

# Role of Molecular Imaging in Management of Nonhypersecreting Adrenal Masses

**F**unctional and symptomatic adrenal lesions are usually discovered through careful study of patient history and physical examination, prompting appropriate laboratory evaluation and diagnostic imaging. Less commonly, they are incidentally discovered during a diagnostic imaging procedure that leads to laboratory investigation. Surgical interventions are then indicated for unilateral aldosteronomas, pheochromocytomas, and adrenocorticotropic-hormone-independent cortisol-producing tumors when they are accurately identified. Adrenal incidentalomas are lesions that are typically discovered during diagnostic imaging for nonadrenal indications, prompting chemical laboratory evaluations that show negative results for excess adrenomedullary and adrenocortical activity.

Appropriate treatment of nonfunctional adrenal lesions is controversial and includes the use of molecular imaging studies performed with radiotracers in nuclear medicine environments. If these nonhypersecreting lesions were invariably asymptomatic, benign, or failed to grow or subsequently produce excess metabolically active hormone, they could be safely ignored. Unfortunately, the occasional tumor can do all of the above and obligate practitioners to grapple with a number of complex issues: patient safety; the performance and cost effectiveness of diagnostic tests; aggravation in obtaining payment approval from third-party payers for desired procedures; or personal liability associated with missing a specific diagnosis, such as pheochromocytoma or adrenal carcinoma, or stemming from an untoward surgical outcome in a patient erroneously referred for adrenalectomy for a nonfunctional benign lesion.

In this issue of *The Journal of Nuclear Medicine*, Maurea et al. (1) have reported their experience with imaging nonhypersecreting adrenal lesions using 3 specific radiotracers—norcholesterol (NP59), <sup>131</sup>I-metaiodobenzylguanidine (MIBG), and <sup>18</sup>F-FDG—with apparent considerable success. Gross et al. (2) successfully characterized clinically silent adrenal masses using norcholesterol, showing 100% specificity for identifying functional nonhypersecreting adenomas with an associated sensitivity of 71%. Maurea et al. (3) previously reported 83% sensitivity and 100% specificity for MIBG in pheochromocytomas, with MIBG proving to be particularly useful in the context of prior surgery when postsurgical anatomy has been distorted, or in the localization of extra-adrenal or metastatic disease. In an excellent review of adrenal incidentalomas, Kloos et al. (4) reported similar success in characterizing nonfunctional adrenal lesions with metabolically active radiotracers, indicating that their greatest use lies in lesions <3 cm in diameter. Test performance with conventional imaging, such as CT, MRI, and sonography, decreases progressively below this size. Unfortunately, NP59 also performs less well because lesion size progressively decreases under 3 cm (5).

In their article, Maurea et al. (1) report that their molecular techniques work well in a consecutive series of 54 patients, each associated with high sensitivity, specificity, accuracy, and positive and negative predictive values. They do not, however, address the obvious issue of selection bias. It is not clear who determined which patients were referred for their adrenal imaging work-up and which specific procedures would be performed. Not all of the 54 patients received all 3 radiotracers. The article also does not explain to what extent CT and MRI findings determined (or contributed to determining) which radionuclide studies were performed and whether surgical resection or fine-needle aspiration biopsy (FNAB) was used for confirmation.

The authors report a greater percentage of adrenal cortical carcinomas (6/54, 11.1%) than would be expected in a small number of adrenal incidentalomas. Among radiographically discovered adrenal masses, approximately 1 of 1,500 is an adrenal cortical carcinoma. Similarly, the authors report 5 pheochromocytomas and 2 ganglioneuromas, or 7 of 54 chromaffin tumors (13%). Whereas up to 5% of adrenal incidentalomas are pheochromocytomas, the vast majority of these are discovered with appropriate medullary chemical testing. It could be argued that through whatever screening processes are in effect at the authors' institution, there is an enrichment of the referred population that renders metabolic imaging more productive than might be expected in screening a group of unselected adrenal incidentalomas. The authors appear to be using their molecular imaging resources efficiently.

Radionuclide studies do not routinely appear in diagnostic algorithms for managing adrenal incidentalomas and are infrequently used in clinical decision making (6,7). Combinations of lesion size, patient age, anatomic imaging with CT (with and without contrast), and MRI with T2-weighted images or chemical shift sequences are frequently used to establish malignancy or benignancy without resorting

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For correspondence or reprints contact: Michael A. Lawson, MD, Samaritan PET Center, 1111 E. McDowell Rd., Phoenix, AZ 85006.

to molecular imaging (7). Therefore, it is incumbent upon those of us who perform molecular imaging to prove that we are making a significant contribution to better defining which patients need surgery and which surgeries should be avoided, because surgery extends the greatest potential benefit and poses the greatest patient risk of all relevant procedures. Surgery is clearly associated with the greatest cost (U.S. \$20,000–\$30,000 for laparotomy, probably somewhat less for laparoscopy because of shorter hospital stays). Norcholesterol, which clearly works well (1,2,4), is used sparingly, possibly because of limited availability, investigational status, high cost, lack of reimbursement, untimeliness of study completion, and perceived lack of necessity. All <sup>131</sup>I-labeled radiotracers also require thyroid blockade with cold iodine. To overcome these barriers, new molecular agents that are labeled with more attractive radionuclides and provide comparable information will need to be developed. An 11 $\beta$ -hydroxylase inhibitor, <sup>11</sup>C-metomidate, has been developed to identify adrenal cortical lesions (8). Norcholesterol labeled with <sup>124</sup>I, which has a 4.2-d half-life, might be an improved PET version of the current <sup>131</sup>I-label radiotracer. PET would provide improved spatial resolution and tomography. <sup>123</sup>I-MIBG, now commercially available, has generally replaced <sup>131</sup>I-MIBG and is frequently used at my institution to locate pheochromocytomas and paragangliomas.

Of potential importance, Maurea et al. (1) have shown in their series of cases that a significant number of patients had nonfunctional pheochromocytomas (1). Others have reported clinically silent pheochromocytomas (9) and their prevalence has been estimated in autopsy series (10). As Maurea et al. suggest, this subgroup of pheochromocytoma patients undergoing FNAB, anesthesia, and surgery may be at similar risk as patients with functional pheochromocytomas. If this assumption is true, MIBG imaging would certainly be warranted before FNAB or surgery provided the preva-

lence of nonsecreting pheochromocytoma is sufficiently high (11,12). The high sensitivity and specificity of FDG PET imaging the authors report in visualizing all neoplasms in their series (13/54) suggest that FDG may be an excellent metabolic marker for both metastatic masses and cortical carcinomas. Other investigators have reported similar experiences (13,14). FDG has also proven useful for imaging pheochromocytomas that are not MIBG positive (15). If FDG PET has the high sensitivity in detecting cancers that the authors report, its performance before CT-guided FNAB would be useful in avoiding the cost and complications of FNAB in benign lesions. PET's whole-body format, which is ideal for tumor staging, might help characterize the primary malignancy and locate additional extra-adrenal metastases. Conversely, if FDG PET findings are positive as a result of a primary adrenal carcinoma, the presence or absence of metastases might be determined (1).

Finally, in addition to laboratory reassessment, the follow-up of most adrenal incidentalomas is predicated on repeated CT imaging for assessment of tumor growth as a marker of malignancy. The yield of this exercise is extraordinarily poor because of lack of specificity (6); when growth is awaited in a true cortical carcinoma, effective therapy may be too late because invasion or metastasis may have occurred already (7). With the high sensitivity and specificity for malignancy, the authors' experience suggests that FDG PET imaging might be preferable to the current practice of watching and waiting for lesion growth on sequential CT scans. Well-designed, prospective, multi-institutional studies will be needed to prove FDG PET's utility in these settings before we can expect changes in existing algorithms and established clinical practice for evaluating incidentally discovered adrenal masses.

**Michael A. Lawson**  
*Samarian PET Center*  
*Phoenix, Arizona*

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