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EDITORIAL

^{68}Ga-DOTATATE PET: The Future of Meningioma Treatment

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Meningiomas are the most common primary brain tumor in North America.[1,2] Surgery is the preferred first line treatment for resectable tumors requiring intervention, but radiation therapy (RT) can be offered for unresectable, recurrent, incompletely resected, and/or higher-grade disease. In many instances, deciding whether to offer close observation or RT depends on reliable recognition of residual, recurrent, and/or the extent of intact disease.[1] Currently, computed tomography (CT) and magnetic resonance imaging (MRI) represent the imaging standard for defining disease extent.[1,3] However, it can be difficult to discern tumor extent with precision using these anatomic imaging modalities alone consequential to clinical factors ranging from challenging location (such as skull base or parasagittal sinus) to bony involvement or confounding postoperative changes.[1,3-5]

In the management of extracranial malignancies, functional, and molecular techniques such as positron emission tomography (PET) imaging routinely supplement anatomic imaging.[1] Because nearly all meningiomas express somatostatin receptor 1/2 (SSTR1/SSTR2), molecular imaging techniques using SSTR ligands (eg, ^{68}Gallium-DOTATATE) have the potential to aid in accurate tumor extent identification.[1] The Response Assessment in Neuro-Oncology (RANO) Working Group recently published guidelines recommending the use of ^{68}Ga-DOTATATE PET imaging in patients with meningioma.[1] Suggested uses include diagnostic confirmation, surgical planning, delineation of RT target volumes, and posttreatment surveillance.[1]

The optimal time to obtain PET imaging for surgical patients may depend on patient presentation, as PET has both preoperative and postoperative utility. In cases where diagnosis remains uncertain or equivocal after MRI, preoperative PET imaging may offer improved sensitivity.[1] One series that included nearly 200 meningiomas found that MRI had a 92% rate of detecting meningiomas identifiable

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by PET.[5] This superior sensitivity with PET was primarily driven by improved performance for tumors invading bone, hidden by calcifications/radiographic abnormalities, centered at the skull base, or located adjacent to the falx cerebri. PET can also be extremely useful for differentiating unresectable optic nerve sheath meningiomas from other tumors.[1] Another potential use for preoperative PET is improved surgical planning, particularly for maximal safe resection of tumors involving eloquent areas or critical organs.[1,6] Coregistration of PET to intraoperative CT or MRI can inform challenging intraoperative decisions such as whether to resect dura, bone, or scar tissue, as it may otherwise be difficult to differentiate involved from uninvolved tissues.[6]

However, in most cases, postoperative PET may have greater use, as it can strongly impact postoperative management.[1,6] In one prospective surgical series, nearly 20% of perceived gross total resections (GTR, Simpson grade 1-2) by intraoperative evaluation and postoperative MRI were revealed by PET to be subtotal resections.[4] Intriguingly, this approximates the long-term rate of relapse after gross total resection of a grade 1 meningioma, with the implication that PET may potentially identify these patients up front, possibly leading to a more robust discussion regarding adjuvant RT or observation and improved therapeutic ratio. Figure 1 demonstrates one such case from our institutions. For this patient, although MRI was consistent with GTR in a challenging to visualize skull base location, PET (standardized uptake value [SUV] 7.43) was consistent with a subtotal resections with avidity in the cribriform plate. The patient declined to purse recommended adjuvant RT, and 2 years later experienced local failure requiring salvage RT at the site of PET-avid disease (now SUV 8.96).

Additionally, PET can help with delineation of RT volumes in both the definitive and adjuvant setting.[1,7-11] PET can identify bony/skull base involvement or nonadjacent areas of disease that may be missed with MRI-based planning alone.[1,10] One such case from our institutions is shown in Figure 2 in a nonsurgical patient whose PET revealed left-sided skull base disease that was poorly visualized with MRI alone. Furthermore, by enhancing the ability to differentiate postoperative changes from residual tumor, PET

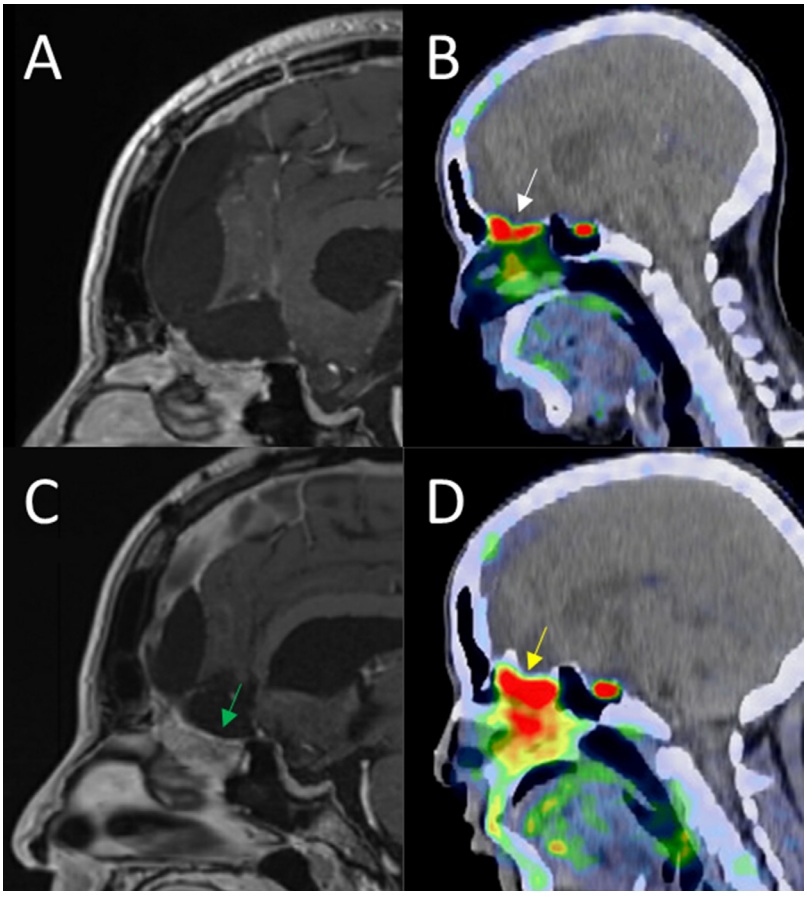

Fig. 1. Postoperative magnetic resonance imaging (A) suggested a gross total resection with contrast enhancing reactive changes only, but positron emission tomography (PET) imaging (B) showed focal uptake along the cribiform plate (standardized uptake value 7.43, white arrow) suspicious for residual disease. The patient declined to pursue recommended adjuvant radiation therapy. Two years later, surveillance magnetic resonance imaging (C) showed increased soft tissue signal (green arrow) in the area of the cribiform plate with prior focal PET uptake with continued avidity (standardized uptake value 8.96, yellow arrow) noted on repeat PET imaging (D).

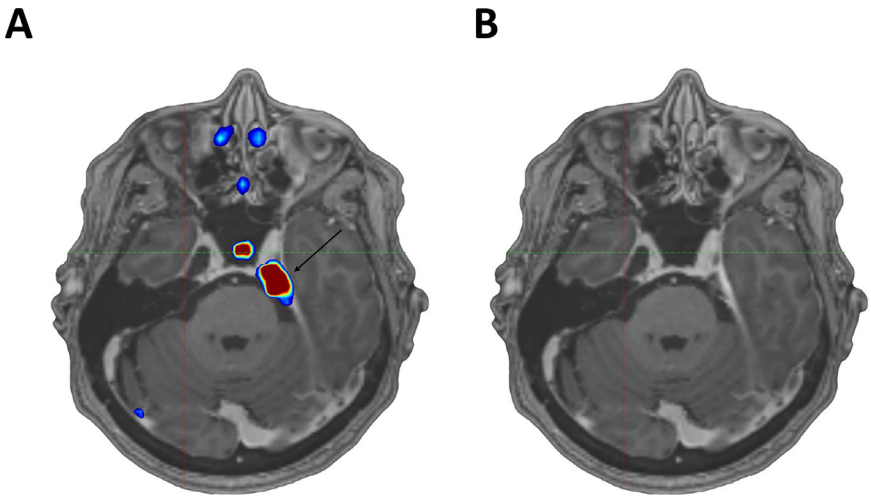

Fig. 2. Positron emission tomography revealed left-sided skull base disease (black arrow, A) that was poorly visualized with magnetic resonance imaging alone (B).

facilitates delineation of more precise and usually smaller gross tumor volumes (GTV) in comparison to MRI-based planning alone.[1,7,9] A smaller GTV translates to a smaller planning treatment volume[1,7,9] and significantly reduces dose to critical organs at risk such as the hippocampi, optic apparatus, brain stem, and pituitary gland.[9] Consequently, incorporating PET in RT planning has the potential to decrease acute and chronic toxicity rates. Despite the decreased treatment volumes, local control remains excellent[9] and possibly even improved in some settings.[8] One series documenting outcomes in patients with 339 meningiomas found that use of PET was independently associated with improved local control and overall survival in low-grade (n = 276) but not higher-grade tumors.[8] Posttreatment, PET can provide useful information in terms of differentiating tumor progression from posttreatment effects, which can be difficult with CT and MRI.[1,5,6]

These benefits have been reported elsewhere[1,4-6,8,9] but have not yet become mainstream in the US because of very limited exposure in the radiation oncology literature, and also general unavailability of the agent until this year.[7,10] With the recent Food and Drug Administration approval for this option, increased awareness within Radiation Oncology might result in more consistent use clinical practice for treatment planning. A key limitation is that to date, the literature evaluating the efficacy of PET imaging is primarily limited to relatively small, retrospective, single institution series, and greater accuracy in tumor delineation with PET imaging has not yet been prospectively linked to improved clinical outcomes. Although lack of prospective data are an obstacle to PET being considered standard of care, lack of awareness of its use in radiation oncology may also be precluding pursuit of prospective confirmation. Future prospective studies should prospectively confirm whether use of PET-based volumes decreases dose to organs at risk and toxicity rates. Local control with PET versus MRI-based planning could be compared prospectively. Additionally, randomized trials could incorporate PET findings into inclusion criteria or patient stratification schemes. For example, on the currently accruing phase III trial BN-003 (NCT03180268), where patients with grade II meningioma are randomized to adjuvant RT versus observation after GTR, PET-positivity or negativity could be an important consideration.

Several limitations of ^{68}Gallium-DOTATATE PET imaging for meningioma should be acknowledged. First, PET avidity is not specific to meningioma; other tumors or inflammatory processes can express SSTRs[1,5] However, these other diseases usually demonstrate reduced uptake relative to meningioma and present with noticeably different CT/MRI characteristics. Furthermore, because the pituitary gland demonstrates physiological uptake, tumor adjacent to it might be difficult to distinguish with clarity.[1] Additionally, due to the limited spatial resolution of PET imaging, it is unlikely to accurately identify potential microscopic disease, and therefore cannot define the clinical target volume with precision. However, this limitation is not unique to PET, as even with MRI-based contouring, an additional estimated clinical target volume is typically used, and these estimates are based on data from the surgical literature as well as from patterns of recurrence studies.

In summary, incorporation of ^{68}Gallium-DOTATATE PET imaging into routine management for meningioma has the potential to overcome some of the limitations of standard of care anatomic imaging. In particular, PET may be useful for disease identification in the skull base or adjacent to the falx or sinuses, identifying bony involvement, and differentiating progression from post-treatment changes. Potential benefits include improved diagnostic sensitivity, surgical planning, determination of the extent of resection, selection of RT target volumes (especially GTV), and differentiation between true and pseudo progression. Increased awareness of the utility of ^{68}Gallium-DOTATATE PET for meningioma is needed. It is also crucial to underscore the need for the conduct of a

well-designed prospective multi-institutional trial to confirm its true utility, and several such trials are under consideration.

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