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Metabolic *in vivo* visualization of pituitary adenomas: a systematic review of imaging modalities

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Abstract

Introduction—Pituitary adenomas are the most common intrasellar mass. Functional pituitary adenomas (PAs) constitute the majority of pituitary tumors and can produce symptoms related to hormonal overproduction. Timely and accurate detection is therefore of vital importance to prevent potentially irreversible sequelae. Magnetic resonance imaging (MRI) is the gold standard for detecting PAs, but is limited by poor sensitivity for microadenomas and an inability to differentiate scar tissue from tumor residual or predict treatment response. Several new modalities that detect pituitary adenomas have been proposed.

Methods—A systematic review of the PubMed database was performed for imaging studies of PAs since its inception. Data concerning study characteristics, clinical symptoms, imaging modalities, and diagnostic accuracy were collected.

Results—After applying exclusion criteria, 25 studies of imaging pituitary adenomas using positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and single photon emission computed tomography (SPECT) were reviewed. PET reliably detects PAs, particularly where MRI is equivocal, though its efficacy is limited by high cost and low availability. SPECT possesses good sensitivity for neuroendocrine tumors but its use with PAs is poorly documented. MRS consistently detects cellular proliferation and hormonal activity but warrants further study at higher magnetic field strength.

Conclusion—PET and MRS appear to have the strongest predictive value in detecting PAs. MRS has the advantage of low cost, but the literature is lacking in specific studies of the pituitary. Due to high recurrence rates of FPAs and low sensitivity of existing diagnostic workups, further investigation of metabolic imaging is necessary.

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Keywords

functional pituitary adenoma; positron emission tomography; single photon emission computed tomography; magnetic resonance spectroscopy; metabolic imaging; hormonally active pituitary adenoma

Introduction

Pituitary adenomas (PAs) are the third most common intracranial brain tumor.¹ Functional adenomas, comprising roughly 70% of PAs,^{1–3} produce excess hormone secretion that can lead to a variety of clinical symptoms and associated syndromes.⁴ The most common functional PAs, in descending order, are prolactin-secreting (prolactinomas), growth hormone (GH)-secreting, corticotropin (ACTH)-secreting, gonadotropin (LH or FSH)-secreting, and thyrotropin (TSH)-secreting adenomas.⁵ The remaining 30% of PAs are classified as nonfunctional, which mainly produce symptoms due to their mass effect. PAs are further subdivided based upon their size into macroadenomas (>10mm) and microadenomas (<10mm). Both the size and functional status can influence the diagnostic workup, treatment plan, and prognosis for these tumors.

Timely identification of pituitary adenomas is crucial for preventing the potential sequelae of aberrant hormone release. Magnetic resonance imaging (MRI) is the current gold standard for detecting pituitary adenomas.⁶ However, MRI has significant limitations, such as a low sensitivity for microadenomas. MRI is also unable to evaluate nonsurgical treatment response. Routine laboratory studies, such as dexamethasone suppression tests, are able to definitively diagnose hormonal disorders at low cost, but suffer from low sensitivity and rates of false positives and negatives in up to 50% of cases.^{4,7,8} Laboratory studies are also unable to localize the site of aberrant hormone secretion. Moreover, there may be a significant time lapse until hormone levels accrue to the point of eliciting detectable alterations in lab values, which can delay appropriate treatment. The clinical application of ¹¹¹In-pentetreotide scintigraphy for detecting GH or TSH-secreting PAs is similarly limited by low diagnostic accuracy.⁹ Cavernous sinus sampling has high diagnostic accuracy but is usually an intolerably stressful experience for the patient.⁷

Several modalities specifically targeting metabolic activity have been proposed for the detection of PAs, namely positron emission tomography (PET), single photon emission computed tomography (SPET/SPECT), and magnetic resonance spectroscopy (MRS).^{3,8,10–19} PET uses radionuclide tracers such as ¹⁸F-fluorodeoxyglucose (FDG) or ¹¹C-L-methionine (MET) to detect glucose uptake and protein synthesis, respectively, often with the concomitant use of computed tomography (CT) to create three-dimensional imaging. SPECT, less commonly known as SPET, also uses radionuclide tracers to indirectly detect metabolic activity by visualizing regional cerebral blood flow (rCBF). MRS is a complementary technique to MRI that uses signals from proton (¹H) nuclei to detect relative concentrations of brain metabolites. These modalities have been studied to varying extents with promising results, though definitive techniques and cost-effectiveness warrant further investigation.⁴

Surgical resection is first-line treatment for both nonfunctional and functional PAs, with the exception of prolactinomas. Recurrence rates following surgery are high, exceeding 50% for GH-secreting and PRL-secreting adenomas. Successful resection is usually confirmed by clinical evaluation and imaging; however, postoperative MRI is unable to differentiate between tissue remodeling, residual tumor, and surgical packing.³ Radiotherapy is accepted as the sole treatment for inoperable patients, and is often given as adjuvant treatment for inaccessible or residual tumor. However, detection of functional tumor recurrence or residual following surgery is limited to abnormal blood tests or evidence of growth on MRI, both of which require significant processing time and are time dependent.

A reliable modality to visualize PAs is necessary for surgical planning and to confirm tumor remission, and would be of great value to patient and surgeon.⁴ The aim of this review is to summarize the existing literature on metabolic visualization modalities used to detect pituitary adenomas *in vivo*, identify hormonally active recurrence or residual, and measure response to treatment.

Methods

Literature Search Strategy

We conducted a literature search of the PubMed, SCOPUS, and Google Scholar databases for relevant clinical studies since its inception. We queried the database using the Medical Subject Heading (MeSH) major topic “pituitary neoplasms” and its subheadings “diagnosis,” “metabolism,” “pathology, and “secretion” combined with the MeSH major topics “positron emission tomography” (subheadings “methods,” “therapeutic use,” “utilization”), “magnetic resonance spectroscopy,” “proton magnetic resonance spectroscopy,” and “tomography, emission-computed, single-photon” (subheadings “methods,” “therapeutic use,” “utilization”). The inclusion criteria were case reports, case series, and clinical studies describing the use of these imaging modalities to identify pituitary adenomas where MRI is equivocal, differentiate scar tissue from tumor recurrence or residual, and to assess the response of pituitary adenomas to surgical or medical therapy. Titles and abstracts were reviewed for the following exclusion criteria: 1) does not address pituitary adenoma; 2) non-human studies; 3) studies not written in English; 4) studies that do not compare the newer imaging modalities to the gold standard techniques or do not assess treatment response; and 5) review articles that offer no new information. After redundant titles were excluded, full text review was performed for publications that met these criteria. Reference lists of all articles reviewed in full were searched to identify additional studies.

Data Collection

All studies that described the use of imaging modalities to detect pituitary adenomas or to measure response to treatment were reviewed. The studies were abstracted for sample size, modality, initial diagnosis, radioactive tracers if used, and significant findings. In studies analyzing different types of brain tumors, only pituitary adenomas were included in this review.

Results

The PubMed search strategy retrieved 154 abstracts. The review of reference lists yielded 16 additional abstracts. A total of 170 abstracts were reviewed. Figure 1 demonstrates a flow chart outlining the selection process for relevant studies.

Twenty-five studies were deemed eligible to be included in this review. Table 1 provides a summary of findings.

Modalities assessed include PET, MRS, and SPECT. Table 2 summarizes the advantages and disadvantages of each technique compared to the current gold standards of MRI and laboratory studies.

PET

Ten studies assessed the use of PET in detecting pituitary adenomas. PET consistently identified metabolically active PAs, particularly in the setting of microadenomas where MRI was equivocal.^{3,4,6,8,20} Ikeda *et al* studied 35 patients with surgically verified Cushing disease and recorded diagnostic accuracies of 100% and 73% for MET-PET and FDG-PET, respectively, compared to the 25% and 57% accuracy of 3T and 1.5T MRI. They included 15 preclinical cases of Cushing disease in their cohort and observed that PET successfully localized microadenomas and “preclinical” disease where conventional MRI failed.

PET was found to be useful for monitoring and predicting treatment response.^{3,18,19} Metabolic activity was found to correlate well with serum hormone levels, and tracer uptake decreased substantially following treatment. Tang *et al* used PET to evaluate 33 patients with history of PA ablation and biological evidence of tumor residual or recurrence. MET-PET detected 91% of the recurrent hypermetabolic lesions, compared to 54% seen on MRI. 80% of patients who underwent subsequent therapeutic intervention had positive outcomes. Muhr *et al* observed that ¹¹C-MET uptake, a marker of D2 receptors, decreased substantially in all tumors with a positive treatment response. Daemen *et al* studied 7 untreated patients with prolactinomas confirmed by serum PRL levels and MRI. Treatment with bromocriptine elicited significantly decreased ¹¹C-tyrosine uptake within a few hours, though FDG-PET was unable to detect the lesions.

In general, PET was found to be complementary to MRI for the identification of tumor residual or recurrence.^{3,21,22} D’Amico *et al* described a case in which ⁶⁸Ga PET showed SST uptake in a residual tumor previously seen as a mass on MRI, which was subsequently resected. Francavilla *et al* in their study of 24 patients with confirmed PRL, GH, and TSH-secreting macroadenomas reported that irradiated PAs exhibited less uptake than non-irradiated tumors, while recurrences displayed similar metabolism to initial tumors. In contrast to Daemen *et al*, they found a rough positive correlation between FDG uptake and serum hormone levels, perhaps because their cohort comprised different FPA subtypes. Taguchi *et al* reported a case where remission was confirmed by lack of FDG uptake, whereas MRI was unable to confirm successful resection due to postsurgical changes.²²

PET sensitivity, where studied, was found to be significantly dependent on the choice of radiotracer. Five authors compared ^{18}F -fluorodeoxyglucose (FDG) radiotracers to methionine (MET) radiotracers, all of whom endorsed the greater diagnostic accuracy and sensitivity of MET-PET.^{8,13,19,20,23} Both Ikeda and Muhr found that only MET-PET was able to diagnose microadenomas, compared to other radiotracers. Authors reported conflicting results on whether metabolic profiles are tumor-type specific. Muhr mapped tumors using more than one metabolic tracer and found different uptake patterns, whereas Francavilla observed no difference in uptake between FPA subtype.^{13,18}

PET positivity was not found to be predictive of invasive behavior.⁶ The role of PET/CT to detect ectopic hormonally active tumors or pituitary metastasis is controversial, and is beyond the scope of this review.

SPECT

Six studies analyzed SPECT and reported mixed results. Like PET, the efficacy of SPECT in detecting pituitary adenomas was largely dependent on the radiotracers used. SPECT was also found to be less sensitive for microadenomas.²⁴ Kurtulmus *et al* observed no significant difference in Tc-99m uptake between PA and normal tissue.

Studies of the ability of SPECT to predict tumor functional status were also few. De Herder *et al* studied ^{123}I -epidepride uptake in 15 NFPAs compared to 4 prolactinomas and noted that the FPAs were more likely to take up ^{123}I -epidepride than NFPAs. However, they did not analyze this finding statistically. Magnani *et al* found positive uptake of in 4 of 5 FPAs (3 GH, 1 TSH, 1 PRL) and 4 of 7 NFPAs but did not comment on its statistical significance.

SPECT was shown to offer some value in predicting and evaluate treatment response. Two authors studied uptake of ^{111}In -pentreotide, a scintigraphic marker of somatostatin receptors.^{16,17} Losa *et al* evaluated 5 TSH-secreting PAs and observed a corresponding decrease in ^{111}In -pentreotide uptake and serum TSH levels in the PAs following a dose of octreotide, though the trend was not statistically significant. Yonekura *et al* additionally observed that positive ^{123}I -epidepride uptake was an indirect marker of D2 receptors and was therefore valuable for diagnosis and treatment planning.

MRS

Nine studies evaluated the application of MRS.^{10–12,25} MRS was found to be complementary to MRI in the differential diagnosis of suprasellar tumors.^{10,26,27} Pituitary adenomas exhibited distinct metabolic profiles compared to other intracranial pathology or normal surrounding tissue. Chernov *et al* investigated the role of ^1H MRS at 1.5T in the characterization of 56 masses. All 19 pituitary adenomas in the cohort were characterized by a significantly reduced N-acetylaspartate (NAA) peak. Of these 19, functional PAs exhibited an increased level of NAA content compared to nonfunctional PAs that approached significance at $p < 0.1$. Falini *et al* reviewed 20 PAs diagnosed with MRI and similarly found lower NAA and higher Cho in the lesions compared to normal brain tissue.

MRS was found to provide important information on the proliferative behavior and malignant potential of PAs. Stadlbauer *et al* performed MR spectroscopy at 1.5T on 37

patients with PAs and found a strong positive correlation between Cho concentration and tumor cellular proliferation measured by Ki-67.¹¹ Stadlbauer *et al* suggest that MRS may be used as a non-invasive method of monitoring proliferative potential, though they caution that acquiring reliable spectroscopy data with adequate signal-to-noise ratio required that lesions measured at least >20 mm across in 2 directions. PAs also demonstrated significantly different metabolic patterns than those of other intracranial tumors. However, the efficacy of MRS in the setting of recurrence is unclear. Chernov *et al* also evaluated three recurrent PAs and noted that MRS may have less diagnostic value in the setting of recurrence, as postoperative scars may have been incorporated into the tissue volume under study.

The diagnostic use of MRS to evaluate the efficacy of medical treatment is poorly documented. Kozic *et al* observed a significant decrease in relative concentration of choline (Cho) and overall tumor volume in a case study of a GH-secreting adenoma after treatment with a somatostatin analog.¹² Their group also suggested that an elevated Cho peak in PAs may serve as a marker of cellular proliferation, corroborating the findings of Stadlbauer *et al*. Kozic *et al* posit that increased proliferation may represent increased hormonal activity. To date, there are no other studies of MRS and treatment response of PAs.

Discussion

Pituitary adenomas, the most common sellar mass, comprise roughly 17% of all intracranial brain tumors.⁵ The excess hormone production of hormonally active PAs can produce clinical sequelae, commonly in the form of Cushing disease or acromegaly. The high recurrence rate after surgical resection warrants regular follow-up imaging of recurrent or residual tumors. However, MRI is largely unable to differentiate between postoperative change and tumor relapse, and laboratory testing carries a high false negative rate. A modality that targets pre- and post-operative metabolic activity of PAs is of substantial value to the neurosurgeon in devising a treatment plan, assessing treatment response, and patient counseling.

Current diagnostic work-ups of PAs are limited in scope and often require disease progression to a certain extent before definitive diagnosis can be made. MRI is considered the gold standard for visualizing PAs, but suffers from low sensitivity for microadenomas, which may delay accurate diagnosis until potentially irreversible symptoms arise. Endocrinopathies are known to significantly increase morbidity and risk of mortality if left untreated.^{3,6,8,12,18,28,29} For example, ACTH-secreting PAs are the most common cause of Cushing disease.³⁰ However, up to 40% of cases of confirmed Cushing's disease are associated with negative MRI findings, attributed to the well-known small size of ACTH-secreting adenomas.^{6,13,31} The cardiovascular risk of Cushing disease in particular has been shown to increase with the duration of disease.²⁸ The prevalence of Cushing disease without typical Cushing syndrome is increasing,⁸ warranting further exploration of a modality that enables detection of corticotroph adenomas prior to symptom onset. Of note, Ikeda *et al* observed that MRI imaging of preclinical Cushing disease was significantly less accurate than that of overt Cushing disease.

Prolactin-secreting PAs account for up to 20% of all intracranial lesions and cause decreased libido and impaired sexual function from high serum prolactin levels.¹⁹ Prolactinomas are sensitive to medical therapy with dopamine agonists, which has replaced surgery as first-line care. GH-secreting PAs cause acromegaly and are responsive to octreotide, a somatostatin analog; however, GH levels normalize in only 30–45% of patients following medical treatment.¹² Thyrotropin (TSH)-secreting adenomas account for 1% of all PAs and are often misdiagnosed as Graves' disease;¹⁶ as a result, tumors tend to be larger and more invasive when finally discovered, rendering surgical removal difficult.^{16,32,33} Eradication of functional residual following surgery is only achieved in about 40% of TSH-secreting PAs, even after adjunctive radiotherapy.³³

Clinicians currently rely on evidence of tumor growth and elevated hormone levels in blood tests to identify recurrence; however, these are relatively crude techniques with a considerable lag between detection and treatment. It is important to note that up to 50% of PAs that are cannot be seen on MRI fail to achieve remission.⁶ Tissue remodeling following surgery or radiotherapy often renders MRI unreliable.³ Some authors have reported that assessing residual tumor using MRI can only be made more than 4 months following surgery.³⁴ Early diagnosis and treatment of endocrinopathies caused by FPAs is therefore crucial to prevent the additive risk of prolonged, undetected disease.^{8,28} The newer modalities reviewed here may enable clinicians to diagnose PAs or detect functional recurrence “preclinically” before symptom onset, greatly reducing the associated morbidity.

The inaccuracies of the existing diagnostic paradigm warrant further investigation and possible modification in order to improve outcomes and operative results of pituitary adenomas. A cost-effective, widely available, reliable imaging modality is needed to facilitate accurate, early diagnosis.

PET

It is well documented in the literature that PET is a powerful, highly sensitive modality for detecting PAs, especially those found incidentally (“incidentalomas”) on whole-body scans for unrelated lesions.^{3,4,6,8,9,13,18,19,22,29,35–44} Figure 2 demonstrates a representative image of an ACTH-producing PA before and after gamma knife radiosurgery. PET has also been shown to detect PAs, particularly microadenomas, where MRI was negative, making it a useful non-invasive complement to routine MRI with a false-positive rate approaching 0.^{4,22,43} In our review, PET was found to be a useful, reliable tool to both predict and monitor adenoma response to medical therapy, exhibiting decreased radiotracer uptake within hours of treatment consistent with hormonal suppression.¹³ PET was also able to confirm tumor remission in one case where MRI was limited by postsurgical change.²² The use of PET to predict malignant potential has not been well studied.

The diagnostic accuracy of PET depends greatly on the radiotracers used. FDG, a marker of glycolytic activity, demonstrates a high uptake in PAs.^{8,13,23} However, FDG is also taken up physiologically by surrounding normal brain tissue due to the high overall glucose utilization of the brain, rendering FDG less accurate for differentiating healthy pituitary from tumoral tissue.^{13,40} Khan *et al* commented that FDG is not ideal for detecting endocrine tumors because FDG is a marker of metabolically active lesions with high grade

and poor differentiation, whereas most endocrine tumors are slow growing and well differentiated.⁴⁰ FDG-PET has also been shown to be more directly related to tumor proliferative potential than to hormonal activity, lowering its diagnostic value for FPA.s.³ Radiolabeled amino acids such as methionine (MET-PET) and tyrosine are involved in protein synthesis and are actively transported into cells, and are therefore thought to have significantly greater ability than FDG-PET to detect protein-synthesizing activity in tumor tissue.^{8,13,19} The ability of MET-PET to detect a PA is dependent upon the functional status of the tumor, due to the higher cellularity and secretory activity of FPA.s.³ Nevertheless, MET and tyrosine are labeled with ¹¹C, which has a short half-life that limits its utility to centers with access to on-site cyclotrons.⁴⁰ MET-PET may also vary with the menstrual cycle, limiting its utility.⁴⁵ Despite its demonstrated utility and high diagnostic accuracy, PET imaging currently remains at the research level due to general clinical unavailability and higher cost than other imaging modalities.^{13,29,40}

SPECT

Pepe *et al* in 2014 published a review stating that SPECT is the most convenient technique for evaluating neuroendocrine tumors (NETs).⁴⁶ Despite the extensive literature on SPECT, there are comparatively few studies of PAs. SPECT has been described as equally accurate as PET scans. Figure 3 shows a representative image of SPECT in a pituitary macroadenoma using Tc-99m tetrofosmin. Patterns of radiotracer uptake seen in both PET and SPECT have been shown to predict treatment response to medical therapy based on receptor density. Like PET, the sensitivity of SPECT is also largely dependent on the choice of radiotracer employed. However, SPECT is much more readily available and carries a lower operating cost than PET, making it an appealing alternative.¹⁴ Overall, our review found mixed reports on SPECT's utility in detecting FPA, with roughly 50% of the authors endorsing its utility.^{47,48} Several studies of SPECT on other NETs have been performed, spurring the authors reviewed here to apply SPECT to PAs. However, the high sensitivity and specificity demonstrated in other tumors did not carry over, attributed to its limited spatial resolution.³ There are few studies focused on the ability of SPECT to differentiate tumor residual or recurrence from normal tissue or postsurgical change.

As we observed in our review of PET studies, certain radiotracers (e.g. ¹²³I-alpha-methyl-tyrosine (IMT), a radiolabeled synthetic amino acid,²⁴ and ¹²³I-methoxybenzamide (IBZM), a radiolabeled dopamine receptor-blocking drug⁴⁹) were found to have more diagnostic accuracy for PAs than others.⁴⁸ For example, Tc-99m is a radiotracer associated with mitochondria and is taken up both physiologically and by PAs.^{48,50} Despite the increased availability and reduced cost, this represents a distinct disadvantage of SPECT compared to PET, since some radiotracers used in PET scans (e.g. MET) are not as readily taken up by normal pituitary glands.³⁹ To the best of our knowledge, there are not yet studies of SPECT used to predict malignant potential.

MRS

Although excellent anatomic information is supplied by MRI, MRS provides metabolic imaging that is useful in the differential diagnosis of intracranial pathology. The distinct metabolic profiles of the different neoplasms identified by MRS makes this modality a

useful complement to MRI. In contrast to the radionuclide imaging employed by PET and SPECT that can demonstrate similar uptake in both normal and abnormal glands, ^1H (proton) MRS demonstrates that tumor tissue and normal brain tissue have distinctly different metabolic profiles. It is well established that PAs show increased Cho levels and low NAA levels regardless of functional status, whereas normal brain tissue has increased NAA and Cho levels approaching zero.¹¹ Figure 4 shows a representative image of the spectra generated from an FSH-secreting pituitary macroadenoma and its characteristic Cho peak. As a component of cell membranes, Cho is thought to be a marker of increased cellular proliferation. NAA is a marker of neuronal viability that decreases with diminishing neuronal integrity. It follows logically that adenomatous tissue would exhibit increased Cho and decreased NAA peaks, due to the aberrant cellular proliferation and unchecked activity characteristic of PAs. The higher NAA levels seen in the functional adenomas may reflect relatively intact tissue capable of hormone production, compared to the more disorganized growth of the NFPAAs.¹⁰

Preliminary studies suggest that MRS may be used to evaluate treatment response. Of note, the metabolites detected by MRS are only indirect markers of FPA activity, and to date no direct measure of hormonal production with MRS exists. Kozic *et al* suggest that Cho concentration in FPAs could be used to evaluate hormonal activity in a FPA undergoing treatment.¹²

Despite a preponderance of literature studying the applications of MRS in other intracranial tumors, disproportionately few studies have been published about its use in describing PAs. The majority of published ^1H -MRS studies investigate parenchymal brain lesions, which may be attributed to the fact that sellar and suprasellar lesions at clinical MRI field strength of 1.5T are difficult to visualize and often too close to “contaminating” local brain tissue or bone.^{19,25} The limitations of MRS in the setting of microadenomas is attributed to the low spatial resolution at standard magnetic field strengths.¹⁰

MRS shows promise in predicting proliferative behavior and malignant potential. In our review we observed strong positive correlation between increased Cho concentration and cellular proliferation index measured by Ki-67 index.¹¹ MRS reliably differentiates between recurrent/residual tumor and postoperative change, offering an advantage over MRI, though there is not yet any study of its ability to detect functional recurrence.⁵² One key drawback is that MRS loses utility in the setting of hemorrhagic lesions due to blood altering the homogeneity of the magnetic field.¹¹ A few authors have studied ^{31}P (phosphorus) MRS signals of intracranial tumors; however, ^1H MRS is preferred due to its increased sensitivity.⁵³ ^{31}P MRS detects seven major metabolite peaks involving phosphate, reflecting energy consumption within brain tissue, while ^1H MRS can identify up to 160 metabolic peaks encompassing cell density, anaplasia, and proliferative index.

Interestingly, all studies of MRS reviewed here were performed at clinical field strength of 1.5T, and all recommended further research of PAs at higher field strengths. Authors cited the improved spectral resolution at higher or ultra-high fields that may be able to distinguish less prominent metabolite peaks and perhaps detect new ones, particularly in tumors that may have been too small to image at lower magnetic field strength.^{51,54,55} The low utility of

MRS may be attributed to the graphical output that is less intuitive than the pictures generated by PET or SPECT. However, MRS may be readily utilized with existing clinical MR units and commercially available software, with a much lower time and resource requirement than PET or SPECT, warranting additional research to validate these early reports. The short duration of testing (often under an hour), non-invasive nature, and overall safety of MRS encourage good patient compliance in the clinical setting.

Conclusions

Pituitary adenomas are the most common intrasellar tumor. Nearly three-quarters of all PAs are hormonally active, able to engender a wide variety of potentially devastating sequelae. Pre- and postoperative knowledge of metabolic activity is crucial for planning treatment, detecting recurrence, and counseling the patient. The existing diagnostic paradigm is limited in scope and may benefit from further investigation. MRI is the current imaging modality of choice. However, MRI alone is not able to evaluate treatment response, nor can it reliably differentiate between residual and postoperative change. MRI is also unable to predict malignant potential or evaluate medical treatment response. A number of imaging techniques targeting metabolic activity have thus been proposed.

PET and SPECT utilize radionuclide tracers to detect metabolic activity. PET reliably detects pituitary adenomas; particularly when methionine tracers are used and especially when MRI is equivocal. PET is also commonly used to evaluate treatment response and confirm tumor remission. However, its efficacy is limited to the research setting due to high cost and low availability. SPECT is more readily available than PET and some authors have deemed it similar in sensitivity to PET. Unfortunately, the majority of SPECT studies have analyzed other neuroendocrine tumors, and its value in diagnosing FPAs is controversial. PET and SPECT are both limited by the diagnostic accuracies of the radiotracers employed. PET appears to be superior to SPECT in measuring tumor response to treatment, and in the setting of microadenomas. MRS generates graphs of tissue metabolite concentrations and consistently differentiates tumor tissue from normal brain. MRS may also be used to predict tumor proliferative behavior and malignant potential. However, there are disproportionately few studies of MRS applied to PAs in the literature, and it is not established whether MRS can detect FPAs when applied at standard magnetic field strength. MRS is the most promising of the three major modalities reviewed here, and preliminary studies demonstrate a correlation between certain metabolite concentrations and cellular proliferation, prompting many authors to call for future study at higher magnetic fields.

Overall, despite the vast amount of literature studying metabolic profiles of intracranial tumors, studies of pituitary adenomas are comparatively few. Of the three major techniques reviewed here, PET and MRS appear to have the strongest predictive value. MRS has the advantage of being a low-cost, readily implementable technique, though additional research of its utility with pituitary adenomas is necessary.

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Figure 1.
Flow chart outlining the selection process of relevant studies

Figure 2. MET-PET of an ACTH-producing PA. Before treatment with gamma-knife radiosurgery (GKRS), abnormal hypermetabolic tissue was present in the left part of the sella turcica, providing a target for GKRS (A). Decreased methionine uptake was observed in the target volume 13.5 months after GKRS treatment that normalized the 24-h cortisol urinary secretion (B). *From Tang et al (2006), European Journal of Nuclear Medicine and Molecular Imaging.* Used with permission.

Figure 3. MRI (A) and single-photon emission computed tomography (SPECT) using technetium-99m (Tc-99m) tetrofosmin (B) of a patient with a nonfunctional pituitary macroadenoma. From Kurtulmus et al (2007), *J Endocrinol Invest*. Used with permission.

Figure 4.

Sagittal T2-weighted MR image (A) of a nonhemorrhagic FSH secreting pituitary adenoma, showing the position and size of the volume of interest (*white rectangle*) in the 1H-MRS experiment. Graph (C) revealing the water-suppressed spectra demonstrating a Cho peak typical of pituitary adenomas, fitted using LCModel (linear combination of model spectra), a user-independent frequency domain spectral fitting program (Stephen Provencher, Inc.). From Stadlbauer et al (2008), *J Neurosurgery*. Used with permission.

Summary of all papers reviewed.

Table 1

Author	Year	N	Modality/ies	Diagnosis/es	Findings
Feng	2016	43	MET-PET, FDG-PET, MRI	15 CD, 16 acromegaly, 12 prolactinoma	-MET-PET more sensitive than FDG-PET, especially with recurrent microadenomas -PET useful where MRI is equivocal
Chittiboina	2015	10	FDG-PET, SE MRI, SPGR MRI	CD	-FDG-PET more sensitive for small functional corticotroph adenomas; SPGR MRI more sensitive than SE MRI and PET -PET positivity did not correlate with dural invasion
D'Amico	2014	1	⁶⁸ Ga-PET, MRI	Acromegaly	68Ga PET showed SST uptake on residual tumor after resection
Ikeda	2010	35	FDG-PET, MET-PET, MRI	CD microadenoma	MET-PET had 100% diagnostic accuracy, FDG-PET had 73%, MRI had 40%
Taguchi	2010	1	FDG-PET, MRI	Acromegaly	No abnormal FDG uptake after resection; MRI limited by postsurgical changes
Alzahrani	2009	12	PET-CT, MRI	CD	PET-CT detected some cases where MRI was negative
Muhr	2006	165	MET-PET, FDG-PET	66 FPA, 82 NFPA	MET-PET superior to FDG-PET in delineating metabolically active areas
Tang	2006	33	MET-PET, MRI	24 FPA, 9 NFPA	-All NFPAs had a high uptake of MET, perhaps due to a high synthesis rate of truncated or incompletely processed pituitary hormones -MET activity strongly correlated with serum PRL, predicted successful treatment
Daeman	1991	4	¹¹ C-PET, FDG-PET	4 FPA	-FDG could not visualize prolactinomas -Bromocriptine therapy decreased tyrosine uptake 30% and serum PRL
Francavilla	1991	32	FDG-PET	29 FPA, 3 NFPA	FDG uptake decreased following bromocriptine therapy
Kurtulmus	2007	15	Tc-99m SPECT	15 FPA	No significant difference in Tc-99m uptake between pituitary adenoma and normal tissue
Plotkin	2005	2	¹²³ I-IMT SPECT	2 PAs, unspecified	SPECT less sensitive for microadenoma, failed to identify one lesion seen on MRI
De Herder	1999	19	SPECT	4 FPA, 15 NFPA	¹²³ I-epidepride is superior to ¹²³ I-IBZM SPET for visualizing D2-receptor positive PAs
Losa	1997	5	SPECT	5 FPA	Observed trend (not statistically significant) of ¹¹¹ In-pentetreotide uptake and suppressed TSH secretion after octreotide
Yonekura	1995	2	¹²³ I-ISP SPECT	1 FPA, 1 NFPA	Positive ¹²³ I-ISP uptake in GH-secreting PA a marker for D2 receptors, predicted positive treatment response with bromocriptine
Magnani	1994	12	ISG, SPECT	5 FPA, 7 NFPA	Combine ISG with pentetreotide scintigraphy to diagnose FPA or NFPA
Faghieh Jouilbari	2012	23	¹ H-MRS	Suprasellar tumors	MRI with MRS had improved accuracy in preoperative diagnosis compared to MRI alone
Chernov	2009	19	¹ H-MRS	12 FPA, 7 NFPA (3 recurrent)	-MRI with MRS was useful for differentiating suprasellar masses -Pituitary adenomas characterized by low NAA, high Cho -MRS less useful for characterizing recurrent neoplasms
Stadlbauer	2008	37	¹ H-MRS	Pituitary macroadenomas	-Strong positive correlation between [Cho] and MIB-1 proliferative cell index from pathology -MRS provided important information on proliferative potential and hemorrhage but only when size exceeded 20mm
Kozic	2007	1	¹ H-MRS	GH-secreting FPA	-Significant decrease in [Cho] 11 months after Lanreotide treatment -Elevated [Cho] could represent active cellular proliferation

Author	Year	N	Modality/ies	Diagnosis/es	Findings
Kinoshita	1997	2	¹ H-MRS	2 PAs, unspecified	-PEA levels increased 4–5× in PAs -MRS may provide information on tumor malignancy and characteristic tumor metabolism, especially where the differential using imaging alone is difficult
Sutton	1997	3	¹ H-MRS	3 PAs, unspecified	-MRS was specific for diagnosis of suprasellar tumors -PAs showed either high Cho or nothing
Falini	1996	20	¹ H-MRS	20 PAs, unspecified	All lesions had lower NAA and higher Cho than normal brain tissue
Usenius	1994	2	¹ H-MRS	2 PAs, unspecified	-[Cho] levels higher in PAs compared to normal white matter -Absolute metabolic concentrations may be more specific than metabolite ratios
Segebarth	1989	1	³¹ P-MRS	Prolactinoma	Significant difference in metabolic ratios between prolactinoma and normal tissue

Key:

PA: pituitary adenoma
 MRI: magnetic resonance imaging
 PET: positron emission tomography
¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose
 MET: methionine
 SUV: standard uptake volume
 ACTH: adrenocorticotrophic hormone
¹H-MRS: proton magnetic resonance spectroscopy
 ISG: immunoscintigraphy

Table 2

Advantages and disadvantages of diagnostic tools used to detect endocrinopathies from functional pituitary adenomas (FPAs).

Modality	Advantages	Disadvantages
PET	Well documented in the literature High diagnostic accuracy Good localization of PAs	Expensive Limited availability Similar uptake in normal and abnormal pituitary glands
FDG-PET	High rate of uptake by PAs	Taken up physiologically by normal brain tissue, leading to false positive results More directly related to tumor proliferative activity than hormonal production
MET-PET	Distinctly greater uptake in tumor tissue High sensitivity for FPAs	Varies with menstrual cycle
SPECT	Inexpensive Generally available	Poor diagnostic accuracy for PAs Similar uptake in normal and abnormal pituitary glands Poorly documented in the literature
MRS	Inexpensive Generally available Able to differentiate FPA from NFPA Low time commitment Consistently differentiates between tumor and normal tissue	Poorly documented in the literature Graphical output difficult to optimize Not useful in the setting of hemorrhage due to alterations in magnetic field
¹H MRS	Higher sensitivity for tumor tissue Detects cellular density, anaplasia, and proliferative index	
³¹P MRS	Detects energy consumption	Lower sensitivity for tumor tissue More complex post-processing Limited role in cancer diagnosis
MRI	“Gold standard” Inexpensive Generally available	Unable to differentiate FPA from NFPA Low sensitivity for microadenomas Unable to distinguish between recurrence (regardless of functional status), postoperative change, and surgical packing material
Laboratory testing	Inexpensive Widely available	Low sensitivity Requires overt disease, cannot diagnose preclinical lesions

Key:

PET: positron emission tomography

¹H-MRS: proton magnetic resonance spectroscopy

SPECT: single photon emission computed tomography

PA: pituitary adenoma

MRI: magnetic resonance imaging