

SNMMI/EANM/ACNM Procedure Standard/Procedure Guideline on the Use of Molecular Imaging for Renal Mass Characterization

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Anatomic imaging of renal masses provides limited information on the histology or likely aggressiveness of the tumor, leading to the use of invasive procedures such as renal mass biopsy or empiric partial or radical nephrectomy. Molecular imaging can assist in risk stratification of indeterminate renal masses, potentially contributing to optimal patient decision-making. Two primary approaches have been explored for renal mass molecular imaging. The first is the use of agents that target carbonic anhydrase IX (CAIX), a cell-surface protein that is over-expressed on clear cell renal cell carcinoma (ccRCC) and generally not expressed on other renal tumors. A recent phase III trial (ZIRCON) is widely believed to have laid the groundwork for United States Food and Drug Administration approval of the CAIX monoclonal antibody ⁸⁹Zr-girentuximab. The second approach is the use of mitochondrial imaging agents, most notably ^{99m}Tc-sestamibi, which are lipophilic cations that accumulate in tumors with an abundance of mitochondria with negative charge potential (e.g., oncocytomas and other benign/indolent lesions) and do not accumulate in tumors with multidrug resistance pumps (e.g., ccRCC). The complementary information from ⁸⁹Zr-girentuximab and ^{99m}Tc-sestamibi can provide improved risk stratification. Further, emerging new targeted radiotracers and techniques such as imaging biomarker discovery with artificial intelligence will bolster those concepts. In this manual, we synthesize key data into a recommended approach.

Key Words: renal mass; renal tumor; molecular imaging; risk stratification; sestamibi; girentuximab

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PREAMBLE

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The SNMMI/EANM/ACNM will periodically define new standards/guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients. Existing standards/guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each standard/guideline, representing a policy statement by the SNMMI/EANM/ACNM, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNMMI/EANM/ACNM recognizes that the safe

and effective use of diagnostic nuclear medicine imaging and therapy requires specific training, skills, and techniques, as described in each document.

The SNMMI, EANM, and ACNM have written and approved these standards/guidelines to promote the use of high-quality nuclear medicine procedures. These standards/guidelines are intended to assist practitioners in providing appropriate care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, the SNMMI/EANM/ACNM cautions against the use of these standards/guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by medical professionals, taking into account the unique circumstances of each case. Thus, there is no implication that an approach differing from the standards/guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the standards/guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the standards/guidelines.

The practice of medicine involves not only the science but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these standards/guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these standards/guidelines is to assist practitioners in achieving this objective.

I. INTRODUCTION

In recent decades, the incidence of indeterminate renal masses has increased (1), yet the ability of conventional anatomic imaging approaches to risk stratify patients harboring those lesions remains inconsistent (2). Further, the use of traditional molecular imaging with FDG PET, although it may have a role in evaluating recurrent or metastatic disease from renal masses (3), is limited for renal mass characterization (4). Further, the high renal excretion of FDG can obscure renal masses and preclude characterization. Renal mass biopsy (RMB) is a useful tool but has a measurable nondiagnostic rate (5) and appears to have a low negative predictive value for ruling out malignancy (6).

There has been significant progress made using advanced imaging techniques (particularly the abstraction of radiomics features (7) and the use of multiparametric MRI [mpMRI] (8)) as well as molecular imaging to characterize renal masses (9). For example, the monoclonal antibody and PET radiotracer ^{89}Zr -girentuximab, which has high affinity for carbonic anhydrase IX (CAIX), can identify malignant clear cell renal cell carcinoma (ccRCC) (10). Further, the single-photon-emitting lipophilic cation $^{99\text{m}}\text{Tc}$ -sestamibi, which is attracted to the negative charge potential across the membranes of mitochondria, localizes to benign/indolent mitochondria-rich tumors, such as oncocytomas (11).

In this article, we will discuss those molecular imaging techniques (i.e., girentuximab PET and sestamibi SPECT [SPECT]). We will also discuss other agents in the pipeline to enter clinical practice. We will endeavor to weave in the appropriate clinical context regarding RMB, financial considerations, and shared decision-making. We will also comment on developing work-up algorithms and future directions.

II. GOALS

The goal of this guideline is to provide nuclear medicine physicians and radiologists with a detailed background of the use of molecular imaging for the noninvasive characterization of indeterminate renal masses.

III. DEFINITIONS

See also the *SNMMI Guideline for General Imaging*.

Renal mass/tumor: a solid, enhancing neoplastic growth arising from the kidney parenchyma

Small renal mass: a renal mass/tumor that meets the American Joint Committee on Cancer *T1a* definition

IV. COMMON CLINICAL INDICATIONS

Common indications for renal mass molecular imaging include, but are not limited to the following:

A patient with an indeterminate, solid, enhancing renal mass who would benefit from noninvasive risk stratification for decision-making/prognostication.

V. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL IN THE UNITED STATES

See also the *SNMMI Guideline for General Imaging*.

Physician

Molecular imaging of solid renal masses should be performed under the supervision of a nuclear medicine physician or radiologist with expertise in the interpretation of both SPECT and PET imaging and who is familiar with common patterns of uptake with ^{89}Zr -girentuximab PET/CT (12) and $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT (13). Such physicians should be appropriately board-certified by specialty or subspecialty organizations. In some jurisdictions, nuclear medicine physicians, specifically, may be required to supervise.

Nuclear Medicine Technologist

Technologists should be registered or certified to perform general nuclear medicine or PET examinations. Additional experience in the use of CT (or MRI) may also be required.

Medical Physicist

The qualified medical physicist will ensure adequate testing of the instrumentation and will assist in providing the lowest radiation dose possible while still achieving diagnostic quality imaging. The medical physicist can also ensure appropriate deployment of dose-reducing protocols and algorithms for the CT component of the imaging procedure.

VI. PROCEDURE/SPECIFICATIONS OF THE EXAMINATION

See also the *SNMMI Guideline for General Imaging*.

A. Request

The requesting physician should provide a requisition that notes the presence of a renal mass. Any relevant information from

previous imaging studies can be included in the indication for the study. If available, histopathology from any prior RMB should be included. The referring clinician should convey whether the patient is pregnant or breastfeeding.

B. Patient Preparation and Precautions

No specific preparations or precautions are necessary for most patients.

For women who are pregnant or breastfeeding, additional instructions may be necessary, and sites should follow local institutional policies in this setting. Specific in utero risks have not been well-studied for the radiopharmaceuticals included in this document. Imaging with nonionizing-radiation-based modalities, such as ultrasound or MRI, are alternatives for pregnant women.

Regarding breastfeeding, the imaging specialist should be aware of the physical half-lives of any administered radiopharmaceuticals (most commonly 6 h for ^{99m}Tc and 78 h for ^{89}Zr). Many institutions recommend a pause in breastfeeding for 24 h after the administration of a ^{99m}Tc -labeled radiotracer. Longer pauses may be appropriate after the administration of a ^{89}Zr -labeled agent.

Renal mass imaging with radiopharmaceuticals is generally not applicable to the pediatric population, as it is likely that any renal mass present in children would be empirically resected. However, in rare instances, a pediatric patient may be imaged (14), and every effort should be made to reduce radiation exposure.

C. Radiopharmaceuticals

The most studied radiopharmaceuticals for renal mass molecular imaging are ^{89}Zr -girentuximab and ^{99m}Tc -sestamibi (Table 1), which are discussed in more depth elsewhere in this document.

D. Administered Activity

The published administered activity of ^{89}Zr -girentuximab is 37 MBq (1 mCi) (12). Typical activities of 925 MBq (25 mCi) of ^{99m}Tc -sestamibi have been reported (15). At the time of this writing, specific pediatric doses have not been explicitly delineated.

E. Uptake Time

A typical uptake time for ^{89}Zr -girentuximab is approximately 5 d (12). A typical uptake time for ^{99m}Tc -sestamibi is approximately 75 min (15).

F. Image Acquisition

The CT obtained for anatomic localization and attenuation correction should match the field of view of either the PET or SPECT acquisition.

Typically, a ^{89}Zr -girentuximab PET scan would be acquired over a single bed position that includes the entirety of the kidneys. On most modern PET scanners, the acquisition would occur in 3D emission mode with CT-based attenuation correction, scatter correction, and iterative reconstruction with vendor-supplied software.

For ^{99m}Tc -sestamibi, the published SPECT protocol was a step-and-shoot, 360° acquisition with attenuation and scatter correction and with a vendor-supplied iterative reconstruction algorithm (15).

G. Interpretation

No widely accepted interpretation criteria have been proposed or adopted for renal mass molecular imaging. The interpretation of ^{89}Zr -girentuximab PET/CT is generally more straightforward than ^{99m}Tc -sestamibi SPECT/CT, given the lack of background uptake in the adjacent kidney. Any mass with uptake of ^{89}Zr -girentuximab above background renal uptake should be interpreted as “hot” or suggestive of a ccRCC, whereas “uptake” that is at or below the level of the adjacent kidney should be interpreted as “cold” or not suggestive of ccRCC. On ^{99m}Tc -sestamibi SPECT/CT, uptake that can be specifically localized within the tumor (even if it is below background renal parenchyma) should be interpreted as “hot” and suggestive of a benign/indolent histology (13). Tumors that specifically lack uptake should be considered “cold” and suggestive of a more aggressive histology.

VII. DOCUMENTATION/REPORTING

The dictated reports should include basic demographic and identifying information of the patient. Further, more specific information, including the identity, administered activity, and route of administration of the radiopharmaceutical, the uptake time, and the acquired field of view, should be included.

A description of the findings should be included and should be detailed enough to guide subsequent clinical decision-making. Typically, the size, laterality, and location within the kidney (e.g., anterior/posterior, upper/lower pole) of any renal masses should be reported. Further, the uptake (or lack thereof) of the administered radiotracer should be included, which, at a minimum, would involve a visual interpretation as “positive,” “negative,” or “equivocal,” and with the inclusion of any quantitative or semiquantitative parameters left to the discretion of the reader. Any technical aspects or artifacts of the scan that limit evaluation should also be included.

VIII. EQUIPMENT SPECIFICATION

It is beyond the scope of this document to address the nuances of specific PET/CT and SPECT/CT scanners. However, broadly, PET/CT scanners should have attenuation (CT-based) and scatter correction. Vendors should supply an appropriate iterative reconstruction algorithm.

Similarly, SPECT/CT scanners should have CT-based attenuation correction, scatter correction, and a vendor-supplied iterative reconstruction algorithm.

TABLE 1
Comparison of Characteristics Between ^{89}Zr -Girentuximab and ^{99m}Tc -Sestamibi for Renal Mass Imaging

Radiotracer	Mechanism of action	Dose	Uptake time	Physical half-life	Most common tumor with uptake
^{89}Zr -girentuximab	Binding to carbonic anhydrase IX	37 MBq (1.0 mCi)	3–5 d	76 h	Clear cell renal cell carcinoma
^{99m}Tc -sestamibi	Affinity for mitochondria	935 MBq (25 mCi)	75 min	6 h	Oncocytoma

IX. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION CONCERNS

Policies and procedures related to quality, patient education, infection control, and safety should be developed and implemented in accordance with good quality control practices.

Quality control should also be done regularly to ensure consistent, accurate physician interpretation of results. Equipment performance monitoring should be in accordance with a recognized accrediting organization.

X. CAIX-TARGETED GIRENTUXIMAB PET

Biology of CAIX

In ccRCC, the loss of the von Hippel-Lindau gene activates downstream mechanisms that involve hypoxia-inducible factor (HIF)-1 α and leads to constitutive CAIX expression (16). The near-universal expression, combined with low levels of expression in benign tissues (17), underlies the utility of CAIX-binding agents in identifying ccRCC.

The monoclonal antibody girentuximab binds to the extracellular domain of CAIX and allows for identification of ccRCC via the use of radiolabeled girentuximab PET/CT.

REDECT Trial Results

Oosterwijk et al. demonstrated the potential of CAIX imaging to identify ccRCC in patients with renal masses using a radiolabeled monoclonal antibody, ^{131}I -mG250 (18). Later, ^{124}I -cG250 (i.e., ^{124}I -girentuximab) PET was evaluated in a phase I study of 26 patients with renal masses scheduled for resection (19). ^{124}I -cG250 PET had a sensitivity of 94%, specificity of 100%, negative predictive value (NPV) of 90%, and positive predictive value (PPV) of 100% for ccRCC.

The open-label, multicenter phase III REDECT study evaluated the sensitivity and specificity of ^{124}I -girentuximab PET/CT for ccRCC compared with multiphasic contrast-enhanced CT (CECT) in patients with renal masses scheduled for surgery (10). The reference standard was tumor histology by blinded central review. PET/CT imaging was performed 2–6 d after intravenous injection of 185 MBq (5 mCi) ^{124}I -girentuximab and evaluated as positive or negative by qualitative assessment. A positive ^{124}I -girentuximab PET/CT scan was defined as a scan with at least 1 positive renal lesion. Of 226 patients recruited, 195 underwent surgery and had complete data available for analysis. The primary renal mass was ≤ 7 cm in diameter (T1b) in 81.0% of patients and ≤ 4 cm in diameter (T1a) in 51.8% of patients. The mean sensitivity for the detection of ccRCC was 86.2% for ^{124}I -girentuximab PET/CT and 75.5% for CECT (95% CI for difference, 2.4%–19%; $P = 0.023$). The mean specificity was 85.9% for ^{124}I -girentuximab PET/CT and 46.8% for CECT (95% CI for difference, 19.5%–58.7%; $P = 0.005$). The NPV, PPV and accuracy were 69.4%, 94.4% and 86.2% for ^{124}I -girentuximab PET/CT and 41.0%, 79.6% and 67.9% for CECT, respectively. The sensitivity of PET/CT for ccRCC lesions was 82.8% for T1a and 95.7% for T1b tumors, respectively. ^{124}I -girentuximab PET/CT showed robust interreader agreement. However, the FDA did not approve ^{124}I -girentuximab and requested a confirmatory phase III trial.

ZIRCON Trial Results

The ZIRCON trial (NCT03849118) was an open-label, multicenter, phase III trial designed to evaluate the performance of ^{89}Zr -girentuximab to detect ccRCC (12). Patients were imaged 3 to 5 days after injection. The required field of view was a single bed position, centered over the kidneys (Figs. 1 and 2).

All patients on ZIRCON were required to have an indeterminate renal mass (≤ 7 cm; cT1) and be scheduled for surgery within 90 d. Blinded central radiology and histology review were performed by 3 reviewers to determine PET/CT and ccRCC status, respectively. The coprimary endpoints were sensitivity and specificity using histology as reference standard.

300 patients were imaged with ^{89}Zr -girentuximab and 284 were evaluable. There were few serious adverse events in the cohort, none of which were potentially attributed to the imaging agent. The sensitivity and specificity were 86% (95% CI [82%, 90%]) and 87% (95% CI [81%, 93%]), respectively. A secondary endpoint was performance in tumors ≤ 4 cm and the data appeared similar. The PPV and NPV for ccRCC in the ZIRCON cohort were 93% (95% CI [90%, 96%]) and 75% (95% CI [71%, 79%]), respectively. A Biologics License Application to the FDA was submitted aiming for FDA-approval of ^{89}Zr -girentuximab.

XI. $^{99\text{m}}\text{Tc}$ -SESTAMIBI SPECT

The Biology of $^{99\text{m}}\text{Tc}$ -Sestamibi

$^{99\text{m}}\text{Tc}$ -sestamibi is a commonly used lipophilic cationic radiopharmaceutical. Preclinical models suggest that retention is related to the negative-charged mitochondria membrane potential (20). Renal oncocytoma and chromophobe RCC both have high mitochondrial content and therefore have a “pink/oncocytic” appearance. With a radiotracer preferentially taken up and retained by mitochondria, those tumors may be visualized with $^{99\text{m}}\text{Tc}$ -sestamibi. Conversely, ccRCC and papillary RCC have downregulation of mitochondrial DNA density (21), suggesting those tumors can be differentiated, as they would appear photopenic with $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT.

Clinical Studies with $^{99\text{m}}\text{Tc}$ -Sestamibi SPECT/CT

$^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT centered at the level of the kidneys is performed approximately 75 min after administration of 925 MBq (25 mCi) (15).

In 1996, it was recognized that the underlying biology of oncocytomas could be leveraged for noninvasive imaging using a mitochondrial binding agent, although the initial report used planar imaging instead of SPECT (22). Subsequently, a pilot study performed with $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT correctly identified 3 oncocytomas and 3 RCCs (15). Typical finding of positive uptake in an oncocytic neoplasm is shown in Figure 3, and typical finding of a lack of uptake

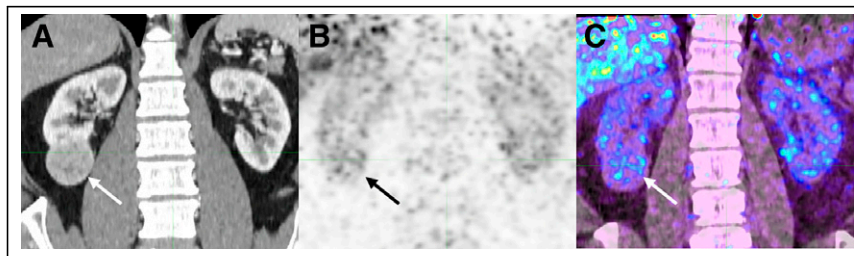


FIGURE 1. 44-y-old man with an enhancing right renal mass on contrast-enhanced CT scan (arrow, coronal image – A). The patient was subsequently imaged with ^{89}Zr -DFO-girentuximab PET/CT (arrows, coronal PET – B, fused PET/CT – C), with no evidence of uptake within the mass above renal background. Surgical pathology demonstrated a chromophobe RCC.

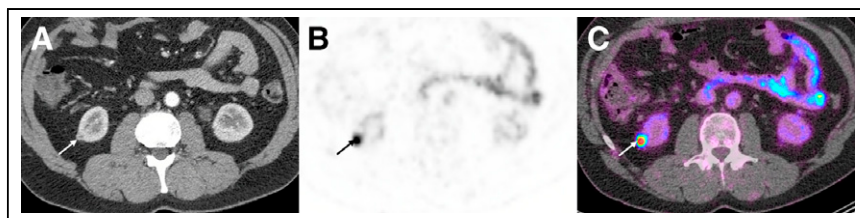


FIGURE 2. 62-y-old man with a small, enhancing, right renal mass. The arterial phase contrast-enhanced CT scan demonstrates the lesion (arrow, axial image – A). ^{89}Zr -DFO-girentuximab PET/CT (arrows, axial PET – B, fused PET/CT – C) demonstrates intense uptake in the mass, which was a ccRCC on surgical biopsy.

in an RCC is shown in Figure 4. A prospective, scan-and-resect, 50-patient clinical trial then reported a sensitivity of 87.5% (95% CI, 47.4%–99.7%) and specificity of 95.2% (95% CI, 83.8%–99.4%) for the identification of oncocytomas and hybrid oncocytic-chromophobe tumors (HOCT) (23). Subsequent studies have generally found similar results (24–27).

A recent metaanalysis of $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT demonstrated sensitivity for oncocytoma and HOCT versus all other renal lesions of 89% (95% CI, 70%–97%), with a comparable specificity of 89% (95% CI 86%–92%) (28). The authors of that metaanalysis note that the specificity of $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT for identifying renal oncocytoma and HOCT relative to ccRCC and papillary RCC was 98% (95% CI, 91%–100%) (28). Due to the heterogeneity among published studies and the risk of bias, the level of evidence was deemed to remain low.

One argument in favor of using $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT is the low cost of the technique. In a cost-effectiveness analysis performed by Su et al. when $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT is used for management of small renal masses, that work-up approach proves to be the most effective (29).

XII. FUTURE AGENTS

New CAIX-Targeting Agents

To circumvent the longer circulation time for imaging that is necessary based on the pharmacokinetics of antibodies, small molecules

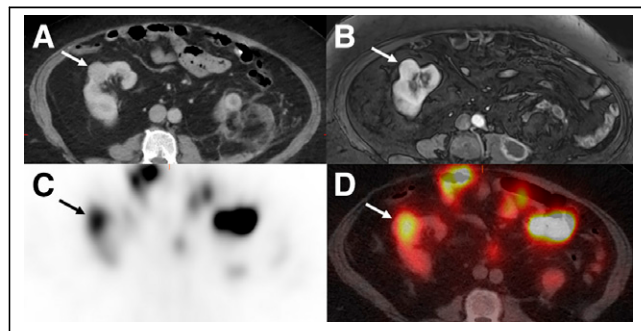


FIGURE 3. 64-y-old woman with enhancing right renal masses detected on a contrast-enhanced CT (arrow, axial image – A) with arterial hyperenhancement on a subsequent MRI (arrow, axial image – B). The masses were deemed suspicious for renal cell carcinoma with a clear-cell likelihood score of 3–4 assigned on the MRI. A $^{99\text{m}}\text{Tc}$ -Sestamibi-SPECT/CT (arrows, axial SPECT – C, fused SPECT/CT – D) showed increased tracer uptake in the masses, higher than that of the adjacent renal parenchyma (mean count ratio of lesion to background renal cortex was 2.3), suggestive of an oncocytic tumor. Pathology from a renal mass biopsy confirmed an oncocytic neoplasm. Patient is on active surveillance, and the masses continue to be stable at 4 y after the initial imaging.

that target CAIX are being investigated. A radiolabeled peptide, [^{68}Ga]Ga-DPI-4452, targeting CAIX has been developed that enables visualization of renal lesions within an hour after injection (30). In a recent phase I study, lesions showed high tumor to background uptake and low uptake in normal kidney (31). The excretion pathway was renal and significant activity was also noted in the GI tract.

Organic small molecules targeting CAIX are also under preclinical assessment or early clinical development (32). For example,

early data and images in 3 patients showed high tumor-to-background contrast but low tumor-to-renal uptake of the agent [^{68}Ga]Ga-NY104 in metastatic ccRCC (33). Many other agents may have similar profiles due to binding to other carbonic anhydrases that may be expressed in normal background kidney, as well as the very high concentrations of bicarbonate that may be in solution. In order to address those concerns, medicinal chemistry approaches have been developed to leverage affinity to a second binding site near the active site of the enzyme (34).

Additional Mitochondrial Imaging Agents

$^{99\text{m}}\text{Tc}$ -tetrafosmin behaves similarly to $^{99\text{m}}\text{Tc}$ -sestamibi in terms of cardiac imaging but may have an advantage in renal imaging in terms of having less hepatobiliary excretion. In a small pilot study, Spiro et al. demonstrated the feasibility of $^{99\text{m}}\text{Tc}$ -tetrafosmin SPECT/CT for renal mass characterization and found similar results to that reported with $^{99\text{m}}\text{Tc}$ -sestamibi (35). Furthermore, PET agents, such as ^{18}F -FBNP (36) might improve spatial and contrast resolution, allowing for characterization of smaller lesions.

Other Targets

PET agents targeting prostate-specific membrane antigen (PSMA) and fibroblast activation protein (FAP) may have utility in renal

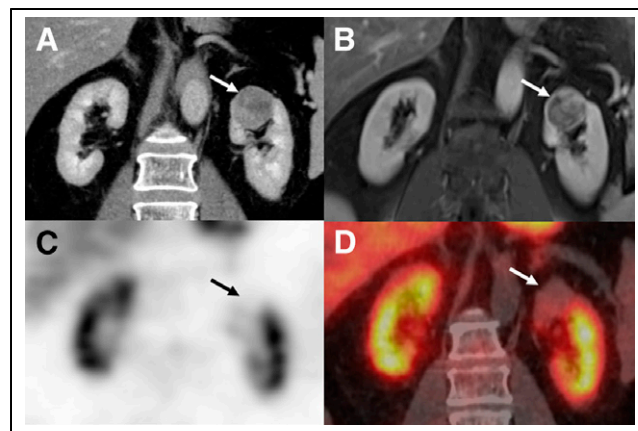


FIGURE 4. 63-y-old man with incidentally detected enhancing mass at the upper pole of the left kidney measuring approximately 3.7 cm on a contrast-enhanced CT (arrow, coronal image – A), with enhancement on MRI (arrow, postcontrast coronal T1 fat saturation image – B) and clear-cell likelihood score of 3. The mass was favored to represent a papillary renal cell carcinoma. A $^{99\text{m}}\text{Tc}$ -Sestamibi-SPECT/CT (arrows, coronal SPECT – C, fused SPECT/CT – D) showed no significant tracer uptake in the renal mass, concerning for renal cell carcinoma. He underwent a left radical nephrectomy with the pathology showing a clear-cell renal cell carcinoma, WHO/ISUP grade 3.

mass characterization. PSMA is highly expressed in the neovascularity of RCC (particularly ccRCC) (37), and its expression intensity is also significantly associated with overall survival. The wide availability of PSMA PET radiotracers have led to investigation in patients with suspicious or confirmed renal masses. A recent systematic review and metaanalysis identified 9 studies with a total of 152 patients (133 with ccRCC, 19 other RCC subtypes) (38). Pooled detection rates were 74% (95% CI [57%, 86%]) for primary or metastatic RCC lesions 87% (95% CI [73%, 95%]) for restaging of metastatic or recurrent RCC. Interestingly, the pooled detection rate was higher for ^{18}F -DCFPyL (92%, (95% CI [76%, 97%]) than for ^{68}Ga -PSMA-11 (85%, 95% CI [62%, 95%]).

FAP was reported to be highly expressed on the cell surface of cancer-associated fibroblasts (CAFs) of the tumor center and infiltrating front of numerous renal cell carcinoma subtypes including ccRCC, papillary RCC, and chromophobe RCC but not in oncocytomas (39). Civan et al. published a series of 18 patients with RCC (6 newly diagnosed, 12 restaging; predominant subtype ccRCC 83%) undergoing ^{18}F -FDG and ^{68}Ga -FAP-04 PET/CT. The authors reported no significant difference between those agents for the median SUV_{max} of all lesions (40). In contrast, ^{68}Ga -FAP-04 had a significantly higher median tumor-to-background ratio than ^{18}F -FDG (5.6 vs. 2.1).

Based on the promising results but overall limited amount of available data, both PSMA- and FAPI-directed imaging are promising candidates for evaluation of patients with RCC as diagnostic tools with potential for theranostic applications as well. Other regulatory-approved radiotracers such as ^{18}F -fluciclovine (41), which targets lipophilic amino acid transporters, and ^{68}Ga -DOTATATE (42), which targets somatostatin receptors, can have uptake in renal tumors, although no efficacy studies for renal tumor characterization have been performed.

XIII. DISCUSSION AND FUTURE DIRECTIONS

Development of a Cohesive Algorithm

There are 3 main considerations for developing an algorithm for molecular imaging of renal masses. The first is the practical use of the agents. The physical characteristics of $^{99\text{m}}\text{Tc}$ -sestamibi (i.e., 140 keV photon emissions and short time from injection to imaging) and ^{89}Zr -girentuximab (i.e., 511 keV photons and longer time from injection to imaging) suggest a practical way to combine the 2 agents that maximizes patient convenience. Essentially, on a patient's first visit, they can be injected and imaged with $^{99\text{m}}\text{Tc}$ -sestamibi, followed by injection of ^{89}Zr -girentuximab. The patient would then return in 3 to 5 days for PET/CT. Reversing the order of the administered agents would necessitate 3 patient visits, with the $^{99\text{m}}\text{Tc}$ -sestamibi scan needing to happen approximately 2 wk after the ^{89}Zr -girentuximab scan (i.e., 5 half-lives after ^{89}Zr -girentuximab administration). The exact use of the agents, in terms of which might be prioritized, will of course be up to individual sites.

The second major consideration is which patients are most appropriate to image. Much of the available data (23) have focused on clinical T1 renal masses, although larger lesions have been imaged (43). An ideal age range to use these techniques has not been defined. Until appropriate-use criteria are proposed and agreed on, individual clinical practices will need to decide which patients would most benefit from further risk stratification. It is likely that many practices will not scan young patients (where any uncertainty in the histologic diagnosis is intolerable) or elderly

patients with significant comorbidities (who would not be candidates for invasive therapy).

The third major consideration for algorithm development is how the information will be used to improve patient care. A central tenet to designing algorithms for using the results of these scans is to determine the role of RMB and how biopsy dovetails with renal mass molecular imaging (9). For example, patients whose tumors are cold on $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT and hot on ^{89}Zr -girentuximab PET/CT almost certainly harbor an RCC and there may be a limited role for RMB. However, a patient whose tumor is cold on both modalities may be a candidate for RMB to better characterize their tumor. Patients with obvious locally advanced disease (e.g., renal vein thrombus) are much more likely to benefit from ^{89}Zr -girentuximab, which might identify ccRCC metastases, than they are to benefit from $^{99\text{m}}\text{Tc}$ -sestamibi. However, $^{99\text{m}}\text{Tc}$ -sestamibi is widely available and inexpensive, as well as a single-photon-emitting radiotracer, and it may be available in parts of the world that lack the infrastructure for deployment of PET agents – hence, it may be the only available option in some contexts (44).

Reimbursement

$^{99\text{m}}\text{Tc}$ -sestamibi is an inexpensive (<\$50) radiotracer that is not protected by intellectual property. As such, within the United States, off-label use of $^{99\text{m}}\text{Tc}$ -sestamibi for renal mass characterization has not faced significant barriers. Ordering the scan with an ICD10 code for “tumor localization” is generally successful.

Given that ^{89}Zr -girentuximab is not yet FDA-approved and is not being marketed, cost is currently unknown. After FDA approval and on initiation of manufacturing, it is anticipated that this will be reimbursed under current CMS rules (45). However, patients may still face a significant copay.

Artificial Intelligence

Radiomic features, which include several quantitative associations among voxels within segmented regions of interest on images, have been used with CT and MRI to suggest renal mass histology (46). However, radiomics alone are unlikely to contribute significantly to improving renal mass molecular imaging, given that the reconstruction algorithms of molecular imaging modalities contain inestimable parameters that negate the reliability of high-frequency features (47).

However, radiomics features from coacquired or contemporaneous CT or MRI scans might be leveraged in a federated way with artificial intelligence (AI)/machine learning (ML) algorithms to maximize the information extracted from the molecular imaging scan(s). Such efforts are already underway, with Klontzas, et al. integrating a mix of qualitative and quantitative features of $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT with CT-based radiomics to augment a radiomics/AI model (48). Such efforts are likely to gain momentum in coming years.

XIV. RADIATION SAFETY IN IMAGING

See also the *SNMMI Guideline for General Imaging*.

It is the position of SNMMI that patient exposure to ionizing radiation should be at the minimum level consistent with obtaining a diagnostic examination. Reduction in patient radiation exposure may be accomplished by administering less radiopharmaceutical when the technique or equipment used for imaging can support such an action. Each patient procedure is unique and the methodology to achieve minimum exposure while maintaining diagnostic

accuracy needs to be viewed in this light. Radiopharmaceutical activity ranges outlined in this document should be considered as a guide. Dose reduction techniques should be used when appropriate. The same principles should be applied when CT is used in a hybrid imaging procedure. CT acquisition protocols should be optimized to provide the information needed while minimizing patient radiation exposure. Minimizing radiation dose is especially important in children.

XV. CONCLUSION

The emerging use of molecular imaging for risk stratification of indeterminate renal masses offers the opportunity to more effectively characterize such lesions and optimize patient management decisions.

XVI. DISCLOSURE

Steven Rowe is a consultant for Lantheus, Telix Pharmaceuticals, and Blue Earth Diagnostics and has a patent for a class of CAIX-binding small molecules. No other potential conflict of interest relevant to this article was reported.

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XVIII. LIABILITY STATEMENT 636

This guideline summarizes the views of the EANM Committee(s) and Council(s) and collaborating society(ies). It reflects recommendations for which the EANM cannot be held responsible. The recommendations should be considered in the context of good practice in nuclear medicine and do not replace national and international legal or regulatory requirements.

XIX. REFERENCES

- Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. *J Natl Cancer Inst.* 2006; 98:1331–1334.
- Pierorazio PM, Hyams ES, Tsai S, et al. Multiphasic enhancement patterns of small renal masses (≤ 4 cm) on preoperative computed tomography: utility for distinguishing subtypes of renal cell carcinoma, angiomyolipoma, and oncocytoma. *Urology.* 2013;81:1265–1271.
- Ma H, Shen G, Liu B, Yang Y, Ren P, Kuang A. Diagnostic performance of ^{18}F -FDG PET or PET/CT in restaging renal cell carcinoma: a systematic review and meta-analysis. *Nucl Med Commun.* 2017;38:156–163.
- Hirota K, Ueno Y, Nogami M, et al. Role of ^{18}F -FDG-PET in renal tumors: insights from WHO 2022 classification. *Jpn J Radiol.* 2025;43:1078–1089.
- Marconi L, Dabestani S, Lam TB, et al. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. *Eur Urol.* 2016;69: 660–673.
- Patel HD, Druskin SC, Rowe SP, Pierorazio PM, Gorin MA, Allaf ME. Surgical histopathology for suspected oncocytoma on renal mass biopsy: a systematic review and meta-analysis. *BJU Int.* 2017;119:661–666.
- Raman SP, Chen Y, Schroeder JL, Huang P, Fishman EK. CT texture analysis of renal masses: pilot study using random forest classification for prediction of pathology. *Acad Radiol.* 2014;21:1587–1596.
- Schieda N, Davenport MS, Silverman SG, et al. Multicenter evaluation of multiparametric MRI clear cell likelihood scores in solid indeterminate small renal masses. *Radiology.* 2022;303:590–599.
- Rowe SP, Pomper MG. Molecular imaging in oncology: current impact and future directions. *CA Cancer J Clin.* 2022;72:333–352.
- Divgi CR, Uzzo RG, Gatsonis C, et al. Positron emission tomography/computed tomography identification of clear cell renal cell carcinoma: results from the REDECT trial. *J Clin Oncol.* 2013;31:187–194.
- Rowe SP, Gorin MA, Solnes LB, et al. Correlation of $^{99\text{m}}\text{Tc}$ -sestamibi uptake in renal masses with mitochondrial content and multi-drug resistance pump expression. *EJNMMI Res.* 2017;7:80.
- Shuch B, Pantuck AJ, Bernhard JC, et al. [^{89}Zr]Zr-girentuximab for PET-CT imaging of clear-cell renal cell carcinoma: a prospective, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2024;25:1277–1287.
- Campbell SP, Tzortzakakis A, Javadi MS, et al. $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT for the characterization of renal masses: a pictorial guide. *Br J Radiol.* 2018;91:20170526.
- Almassi N, Gorin MA, Purysko AS, et al. Use of $^{99\text{m}}\text{Tc}$ -sestamibi single-photon emission computed tomography/x-ray computed tomography in the diagnosis of hybrid oncocytic/chromophobe tumor in a pediatric patient. *Urology.* 2018;113:206–208.
- Rowe SP, Gorin MA, Gordetsky J, et al. Initial experience using $^{99\text{m}}\text{Tc}$ -MIBI SPECT/CT for the differentiation of oncocytoma from renal cell carcinoma. *Clin Nucl Med.* 2015;40:309–313.
- Bui MH, Seligson D, Han KR, et al. Carbonic anhydrase IX is an independent predictor of survival in advanced renal clear cell carcinoma: implications for prognosis and therapy. *Clin Cancer Res.* 2003;9:802–811.
- Yousef A, Kim SS, Krizova A. CAIX Immunostaining in non-neoplastic renal diseases. *Cancer Diagn Progn.* 2022;2:661–667.
- Oosterwijk E, Bander NH, Divgi CR, et al. Antibody localization in human renal cell carcinoma: a phase I study of monoclonal antibody G250. *J Clin Oncol.* 1993; 11:738–750.
- Divgi CR, Pandit-Taskar N, Jungbluth AA, et al. Preoperative characterisation of clear-cell renal carcinoma using iodine-124-labelled antibody chimeric G250 (^{124}I -cG250) and PET in patients with renal masses: a phase I trial. *Lancet Oncol.* 2007;8:304–310.
- Backus M, Piwnicka-Worms D, Hockett D, et al. Microprobe analysis of Tc-MIBI in heart cells: calculation of mitochondrial membrane potential. *Am J Physiol.* 1993;265:C178–87.
- Chen F, Zhang Y, Şenbabaoglu Y, et al. Multilevel genomics-based taxonomy of renal cell carcinoma. *Cell Rep.* 2016;14:2476–2489.
- Gormley TS, Van Every MJ, Moreno AJ. Renal oncocytoma: preoperative diagnosis using technetium $^{99\text{m}}$ sestamibi imaging. *Urology.* 1996;48:33–39.
- Gorin MA, Rowe SP, Baras AS, et al. Prospective Evaluation of $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT for the diagnosis of renal oncocytomas and hybrid oncocytic/chromophobe tumors. *Eur Urol.* 2016;69:413–416.
- Schober JP, Braun A, Ginsburg KB, et al. Clinical performance of technetium- $^{99\text{m}}$ -sestamibi SPECT/CT imaging in differentiating oncocytic tumors from renal cell carcinoma in routine clinical practice. *J Urol.* 2023;210:438–445.
- Asi T, Tuncali MC, Tuncel M, et al. The role of Tc- $^{99\text{m}}$ MIBI scintigraphy in clinical T1 renal mass assessment: does it have a real benefit? *Urol Oncol.* 2020;38:937.e11–937.e17.
- Parihar AS, Mhlana J, Ronstrom C, et al. Diagnostic accuracy of $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT for characterization of solid renal masses. *J Nucl Med.* 2023;64:90–95.
- Tzortzakakis A, Gustafsson O, Karlsson M, Ekström-Ehn L, Ghaffarpour R, Axelsson R. Visual evaluation and differentiation of renal oncocytomas from renal cell carcinomas by means of $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT. *EJNMMI Res.* 2017;7:29.
- Basile G, Fallara G, Verri P, et al. The role of $^{99\text{m}}\text{Tc}$ -sestamibi single-photon emission computed tomography/computed tomography in the diagnostic pathway for renal masses: a systematic review and meta-analysis. *Eur Urol.* 2024;85:63–71.
- Su ZT, Patel HD, Huang MM, et al. Cost-effectiveness analysis of $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT to guide management of small renal masses. *Eur Urol Focus.* 2021;7: 827–834.
- Massière F, Wiedemann N, Borrego I, et al. Preclinical characterization of DPI-4452: a $^{68}\text{Ga}/^{177}\text{Lu}$ theranostic ligand for carbonic anhydrase IX. *J Nucl Med.* 2024;65:761–767.
- Hofman MS, Tran B, Feldman DR, et al. First-in-human safety, imaging, and dosimetry of a carbonic anhydrase IX-targeting peptide, [^{68}Ga]Ga-DPI-4452, in patients with clear cell renal cell carcinoma. *J Nucl Med.* 2024;65:740–743.
- Chen KT, Seimille Y. New developments in carbonic anhydrase IX-targeted fluorescence and nuclear imaging agents. *Int J Mol Sci.* 2022;23:6125.
- Zhu W, Li X, Zheng G, et al. Preclinical and pilot clinical evaluation of a small-molecule carbonic anhydrase IX targeting PET tracer in clear cell renal cell carcinoma. *Eur J Nucl Med Mol Imaging.* 2023;50:3116–3125.

34. Yang X, Minn I, Rowe SP, et al. Imaging of carbonic anhydrase IX with an ^{111}In -labeled dual-motif inhibitor. *Oncotarget*. 2015;6:33733–33742.
35. Spiro E, Murtazaliev S, Amindarolzarbi A, et al. The use of $^{99\text{m}}\text{Tc}$ -tetrafosmin in the characterisation of indeterminate renal masses: a pilot study. *BJU Int*. 2024;134:929–931.
36. Madar I, Naor E, Holt D, Ravert H, Dannals R, Wahl R. Brown adipose tissue response dynamics: in vivo insights with the voltage sensor ^{18}F -fluorobenzyl triphenyl phosphonium. *PLoS One*. 2015;10:e0129627.
37. Spatz S, Tolkach Y, Jung K, et al. Comprehensive evaluation of prostate specific membrane antigen expression in the vasculature of renal tumors: implications for imaging studies and prognostic role. *J Urol*. 2018;199:370–377.
38. Sadaghiani MS, Baskaran S, Gorin MA, et al. Utility of PSMA PET/CT in staging and restaging of renal cell carcinoma: a systematic review and metaanalysis. *J Nucl Med*. 2024;65:1007–1012.
39. Solano-Iturri JD, Errarte P, Etchezarraga MC, et al. Altered tissue and plasma levels of fibroblast activation protein- α (FAP) in renal tumours. *Cancers (Basel)*. 2020;12:3393.
40. Civan C, Kuyumcu S, Has Simsek D, et al. The role of [^{68}Ga]Ga-FAPI-04 PET/CT in renal cell carcinoma: a preliminary study. *Eur J Nucl Med Mol Imaging*. 2024;51:852–861.
41. Parihar AS, Schmidt LR, Dehdashti F, Wahl RL. Detection of additional primary neoplasms on ^{18}F -fluciclovine PET/CT in patients with primary prostate cancer. *J Nucl Med*. 2022;63:713–719.
42. Filizoglu N, Ozguven S. Renal cell carcinoma with tumor thrombus extending into the inferior vena cava and the right atrium demonstrated by ^{68}Ga -DOTATATE PET/CT. *Clin Nucl Med*. 2024;49:e630–e631.
43. Rowe SP, Gorin MA, Javadi MS, Allaf ME. Evaluation of a large renal mass using $^{99\text{m}}\text{Tc}$ -MIBI SPECT/CT in a patient with chronic kidney disease. *Clin Nucl Med*. 2017;42:e166–e167.
44. Sheikhbahaei S, Jones CS, Porter KK, et al. Defining the added value of $^{99\text{m}}\text{Tc}$ -MIBI SPECT/CT to conventional cross-sectional imaging in the characterization of enhancing solid renal masses. *Clin Nucl Med*. 2017;42:e188–e193.
45. CY 2025 Medicare Hospital Outpatient Prospective Payment System and Ambulatory Surgical Center Payment System final rule (CMS 1809-FC). Centers for Medicare and Medicaid Services website. <https://www.cms.gov/newsroom/fact-sheets/cy-2025-medicare-hospital-outpatient-prospective-payment-system-and-ambulatory-surgical-center-0>. Accessed September 25, 2025.
46. Dehghani Firouzabadi F, Gopal N, Homayounieh F, et al. CT radiomics for differentiating oncocytoma from renal cell carcinomas: systematic review and meta-analysis. *Clin Imaging*. 2023;94:9–17.
47. Werner RA, Habacha B, Lütje S, et al. Lack of repeatability of radiomic features derived from PET scans: results from a ^{18}F -DCFPyL test-retest cohort. *Prostate*. 2023;83:547–554.
48. Klontzas ME, Koltsakis E, Kalarakis G, et al. Machine learning integrating $^{99\text{m}}\text{Tc}$ sestamibi SPECT/CT and radiomics data achieves optimal characterization of renal oncocytic tumors. *Cancers (Basel)*. 2023;15.