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The Complementary Role of ^{68}Ga-DOTATATE PET/CT in Diagnosis of Recurrent Meningioma

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The authors have no disclosure to claim. The off-label use of Ga68-DOTATATE tracer in diagnosis of recurrent meningioma is discussed in the manuscript.

Part of the content were presented as an Educational Exhibit at RSNA 2019.

Short title: DOTATATE PET in Diagnosis of Meningioma

Abstract:

Introduction: Contrast-enhanced brain MRI is the choice of imaging modality in diagnosis and posttreatment evaluation, its role is limited in distinguishing recurrent lesion from postoperative change. ^{68}Ga-DOTATATE is a somatostatin analog PET tracer which has high affinity to meningioma expressing somatostatin receptor. **Methods and subjects**: In this case series review, we described 8 patients with brain MRI suspected of recurrent meningioma who underwent focused ^{68}Ga-DOTATATE PET/CT scan for radiation treatment planning. **Results**: The combined brain MRI and PET/CT allowed improved conspicuity of the lesions and aided radiation treatment planning. The time from the initial surgery to PET/CT scans varied widely ranging from 1 year to 12 years. Three patients had PET/CT shortly after the initial surgery (1-3 years) and underwent targeted radiation therapy. Subsequent imaging showed no evidence of recurrence. Four patients had prolonged time between the PET/CT and the initial surgery (7-12 years) which showed extensive tumor burden. All four patients expired shortly after the last PET/CT scan. **Conclusion**: ^{68}Ga-DOTATATE PET shows promising complementary role in detection and treatment planning of recurrent meningioma.

Key words: Meningioma; somatostatin receptor; DOTATATE; octreotide

Introduction

Meningioma is the most common primary central nervous tumor accounting for approximately 27% of all intracranial tumors. (*1-3*) Based on histologic features and its local aggressiveness, meningiomas are grouped into three types in WHO grading scale: WHO grade I-III. While the majority of meningiomas are grade I, factors such as mitoses and aggressive histology can predict for higher rate of recurrence. (*4*) The most common locations of meningioma are the sites of dural reflection, including falx cerebri, tentorium cerebelli, and venous sinuses. (*5*) Certain locations of the meningioma are associated with increased morbidity and mortality, and poses challenge in treatment, regardless of its grading.

The standard treatment for symptomatic meningioma is surgical resection with complete removal of the tumor being the main determinant factor for its prognosis. Meningioma recurrence requiring a second operation is a poor prognostic factor, along with malignant degeneration of the recurrent tumors. (*6,7*) Radiation therapy is another treatment option for malignant and recurrent meningioma although its role in benign meningioma remains controversial.(*7*) Despite these therapeutic options, the overall 10-year survival of benign meningioma is 87% while the 10-year survival for malignant meningioma remains approximately at 60%.(*8*)

Contrast enhanced magnetic resonance imaging (CE-MRI) is the choice of imaging modality in diagnosis, treatment planning and post-operative evaluation of meningioma. However, CE-MRI has a limited role in distinguishing recurrent tumor from postoperative change. (9) Meningiomas exhibit strong somatostatin receptor expression, especially type 2 (SSTR-2), which can be detected by octreotide-based scintigraphy, ^{111}Indium-Octreotide SPECT (Octreoscan).(*10,11*) In the last decade, ^{68}Gallium(Ga)-labelled somatostatin analog PET tracers

have been used in the diagnosis and staging of gastroenteropancreatic neuroendocrine tumor (GEP-NET). Among them, ^{68}Ga-DOTATATE has gained growing popularity in imaging of meningioma given its high specificity and near 10-fold increased affinity to SSTR-2 compared to Octreoscan. ^{68}Ga-DOTATATE PET/CT plays a complementary role in imaging meningioma including recurrent and residual lesions. (*10,12-15*)

In this article, we report our initial experience in using combined brain CE-MRI and ^{68}Ga-DOTATATE PET/CT scans to identify recurrent meningioma and aid radiation therapy. We also discuss the potential theragnostic application of ^{68}Ga-DOTATATE in management of recurrent or nonresectable meningioma.

Case series

This study was conducted under the approval of the **institutional** review board. Patients who were diagnosed with recurrent meningioma or under clinical suspicion for recurrent meningioma in 2017- 2021 were retrospectively identified.

Surveillance CE-MRIs with ^{68}GaDOTATATE PET/CT scan were performed on all cases. Brain MRI scans were performed on 1.5T or 3T scans under routine MRI brain tumor protocol with multiple sequences consisting of 3-dimensional (3-D) T1, T2, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and gadolinium contrast enhanced 3-D T1, and T1-weighted spoiled gradient echo (GRE) sequences. Dedicated brain MRI images are interpreted by fellowship trained neuroradiologists. To further define the tumor burden and guide subsequent treatment strategy, patients with suspicious focal enhancement on post contrast enhanced MR images underwent ^{68}Ga-DOTATATE PET/CT scan.

^{68}Ga-DOTATATE PET/CT scan of the head was performed 40 minutes after intravenous injection of 185±10% MBq ^{68}Ga-DOTATATE, with additional bone algorithm reconstruction CT images. Head PET/CT images were sent to an independent workstation (MIM Software, Inc) for interpretation by dual board (American Board of Radiology and American Board of Nuclear Medicine) certified nuclear radiologists.

The ultimate diagnosis of meningioma recurrence was made based on imaging. Diagnostic criteria included: 1) CE-MRI: Dura-based enhancing focus at the surgical bed, or new enhancing meningeal focus at other meningeal regions; 2) ^{68}Ga-DOTATATE PET/CT: Focal meningeal radiotracer uptake with corresponding dura-based mass on non-contrast CT. The head PET/CT data were subsequently co-registered with high resolution 3-D spoiled GRE sequences of brain MRI for further localization.

Results

Total of 8 patients with histopathologically proven meningioma following surgical resection were identified (Table 1). Each underwent CE-MRI and ^{68}GaDOTATATE PET/CT as a part of the post-surgical surveillance.

One patient showed no evidence of disease recurrence on 2 consecutive PET/CT's following surgical resection (case # 7) and remained well as of his last clinic visit without evidence of recurrence. The remaining 7 patients had PET positive recurrent lesions corresponding to the findings visualized on CE-MRI.

The time from the initial surgery to obtaining the PET/CT scans varied widely ranging from 1 year to 12 years (mean: 6.75 years). Three patients (case # 2, 6 and 8) obtained the

PET/CT scans in a relatively short period of time from the initial surgery (1, 3 and 1 years respectively) and both PET and MR imaging showed evidence of recurrence. Proton beam therapy and stereotactic radiation therapy plans were adjusted based on the PET/CT findings. This included changes in the radiation beam entry point and the trajectory of the radiation. Patients showed improvement in tumor burden on subsequent follow up CE-MRI and were doing well as of the last clinical follow-up visit without evidence of recurrence.

Four patients (case# 1, 3, 4, 5) obtained PET/CT after a longer period from the initial surgery (12, 8, 10 and 7 years respectively). Although octreotide therapy was initiated based on the PET/CT findings, all 4 patients had extensive tumor burden on the initial PET/CT and expired shortly after.

Case #1: A 69-year-old woman has clinical history of recurrent WHO grade 1 meningiomatosis, status post three craniotomies and one course of Cyberknife therapy. CE-MRI revealed multiple recurrent meningiomas. To accurately evaluate the recurrent tumoral burden, ^{68}Ga-DOTATATE PET/CT scan was performed. The combined brain MR and PET images depicted multiple variable sized, contrast enhanced somatostatin receptor positive meningiomas. The patient received embolization therapy followed by bevacizumab and octreotide. Patient died from progression of disease one year after the PET/CT scan. (**Figure 1**)

Case #2: An 82-year-old woman has history of WHO grade 2 atypical meningioma with invasion of the right temporalis muscle, calvarium, and dura status post subtotal resection. Large enhancing mass was confirmed on CE-MRI. Following surgical resection of the tumor, ^{68}Ga-

DOTATATE PET/CT was performed and showed recurrent disease at the surgical bed. This was not identified on CE-MRI due to surrounding post-surgical changes. This led to repeat craniotomy and definitive proton beam therapy. The ^{68}Ga-DOTATATE PET/CT was used to assist proton beam treatment planning. The patient remained free of residual tumor after the radiotherapy. (**Figure 2**)

Case # 6: A 72-year-old man has history of left frontal-parietal atypical meningioma (WHO grade 2), status post total tumor resection. The ^{68}Ga-DOTATATE PET images showed two recurrent foci at the vertex, which were not well-seen on CE-MRI given their locations. Radiation therapy planning was adjusted based on PET/CT findings including changes in radiation beam trajectory. Patient received 6000 cGy external beam therapy and had been symptom free since therapy. (**Figure 3)**

Discussion:

CE-MRI is the imaging of choice in the diagnosis of recurrent and residual meningioma. However, its role is limited as it cannot accurately distinguish viable tumors from post treatment change. Somatostatin receptor is a G-protein-coupled cell membrane receptor and can be activated by somatostatin or its synthetic analogs. In the brain, expression of SSTR-2 has been observed in meningioma. (*11,16*) While Octreoscan is a traditionally complementary imaging modality in surveillance of meningioma in post treatment patient population, ^{68}Ga-DOTATATE PET/CT scan is shown to be more effective in imaging meningioma given its high specificity and robust affinity to SSTR-2 with 10-fold increase compared to Octreoscan. (*10, 17-18*) Accumulating literatures have shown that PET/CT ligated to ^{68}Ga-DOTA analogues, including

DOTATOC, DOTANOC, and DOTATATE, have promising role in identifying and localizing meningioma and may play a complementary role in guiding therapy and predicting survival in select patients. (*12-15,19-23*)

In addition to meningioma, ^{68}Ga-DOTATATE uptake can be seen in other primary and secondary brain tumors, including hemangiopericytoma, and intracranial metastatic neuroendocrine tumor. Pituitary gland also demonstrates physiologic SSTR-2 expression, which could limit evaluation of an adjacent skull base meningioma. (*24-26*) Combined molecular imaging with CE-MRI is extremely helpful in this setting as it may help define the tumor margin and avoid unnecessary radiation exposure to the patient. We implemented bone reconstruction algorithm in our PET/CT protocol to aid visualization of osseous tumoral infiltration given its superiority in detecting subtle transosseous involvement. (*27*)

Our single center experience with fusion of ^{68}Ga-DOTATATE PET/CT and CE-MRI in a small cohort of patient group concurred with prior works that demonstrated vital role of the complementary ^{68}Ga-DOTATATE PET/CT scan in identifying recurrent meningiomas. For example, in case #2, the patient had WHO II meningioma which recurred following initial craniotomy. Despite CE-MRI showing no evidence of recurrence, follow-up ^{68}Ga-DOTATATE PET/CT demonstrated focal uptake suspicious for recurrence. This prompted repeat craniotomy and targeted proton beam therapy. The patient was clinical well as of the last clinic visit without evidence of recurrence on follow-up CE-MRI.

^{68}Ga-DOTATATE PET may also provide therapeutic potential when surgery is of limited role in certain patients. The somatostatin receptor targeted treatments consist of octreotide treatment and peptide receptor radionuclide therapy (PRRT). Clinical trials have shown long-acting somatostatin analogs' role in inhibiting the meningiomas proliferation. Schulz et al treated

8 patients with a progressive residual skull base meningioma after surgery using 30 mg octreotide. They found that octreotide stabilized the progression of recurrent skull base meningioma despite no convincible imaging evidence of tumor regression. (*28*) In our small cohort of patients, 4 patients received octreotide therapy and ^{68}Ga-DOTATATE PET/CT was used in identifying potential candidates for this pharmacologic therapy. Unfortunately, all 4 patients expired shortly after initiation of the therapy, likely due to the already extensive tumor burden at the time of diagnosis leading to limited octreotide therapy response. Perhaps the most potential treatment approach of recurrent meningioma is somatostatin receptor targeted PRRT, which is a novel theragnostic approach using either beta emission ^{90}Yttrium (Y) or ^{177}Lutetium (Lu) agents. Clinical trials for non-resectable and recurrent meningiomas have confirmed that PRRT has a promising role in treatment of unresectable meningioma with improved progression free status and may be an alternative approach in those with unfavorable response to traditional therapy. (*29-33*)

Our small retrospective case series has several limitations. None of our patients had histopathological correlation of ^{68}Ga-DOTATATE PET/CT findings and the diagnosis was made solely based on visual inspection of brain CE-MRI and ^{68}Ga-DOTATATE PET/CT images. We did not apply the standard uptake value (SUV) measurement to aid the diagnosis since there is no established standard imaging protocol among different institutions in imaging meningioma. Use of maximal SUV 2.3 as a cutoff value as used in Rachinger et al. to delineate tumor and tumor-free tissue is one of the examples that can be used in future studies. (*15*) Another limitation is no direct comparison of the diagnostic performance of brain MRI and ^{68}Ga-DOTATATE PET/CT in lesion detection given the lack of histopathological evidence as gold standard and the nature of

the study. Future large-scale, prospective investigation of ^{68}Ga-DOTATATE PET/CT in diagnosis of recurrent meningioma needs to overcome the shortcomings of this study.

Conclusion:

^{68}Ga-DOTATATE PET/CT is a promising complementary molecular imaging tool in detection of recurrent meningiomas. It may improve diagnostic accuracy and confidence in guiding clinical management, particularly in surgically challenging cases. ^{68}Ga-DOTATATE PET/CT also serves a vital role in radiation therapy planning. With somatostatin receptor targeted therapy on the horizon, ^{68}Ga-DOTATATE PET/CT may aid in selection of appropriate patients for PRRT, an emerging theragnostic approach in management of meningioma.

KEY POINTS:

QUESTION: What is the role of ^{68}Ga-DOTATA PET/CT in imaging meningioma?

PERTINENT FINDINGS: For recurrent meningioma, combined use of ^{68}Ga-DOTATATE PET/CT may enhance diagnostic accuracy and further guide clinical management. It has great potential to improve treatment outcome and prolong patient's life expectancy.

IMPLICATION FOR PATIENT CARE: ^{68}Ga-DOTATATE PET and brain MRI play a complementary role in imaging complicated recurrent meningioma.

Reference

1. Baldi I, Engelhardt J, Bonnet C, et al. Epidemiology of meningiomas. Neurochirurgie. 2018;64:5-14.

2. Davis FG, Kupelian V, Freels S, McCarthy B, Surawicz T. Prevalence estimates for primary brain tumors in the United States by behavior and major histology groups. Neuro Oncol. 2001;3:152-158.

3. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro Oncol. 2002;4:278-299.

4. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131:803-820.

5. Whittle IR, Smith C, Navoo P, Collie D. Meningiomas. Lancet. 2004;363:1535-1543.

6. Condra KS, Buatti JM, Mendenhall WM, Friedman WA, Marcus RB, Jr., Rhoton AL. Benign meningiomas: primary treatment selection affects survival. Int J Radiat Oncol Biol Phys. 1997;39:427-436.

7. Marosi C, Hassler M, Roessler K, et al. Meningioma. Crit Rev Oncol Hematol. 2008;67:153-171.

8. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2013-2017. Neuro Oncol. 2020;22:iv1-iv96.

9. Nowosielski M, Galldiks N, Iglseder S, et al. Diagnostic challenges in meningioma. Neuro Oncol. 2017;19:1588-1598.

10. Dromain C, Deandreis D, Scoazec JY, et al. Imaging of neuroendocrine tumors of the pancreas. Diagn Interv Imaging. 2016;97:1241-1257.

11. Schulz S, Pauli SU, Schulz S, et al. Immunohistochemical determination of five somatostatin receptors in meningioma reveals frequent overexpression of somatostatin receptor subtype sst2A. Clin Cancer Res. 2000;6:1865-1874.

12. Bashir A, Larsen VA, Ziebell M, Fugleholm K, Law I. Improved detection of postoperative residual meningioma with [(68)Ga]Ga-DOTA-TOC PET imaging using a high-resolution research tomograph PET scanner. Clin Cancer Res. 2021;27:2216-2225.

13. Galldiks N, Albert NL, Sommerauer M, et al. PET imaging in patients with meningioma-report of the RANO/PET Group. Neuro Oncol. 2017;19:1576-1587.

14. Ivanidze J, Roytman M, Lin E, et al. Gallium-68 DOTATATE PET in the evaluation of intracranial meningiomas. J Neuroimaging. 2019;29:650-656.

15. Rachinger W, Stoecklein VM, Terpolilli NA, et al. Increased 68Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. J Nucl Med. 2015;56:347-353.

16. Dutour A, Kumar U, Panetta R, et al. Expression of somatostatin receptor subtypes in human brain tumors. Int J Cancer. 1998;76:620-627.

17. Klutmann S, Bohuslavizki KH, Brenner W, et al. Somatostatin receptor scintigraphy in postsurgical follow-up examinations of meningioma. J Nucl Med. 1998;39:1913-1917.

18. Nathoo N, Ugokwe K, Chang AS, et al. The role of 111indium-octreotide brain scintigraphy in the diagnosis of cranial, dural-based meningiomas. J Neurooncol. 2007;81:167-174.

19. Afshar-Oromieh A, Giesel FL, Linhart HG, et al. Detection of cranial meningiomas: comparison of (6)(8)Ga-DOTATOC PET/CT and contrast-enhanced MRI. Eur J Nucl Med Mol Imaging. 2012;39:1409-1415.

20. Afshar-Oromieh A, Wolf MB, Kratochwil C, et al. Comparison of (6)(8)Ga-DOTATOC-PET/CT and PET/MRI hybrid systems in patients with cranial meningioma: Initial results. Neuro Oncol. 2015;17:312-319.

21. Collamati F, Pepe A, Bellini F, et al. Toward radioguided surgery with beta- decays: uptake of a somatostatin analogue, DOTATOC, in meningioma and high-grade glioma. J Nucl Med. 2015;56:3-8.

22. Henze M, Dimitrakopoulou-Strauss A, Milker-Zabel S, et al. Characterization of 68Ga-DOTA-D-Phe1-Tyr3-octreotide kinetics in patients with meningiomas. J Nucl Med. 2005;46:763-769.

23. Nyuyki F, Plotkin M, Graf R, et al. Potential impact of (68)Ga-DOTATOC PET/CT on stereotactic radiotherapy planning of meningiomas. Eur J Nucl Med Mol Imaging. 2010;37:310-318.

24. Hoberuck S, Michler E, Zophel K, Platzek I, Kotzerke J, Brogsitter C. Brain metastases of a neuroendocrine tumor visualized by 68Ga-DOTATATE PET/CT. Clin Nucl Med. 2019;44:50-52.

25. Kota G, Gupta P, Lesser GJ, Wilson JA, Mintz A. Somatostatin receptor molecular imaging for metastatic intracranial hemangiopericytoma. Clin Nucl Med. 2013;38:984-987.

26. Moradi F, Jamali M, Barkhodari A, et al. Spectrum of 68Ga-DOTA TATE uptake in patients with neuroendocrine tumors. Clin Nucl Med. 2016;41:e281-287.

27. Kunz WG, Jungblut LM, Kazmierczak PM, et al. Improved detection of transosseous meningiomas using 68Ga-DOTATATE PET/CT compared with contrast-enhanced MRI. J Nucl Med. 2017;58:1580-1587

28. Schulz C, Mathieu R, Kunz U, Mauer UM. Treatment of unresectable skull base meningiomas with somatostatin analogs. Neurosurg Focus. 2011;30:E11. doi: 10.3171/2011.1.FOCUS111.

29. Bartolomei M, Bodei L, De Cicco C, et al. Peptide receptor radionuclide therapy with (90)Y-DOTATOC in recurrent meningioma. Eur J Nucl Med Mol Imaging. 2009;36:1407-1416.

30. Gerster-Gillieron K, Forrer F, Maecke H, Mueller-Brand J, Merlo A, Cordier D. 90Y-DOTATOC as a therapeutic option for complex recurrent or progressive meningiomas. J Nucl Med. 2015;56:1748-1751.

31. Kreissl MC, Hanscheid H, Lohr M, et al. Combination of peptide receptor radionuclide therapy with fractionated external beam radiotherapy for treatment of advanced symptomatic meningioma. Radiat Oncol. 2012;7:99.

32. Seystahl K, Stoecklein V, Schuller U, et al. Somatostatin receptor-targeted radionuclide therapy for progressive meningioma: benefit linked to 68Ga-DOTATATE/-TOC uptake. Neuro Oncol. 2016;18:1538-1547.

33. Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and treatment of meningiomas. Lancet Oncol. 2016;17:e383-391.

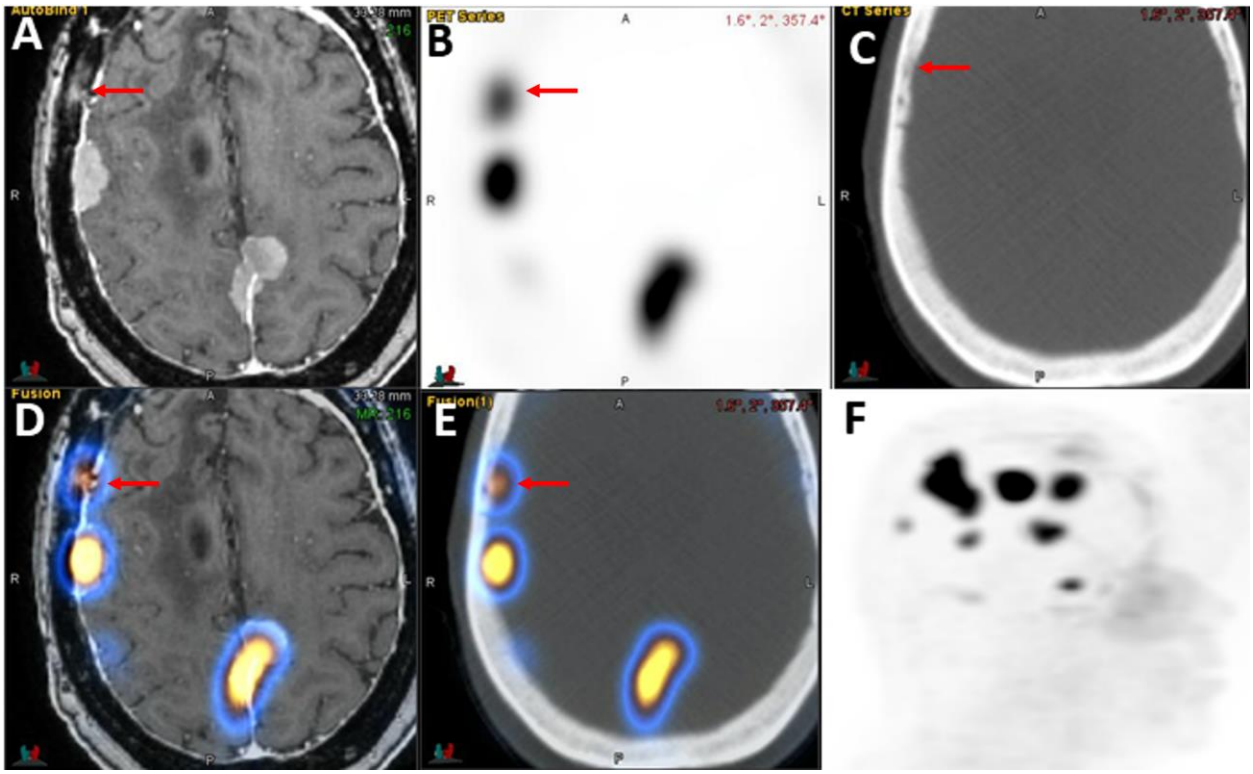

Figure 1. There are multiple variable-sized, dura-based enhancing lesions exhibiting somatostatin receptor positivity on ^{68}Ga-DOTATATAE PET/CT. Among the lesions, there is one tracer avid bone marrow focus on the right frontal bone, concerning for meningioma transosseous infiltration (red arrows). The Maximal intensity projection (MIP) image exhibited extensive tumor burden of recurrent meningioma. A: CE-MRI; B:^{68}Ga-DOTATATE PET; C: Low dose CT; D: PET/MR fusion; E: PET/CT fusion, and F: PET-MIP image.

CT

PET

CE-MRI

PET/MR Fusion

PET/CT Fusion

F/u CE MRI

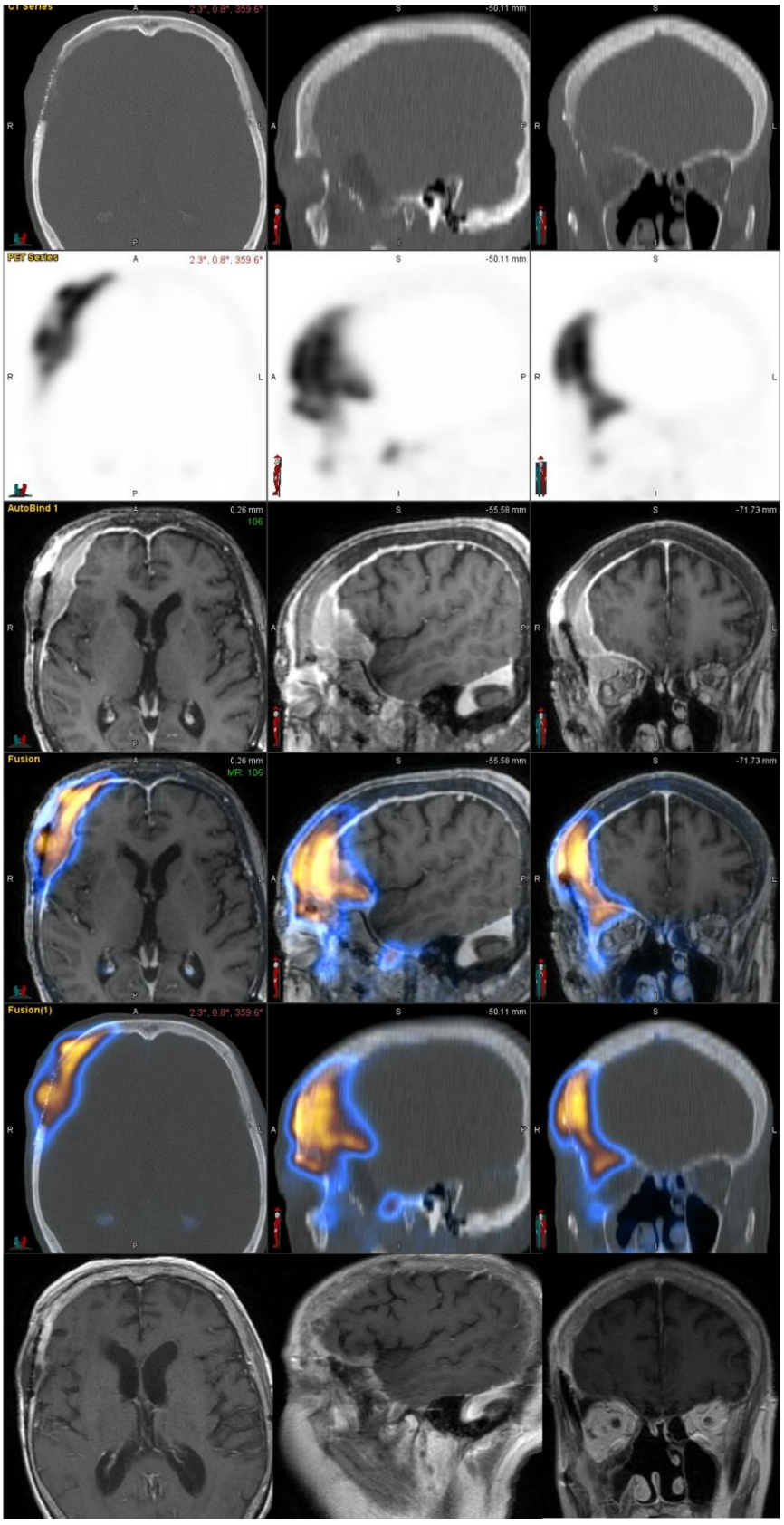

Figure 2. ^{68}Ga-DOTATATE PET/CT/MR fusion series showed enhancing lesions centered at right temporal craniectomy site, indicating residual tumor after subtotal resection. The fusion PET/MR was adapted for radiation therapy planning for proton bean therapy. Three-year follow-up CE-MRI showed deceased size of tumor, indicating favorable response to radiation therapy.

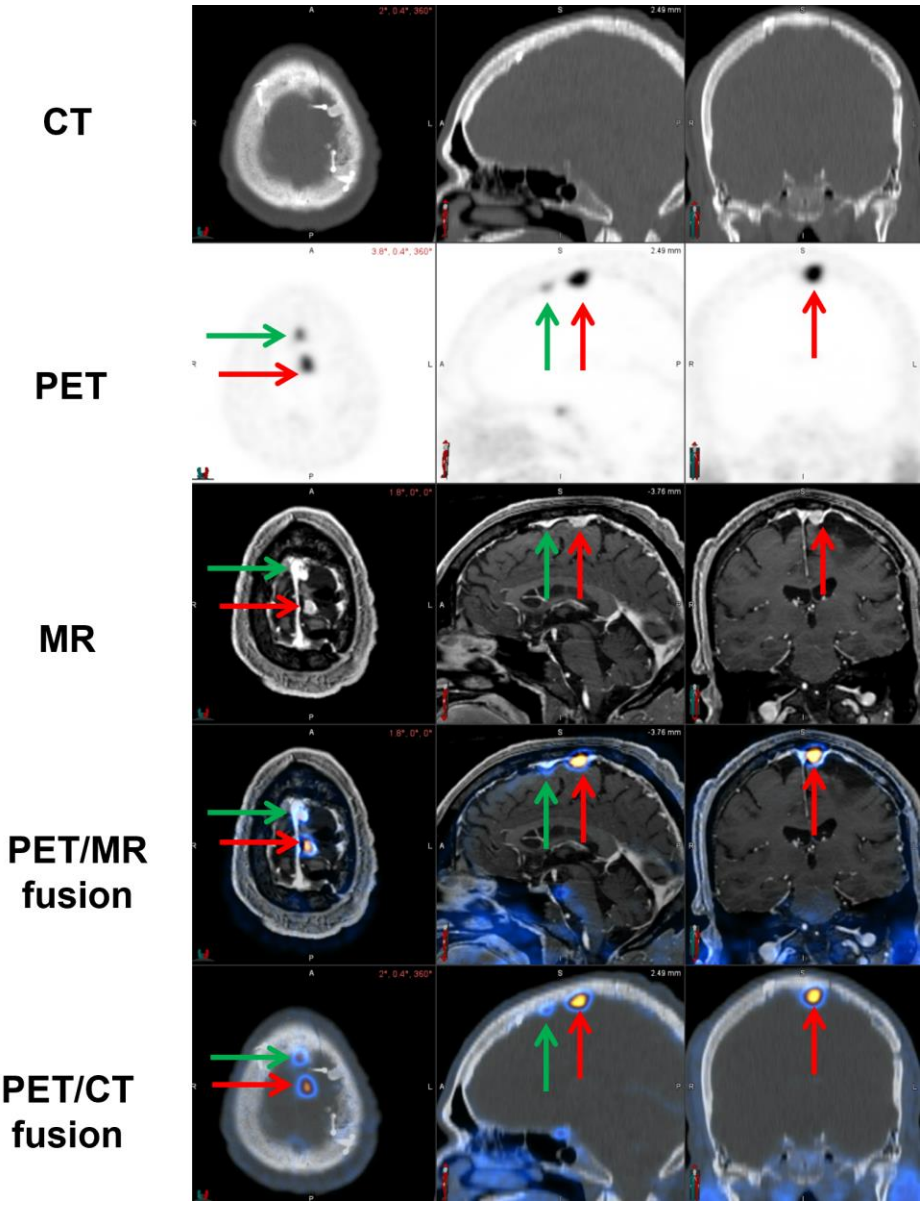

Figure 3. ^{68}Ga-DOTATATE PET/CT/MR fusion series. CE-MRI demonstrated enhancing focus at parietal vertex which exhibited PET avidity (red arrows). PET/CT was able to identify another PET-avid focus at the parasagittal left frontal region, indicative of recurrence (green arrows).

Table 1. Demography of Meningioma patients

Case #	Sex	WHO grade	Age	Initial location	Onset	Treatment History	PET/CT time (years)	PET/CT Findings	Follow-up therapy	Outcome
1	F	1	69	Right frontal	2005	Craniotomy x3, CyberKnife Embolization	12	Positive	Bevacizumab Sandostatin	Deceased
2	F	2	82	Right sphenoid	2016	Craniotomy x 2	1	Positive x 2	Proton beam therapy	Survived
3	M	2	72	Bi frontal	2009	Craniotomy x 3, Radiation therapy	8	Positive	Sandostatin	Deceased
4	M	2	59	Left skull base	2008	Gamma Knife	10	Positive	Sandostatin	Deceased
5	M	2	77	Bifrontal	2012	Radiosurgery Craniotomy x 2	7	Positive	Sandostatin Avastin	Deceased
6	M	2	72	Left frontoparietal	2015	Craniotomy x 1, Radiation therapy	3	Positive	Proton beam therapy	Survived
7	F	3	47	Right frontal	2008	Craniotomy x 1	12	Negative x 2	Surveillance	Survived
8	F	1	68	Right skull base	2021	Partial resection	1	Positive	Radiation therapy	Survived