Using Molecular Imaging to Enhance Decision Making in the Management of Pituitary Adenomas

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In most patients with suspected or confirmed pituitary adenomas (PAs), MRI, performed using T1- (with or without gadolinium enhancement) and T2-weighted sequences, provides sufficient information to guide effective clinical decision making. In other patients, additional MR sequences (e.g., gradient recalled echo, fluid-attenuation inversion recovery, MR elastography, or MR angiography) may be deployed to improve adenoma detection, assess tumoral consistency, or aid distinction from other sellar/parasellar lesions (e.g., aneurysm, meningioma). However, there remains a small but important subgroup of patients in whom primary or secondary intervention (e.g., first or redo transsphenoidal surgery, stereotactic radiosurgery) is limited by the inability of MRI to accurately localize the site(s) of de novo, persistent, or recurrent PA. Emerging evidence indicates that hybrid imaging, which combines molecular (e.g. ^{11}C-methionine PET) and cross-sectional (MRI) modalities, can enable the detection and precise localization of sites of active tumor to guide targeted intervention. This not only increases the likelihood of achieving complete remission with preservation of remaining normal pituitary function but may mitigate the need for long-term (even lifelong) high-cost medical therapies. Here, we review published evidence supporting the use of molecular imaging in the management of PAs, including our own 10-y experience with ^{11}C-methionine PET.

Key Words: pituitary adenoma; molecular imaging; ^{11}C-methionine

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Pituitary adenomas (PAs) are among the most commonly occurring intracranial tumors, affecting all age groups from early childhood onward. It is now estimated that clinically apparent PA affect around 1:1,200 of the general population, signifying a prevalence rate that is 3.5 to 5 times higher than previously suspected (*1*). It is possible that even this represents an underestimate as 10%–15% of the population have a pituitary abnormality on MRI, but a significant proportion are never referred for formal endocrine evaluation.

In some patients, reliable identification of the site(s) of small volume de novo, residual, or recurrent PA (e.g. after transsphenoidal surgery [TSS]) is challenging due to the limitations of standard cross-sectional imaging techniques (MRI and CT) (*2*,*3*). For example, MRI does not always reliably distinguish between residual functioning tumor, postsurgical change, and normal pituitary gland (*4*,*5*). However, accurate localization of the tumor has important therapeutic implications because these patients can then be triaged to (repeat) TSS or stereotactic radiosurgery (SRS) with curative intent (*6*). In contrast, for patients lacking a clear treatment target, the options lie between "blind" surgical exploration, medical therapy, or conventional fractionated radiotherapy of the whole sella (±parasellar regions). Although often effective, medical therapy may be associated with side effects and significant cost (>$12,000 per annum), with treatment required long-term (even lifelong). In other patients, medical therapy fails to achieve full disease control and can be associated with unwanted side effects (*7*–*9*). Radiotherapy predisposes to hypopituitarism, second tumors (e.g., meningioma), and stroke (*10*), and in many patients there is a delay (months or even years) before maximum benefits are seen.

Several groups have therefore examined the potential roles for molecular (functional) imaging in PA management, and emerging evidence suggests it can significantly augment clinical decision making in a subgroup of patients. A variety of radiotracers, targeting different molecular pathways, have been used in conjunction with conventional scintigraphy or PET and will be considered here (Fig. 1).

MEMBRANE RECEPTOR BINDING RADIOTRACERS

Somatostatin and dopamine receptor ligands are commonly used in the management of PAs, either as primary therapy (e.g., prolactinoma) or for the control of residual disease when surgery is unable to deliver full clinical and biochemical remission (e.g., acromegaly, Cushing disease). The clinical effectiveness of somatostatin receptor (SSTR) ligands (SRLs) (e.g., octreotide, lanreotide, pasireotide) or dopamine agonists (DAs) (e.g., bromocriptine, cabergoline, quinagolide) is linked to the expression of their corresponding G-protein–coupled receptors. Radiotracers targeting these receptors have been used to identify sites of de novo, residual, or recurrent PA and to examine the potential correlation between tracer uptake and efficacy of corresponding medical therapy (Supplemental Tables 1 and 2; supplemental materials are available at http://jnm.snmjournals.org). Recently, the corticotropin-releasing hormone (CRH) receptor subtype 1 (CRH-R1, another member of the G-protein–coupled receptor superfamily) has been identified as a potential target for imaging in corticotroph tumors, consistent with the observation that most adrenocorticotropic hormone (ACTH)–secreting PAs retain sensitivity to CRH, acting via CRH-R1.

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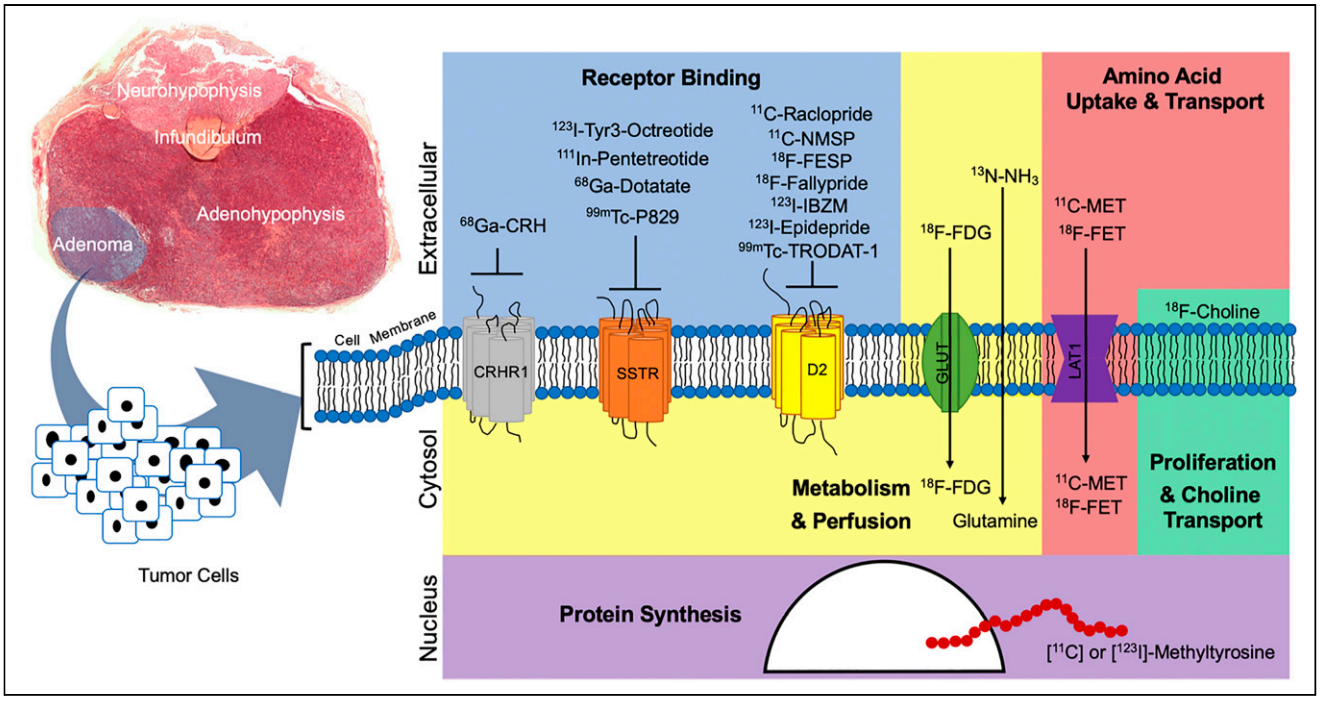

FIGURE 1. Radiotracers and molecular pituitary imaging. Schematic representation showing various radiotracers that have been deployed for imaging PAs, together with their corresponding molecular targets. C = carbon; CRH = corticotropin releasing hormone; D2 = dopamine receptor subtype 2; F = fluorine; FESP = fluoroethylspiperone; FET = fluoroethyltyrosine; Ga = gallium; GLUT = glucose transporter; I = iodine; IBZM = iodobenzamide; In = indium; LAT1 = L-type amino acid transporter 1; MET = methionine; N = nitrogen; NH_3 = ammonia; NMSP = 3N-methylspiperone; SSTR = somatostatin receptor; Tc = technetium; TRODAT-1 = tropane dopamine transporter imaging agent.

SSTR Imaging (Supplemental Table 1)

To date, 6 SSTR subtypes have been cloned in mammals (SSTR1, SSTR2A, SSTR2B, SSTR3, SSTR4, and SSTR5), with a predominance of subtypes 2 and 5 in neoplastic and normal pituitary cells (*11*,*12*). SSTR expression differs between PA subtypes (*11*–*14*). For example, growth-hormone–secreting adenomas express SSTR2, SSTR3, and SSTR5 (*11*); thyrotropin-producing adenomas (thyrotropinoma, "TSHoma") express SSTR2 and SSTR5; and corticotroph adenomas express SSTR2A, SSTR3, and SSTR5 (*13*). In contrast, clinically nonfunctioning PAs (NFPAs) express mainly SSTR3 (*11*,*14*).

Initially, ^{123}I-Tyr3-octreotide was used for SSTR imaging (*15*), but was soon replaced by ^{111}In-pentetreotide (*16*). Several groups have examined the correlation between scintigraphic findings, tumoral SSTR expression (*14*,*17*,*18*), and the clinical/biochemical response to medical therapy (*19*,*20*), concluding that SSTR scintigraphy may help identify patients who would benefit from a trial of SSTR ligands; however, these findings have not been reproduced by other workers (*21*–*23*).

For thyrotropinomas, correlation between the intensity of ^{111}In-pentetreotide uptake and the degree of TSH suppression after acute administration of octreotide has been assessed in a small number of cases, where it showed a positive (but nonsignificant) trend (*24*).

In a single case of a treatment-resistant prolactinoma, ^{111}In-pentetreotide scintigraphy informed the decision to initiate depot SRL therapy, with subsequent stabilization of hyperprolactinaemia and tumor volume (and reduced cabergoline requirement), although the patient had also received prior pituitary radiotherapy (*25*).

Tumor shrinkage in response to somatostatin analog therapy has not been generally observed in NFPAs that exhibit positive SSTR scintigraphy (*22*,*26*), although clinically relevant improvements in visual field deficits may still be observed in some patients with positive scans (but not in those with negative scans) during subsequent octreotide therapy (*20*).

In Cushing syndrome, the main application of SSTR scintigraphy has been in the investigation of the ectopic adrenocorticotropic hormone syndrome, where it may aid tumor localization (*27*,*28*).

Several groups have also evaluated the ability of SSTR scintigraphy to identify sites of residual or recurrent PA after primary treatment. Again divergent findings have been reported, with some workers concluding that SSTR scintigraphy confers no advantage compared with MRI alone (*22*), whereas others have reported positive localization in a subgroup of patients (*29*,*30*).

One of the key limitations with scintigraphy is its restricted spatial resolution (even when using SPECT/CT), and this hinders its ability to detect small lesions. In contrast, PET, especially when combined with CT (PET/CT) or MRI (PET/MR), affords greater sensitivity and may even permit the detection of lesions $<$ 1 cm in size. For example, ^{68}Ga-DOTA-Tyr3-octreotate (^{68}Ga-DOTATATE) PET/CT is the preferred molecular imaging modality for neuroendocrine tumors (including ectopic adrenocorticotropic hormone syndrome) because of its superior detection rates when compared with classic SSTR scintigraphy (*31*,*32*). In pituitary disease, combined use of ^{68}Ga-DOTATATE PET and ^{18}F-FDG PET has been proposed to differentiate recurrent/residual PA from normal pituitary tissue (*33*,*34*) and to inform decision making for aggressive pituitary tumors (*35*,*36*).

Dopamine Receptor Imaging (Supplemental Table 2)

Prolactin secretion from normal lactotrophs is subject to tonic dopaminergic inhibition, which is predominantly mediated by

dopamine receptor subtype 2 (D2R) (*37*). Medical therapy with D2R agonists remains the treatment of choice for most prolactinomas, achieving normalization of serum prolactin and tumor shrinkage in most patients (*38*).

Assessment of D2R density on PAs has been reported using ^{11}C-raclopride and ^{11}C-*N*-methylspiperone PET (*4*,*39*–*40*), with higher D2R binding in patients with prolactinomas and growth hormone–secreting adenomas who respond to DA therapy than in treatment-resistant patients (Supplemental Table 2) (*4*,*41*). Several other D2R radioligands have been used with varying success (Supplemental Table 2), although none are in routine clinical use, likely reflecting their limited utility in tumors which are predominantly managed medically. In contrast, in acromegaly, where only 25%–30% of somatotroph adenomas respond to DA therapy molecular imaging could help inform which patients might be considered for a trial of DA for residual/recurrent disease (*4*).

An interesting alternative approach to imaging D2R-expressing lactotroph tumors has been identified through a small number of case reports using ^{18}F-DOPA as a ligand. Here, it is speculated that DOPA enters dopaminergic cells in the arcuate nucleus of the hypothalamus and is converted and secreted into the cleft between dopamine-secreting neurons and lactotroph cells (*42*,*43*).

CRH Receptor Imaging

Recently, a novel PET tracer (^{68}Ga-DOTA-CRH) that binds to CRH-R1 on pituitary corticotrophs has been proposed for imaging in Cushing disease (*44*). Although autonomous, most (>90%) corticotroph tumors retain CRH-R1 expression and exhibit responsiveness to exogenous CRH (as exemplified in both peripheral CRH testing and bilateral inferior petrosal sinus sampling with CRH stimulation). In a single study to date, ^{68}Ga-DOTA-CRH PET/CT was reported to be positive in all 24 cases of Cushing disease studied, with intraoperative and histologic confirmation of PET findings. However, as a cautionary note, only 10 patients had microadenomas < 6 mm in size and, of these, only 4 had no lesion visible on MRI (*44*). Further studies will therefore be required to confirm whether these initial findings represent a significant step-change in functional imaging of corticotroph adenomas.

RADIOTRACERS TARGETING TUMOR METABOLISM, PERFUSION, AND PROLIFERATION

^{18}F-FDG

^{18}F-FDG is a well-established PET tracer that is commonly used in oncology practice. Importantly, in a large retrospective study that assessed pituitary uptake in 40,967 subjects undergoing ^{18}F-FDG PET/CT for other indications, focal abnormal uptake was observed in just 0.073% of patients, several of whom were subsequently shown to have PAs (*45*); in a second study with a smaller sample size (13,145 subjects), incidental pituitary uptake was noted in 0.8% of subjects (*46*). Together, these studies point to a likely low risk of false-positive scans (<1%) and emphasize the importance of further assessment in any patient with incidentally detected pituitary ^{18}F-FDG uptake (Fig. 2). Consistent with this, there are numerous case reports in the literature of different PA subtypes discovered incidentally during ^{18}F-FDG PET/CT (NFPA (*47*), prolactinoma (*48*), gonadotropinoma (*49*), somatotropinoma (*50*), and corticotropinoma (*51*)).

Several groups have examined the utility of ^{18}F-FDG as a tracer for the detection of de novo and residual/recurrent PA (Supplemental Table 3). In a prospective study, which included 24 patients with different subtypes of PA, all macroadenomas (n = 14) and half of microadenomas (n = 5) demonstrated increased ^{18}F-FDG uptake (*52*). However, perhaps the greatest interest in the application of ^{18}FDG PET in the management of pituitary disease has been directed toward Cushing disease, where up to 40% of microadenomas can go unidentified on MRI. In a study of 12 patients with pituitary-dependent Cushing syndrome, ^{18}F-FDG PET was found to be comparable to MRI for the localization of corticotroph adenomas, with a detection rate of approximately 60%, albeit without complete overlap between the 2 imaging modalities (*53*). In a prospective study of 10 patients with Cushing disease, Chittiboina et al. were able to show slight superiority of ^{18}F-FDG PET in comparison with conventional spin-echo (SE) MRI but, in the same cohort, spoiled gradient recalled echo (SPGR, that is, volumetric) MRI was superior to ^{18}F-FDG PET (*54*). However, more recently the same group has shown that prior stimulation with CRH may enhance the ability of ^{18}F-FDG PET to detect corticotropinomas (*55*).

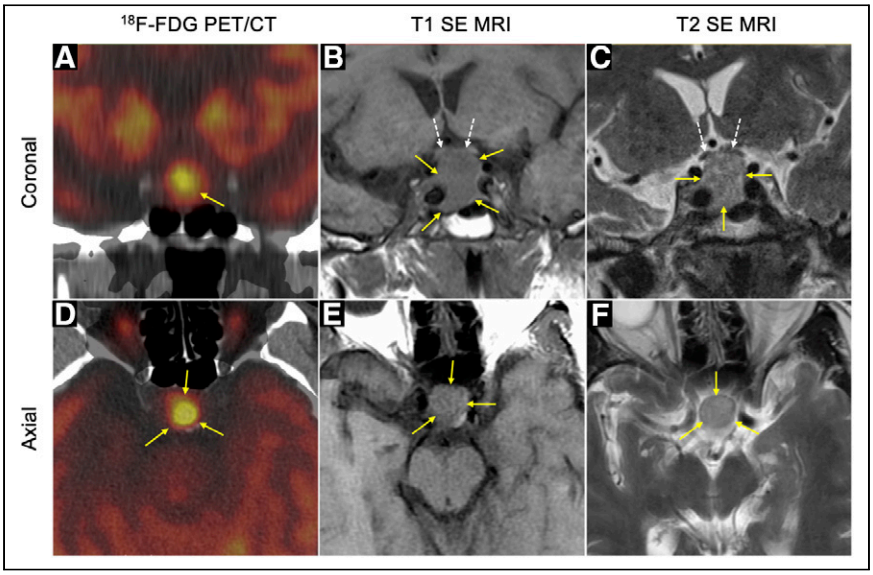

FIGURE 2. Nonfunctioning pituitary macroadenoma incidentally detected on ^{18}F-FDG PET/CT. (A and D) Coronal and axial PET/CT demonstrating focal ^{18}F-FDG sella uptake. (B, C, E, and F) Coronal and axial T1 and T2 SE MRI confirms a macroadenoma (yellow arrows) with suprasellar extension and optic chiasm displacement/compression (dotted white arrows). SE = spin echo.

It is important to note that other metabolically active lesions (e.g., infective/inflammatory pathologies or metastatic sellar tumors) may result in increased tracer uptake and therefore represent a false-positive finding when investigating for a suspected PA.

Finally, combining findings from ^{18}F-FDG PET/MR and ^{68}Ga-DOTATATE PET/MR has been suggested as a means to distinguish normal and tumoral pituitary tissue (*33*).

^{13}N-Ammonia

^{13}N-ammonia, a PET tracer used to profile myocardial blood flow, has been proposed as a means of assessing normal pituitary gland perfusion and metabolism,

FIGURE 3. Confirmation of the site of residual tumor in a middle-aged man with ongoing active acromegaly after primary TSS. (A and D) Preoperative coronal T1 and axial T2 SE MRI reveals a macroadenoma with right cavernous sinus extension (Knosp grade 3A). (B and E) Postoperative FSPGR MRI shows satisfactory surgical debulking, but with a suspected tumor remnant in the right lateral sella/parasellar region (yellow arrows). (C and F) Met-PET/MR^{CR} confirms focal tracer uptake in this area, but without clear extension beyond the lateral wall of the cavernous sinus (yellow arrows); tracer uptake in the remaining normal gland is also seen (white arrows). (G) Three-dimensional reconstruction using the PET, CT, and MRI datasets shows location of remnant tumor (yellow arrow), residual normal gland (white arrow), and intracavernous carotid artery. FSPGR = fast spoiled gradient recalled echo; Gad = gadolinium; Met-PET/MR^{CR} = ^{11}C-methionine PET/CT coregistered with FSPGR MRI; SE = spin echo; TSS = transsphenoidal surgery.

allowing the detection of normal functioning tissue, and contrasting with reduced/absent uptake after pituitary injury (*56*). Potentially consistent with this, in a single study of ^{13}N-ammonia PET/CT in a cohort of patients with different subtypes of PA, higher tracer uptake was observed in normal residual pituitary tissue than adenoma, which was in direct contrast to the findings on ^{18}F-FDG PET/CT (*57*).

^{18}F-Choline

^{18}F-choline, a PET tracer used in the staging and restaging of prostate cancer, is taken up by the normal pituitary gland (*58*,*59*), raising the possibility of a role in imaging PAs. However, to date, support for such a role is limited to a small number of case reports of incidentally detected pituitary macroadenomas (*60*,*61*). It is also unclear whether uptake in PAs is dependent on cellular proliferation (with incorporation into cell membranes), or reflects other aspects of choline transport/metabolism, as has been proposed for other well-differentiated endocrine tumors (*62*).

RADIOTRACERS TARGETING AMINO ACID TRANSPORT/UPTAKE

^{11}C-Methionine

Several studies have established the utility of ^{11}C-methionine PET (^{11}C-Met PET) for the detection of PAs (*63*–*65*); ^{11}C-Met PET demonstrates lower brain uptake (yielding a more favorable target-to-background ratio) and increased sensitivity compared with ^{18}F-FDG PET (*64*,*66*,*67*). However, its ability to guide precision surgery or radiotherapy has historically been limited by the spatial resolution and soft-tissue contrast of SPECT or PET/CT systems. This is particularly problematic when trying to accurately localize small lesions that may not be readily differentiated from ^{11}C-Met uptake into adjacent normal pituitary tissue (*66*), which may potentially result in a false-positive interpretation of the scan. To address this, we and others have used coregistered PET/CT and MRI (Met-PET/MR^{CR}) to improve anatomic delineation at sites of ^{11}C-methionine uptake, and to guide treatment decisions and clinical outcomes (*63*,*65*,*68*). However, with the advent of hybrid PET/MR systems this is now even more readily achieved (*69*).

In general, the application of Met-PET/MR^{CR} or Met-PET/MR in PA should be restricted to patients with small de novo, residual, or recurrent functioning adenomas, in whom conventional MRI has not reliably identified a culprit lesion but in whom (further) targeted intervention (e.g., TSS or SRS) is being considered. Patients treated with agents that suppress tumor function (e.g., SSTR ligands or DA therapy) should undergo a period of medication washout (3 mo for the former and 4 wk for the latter) before imaging, and biochemical assessment should be undertaken on the day of the scan to confirm disease activity.

Acromegaly

Somatotroph tumors are typically readily visualized with ^{11}C-methionine (Fig. 3). Several groups have reported on the use of Met-PET/MR^{CR} to inform decision making (e.g., further TSS vs. SRS vs. fractionated radiotherapy vs. medical therapy) in patients with residual active disease after primary treatment (*65*,*68*). We have also recently reported our experience in patients who were initially deemed to have unresectable lateral disease remnants, but in whom Met-PET/MR^{CR} identified a surgical target, with control/normalization of serum IGF-1 in all cases after PET-guided redo TSS (*70*).

Cushing Disease

Corticotroph adenomas exhibit variable, often modest, ^{11}C-methionine uptake when compared with other PA subtypes. The reason for this is not well understood, but may reflect several factors including the relatively small representation of corticotrophs in the anterior pituitary, their central location within the gland (such that tracer uptake is merged with that of the background normal gland), and the periodic/cyclical nature of ACTH production. Consequently, the detection rate of active corticotroph adenomas by this technique is estimated at approximately 70% (Supplemental Fig. 1) (*63*).

Prolactinoma

Most patients with lactotroph adenomas are effectively treated with DA therapy. However, in a small subset of patients in whom pituitary surgery or radiotherapy is indicated (e.g. due to DA intolerance or resistance), Met-PET/MR^{CR} can aid precise localization of the de novo or residual tumor (Supplemental Fig. 2).

Thyrotropinoma (TSHoma)

Similar to prolactinomas, thyrotropinomas show high avidity for ^{11}C-methionine and are readily visualized in most cases (Supplemental Fig. 3). A short trial of depot SSTR ligand therapy can be used as an endocrine switch to confirm the location of an occult microthyrotropinoma, with scanning before and after treatment (*71*).

CONCLUSION

PAs may be associated with significant morbidity and increased mortality as a consequence of disruption to normal pituitary gland function and impingement on important adjacent structures (e.g., optic chiasm). For many patients, pituitary surgery in the form of selective adenomectomy remains the mainstay of treatment. However, in a significant proportion of cases the surgeon is unable to achieve complete resection of the adenoma; challenges in reliable visualization of the site(s) of de novo (e.g., Cushing disease) or residual/recurrent (e.g., acromegaly) tumor may contribute to the failure of surgery to achieve disease remission, or may even dissuade the multidisciplinary team from considering further definitive intervention (e.g., redo TSS or SRS). In these contexts, molecular pituitary imaging can complement standard cross-sectional imaging to allow more precise localization of the site(s) of de novo or residual/recurrent PA and, in so doing, enable an important subgroup of patients to be offered (further) surgery or radiosurgery with curative intent.

DISCLOSURE

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This project received Institutional approval, with all patients providing informed consent for PET imaging.

KEY POINTS

QUESTION: When should molecular imaging be considered in the modern management of pituitary adenomas?

PERTINENT FINDINGS: In cases where MRI returns equivocal or indeterminate findings, molecular imaging (e.g., with ^{11}C-methionine PET) can aid localization of sites of de novo, persistent, or recurrent pituitary adenoma.

IMPLICATIONS FOR PATIENT CARE: Increased use of molecular pituitary imaging may enable more patients to undergo treatment with curative intent (e.g., repeat TSS or SRS).

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