effective dose of 75.83 Gy and EQD2 of 56.88 Gy, which is in line with the recommended dosing of the aforementioned studies.

Limitations of our study include a small sample size and lack of long-term clinical follow-up beyond 6 months. A randomized trial comparing DOTATATE PET-based planning to SOC planning is warranted to definitely determine the benefit of this emerging modality. Furthermore, a single case of an SSTR2-negative meningioma has recently been reported,[37] and while this is rare given previously reported 100% sensitivity of SSTR2 for meningioma in the pathology literature,[38] it is an additional consideration in PET-negative patients. Finally, small PET-negative foci of enhancement on MRI may potentially reflect foci of meningioma below the resolution of PET; thus, MRI data must be incorporated when differentiating meningioma from post-treatment change. Another limitation entails impact of the tumor location on resection extent and subsequent radiotherapy planning. As discussed above, MRI-based CTV planning can be reduced from 1.0 to 0.5 cm if there is a barrier to tumor spread. Additionally, meningiomas involving the SSS

create significant technical resection challenges due to their relationship with critical vascular structures, which will directly impact radiotherapy planning.[39,40] A larger treatment cohort is warranted to elucidate potential anatomical factors negatively impacting sustained local control following adjuvant radiotherapy.

[68Ga]-DOTATATE-PET/MRI improves target delineation for radiotherapy in patients with intracranial meningiomas in the postoperative setting, resulting in GTV reduction and decreased OAR dose, compared with plans generated from only MRI-based planning. This in turn promotes the feasibility of using fSRS for postoperative meningioma EBRT. Our findings warrant larger studies evaluating DOTATATE-PET/MRI in the radiotherapeutic planning of meningiomas.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

meningioma | [68Ga]-DOTATATE PET/MRI | radiosurgery | somatostatin receptor 2

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Authorship Statement. Conceptualization: J.I. Patient management: J.I., J.P.S.K., E.L., A.B., S.C.P., R.R., and P.E.S. Data curation: S.S.M., D.A.R., D.N., M.R., M.E.S., and E.L. Formal analysis: J.I., S.S.M., and D.A.R. Writing review and editing: S.S.M., D.A.R., M.R., M.E.S., E.L., N.A.K., J.R.O., A.B., S.C.P., R.R., P.E.S., J.P.S.K., and J.I. Authors responsible for statistical analyses: D.A.R. and J.I.

Data Availability

All data generated and analyzed during this study are included in this published article. Clinical trial information: *DOMINO-START* (https://clinicaltrials.gov/ct2/show/NCT04081701)

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