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European Association of Urology

Platinum Priority – Brief Correspondence

Editorial by Renato A. Valdés Olmos, Lioe-Fee de Geus-Oei, Clemens H.J.M. Ticheler and Johan L. Bloem on pp. 417–418 of this issue

Prospective Evaluation of ^{99m}Tc-sestamibi SPECT/CT for the Diagnosis of Renal Oncocytomas and Hybrid Oncocytic/Chromophobe Tumors

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Article info

Article history:
Accepted August 31, 2015

Associate Editor:
James Catto

Keywords:
Oncocytoma
^{99m}Tc-sestamibi
Renal cell carcinoma
Risk stratification
Small renal mass

Abstract

Nuclear imaging offers a potential noninvasive means of determining the histology of renal tumors. The aim of this study was to evaluate the accuracy of technetium-99m (^{99m}Tc)–sestamibi single-photon emission computed tomography/x-ray computed tomography (SPECT/CT) for the differentiation of oncocytomas and hybrid oncocytic/chromophobe tumors (HOCTs) from other renal tumor histologies. In total, 50 patients with a solid clinical T1 renal mass were imaged with ^{99m}Tc-sestamibi SPECT/CT prior to surgical resection. Preoperative SPECT/CT scans were reviewed by two blinded readers, and their results were compared with centrally reviewed surgical pathology data. Following surgery, 6 (12%) tumors were classified as renal oncocytomas and 2 (4%) as HOCTs. With the exception of 1 (2%) angiomyolipoma, all other tumors were renal cell carcinomas (82%). ^{99m}Tc-sestamibi SPECT/CT correctly identified 5 of 6 (83.3%) oncocytomas and 2 of 2 (100%) HOCTs, resulting in an overall sensitivity of 87.5% (95% confidence interval [CI], 47.4–99.7%). Only two tumors were falsely positive on SPECT/CT, resulting in a specificity of 95.2% (95% CI, 83.8–99.4%). In summary, ^{99m}Tc-sestamibi SPECT/CT is a promising imaging test for the noninvasive diagnosis of renal oncocytomas and HOCTs.

Patient summary: We found that the imaging test ^{99m}Tc-sestamibi SPECT/CT can be used to accurately diagnose two types of benign kidney tumors. This test may be eventually used to help better evaluate patients diagnosed with a renal tumor.

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Recent decades have witnessed a marked increase in the incidental detection of renal tumors. This has resulted in the overtreatment of benign and indolent lesions, which cannot be reliably differentiated from aggressive tumors on conventional imaging. Among renal mass histologies, benign oncocytomas and hybrid oncocytic/chromophobe tumors (HOCTs) are unique in that they are composed of cells with numerous densely packed mitochondria [1,2]. In the field of nuclear medicine, technetium-99m (^{99m}Tc)–sestamibi is a widely available mitochondrial imaging agent

http://dx.doi.org/10.1016/j.eururo.2015.08.056
0302-2838/

that is commonly used for the localization of parathyroid adenomas [3] and myocardial perfusion imaging [4].

We recently carried out a pilot study evaluating ^{99m}Tc-sestamibi single-photon emission computed tomography/x-ray computed tomography (SPECT/CT) for the imaging of renal tumors [5]. In this study, we imaged three oncocytomas and three renal cell carcinomas (RCCs). Consistent with an earlier report in which a single oncocytoma was imaged with ^{99m}Tc-sestamibi [6], we observed that the three oncocytomas accumulated radiotracer at levels near or above that of the normal renal parenchyma. In contrast, the three RCCs were profoundly photopenic and thus readily distinguishable from the oncocytomas. Given these encouraging data, we next embarked on a prospective study to evaluate the accuracy of ^{99m}Tc-sestamibi SPECT/CT for the diagnosis of renal oncocytomas and HOCTs.

Patients presenting with a solid solitary clinical T1 renal mass were imaged with ^{99m}Tc-sestamibi SPECT/CT prior to surgery. SPECT/CT scans were analyzed independently by two blinded nuclear medicine attending physicians (L.B.S., M.S.J.) in two separate random orders. Readers categorized tumors as positive (ie, "hot") (Fig. 1A–1C) or negative

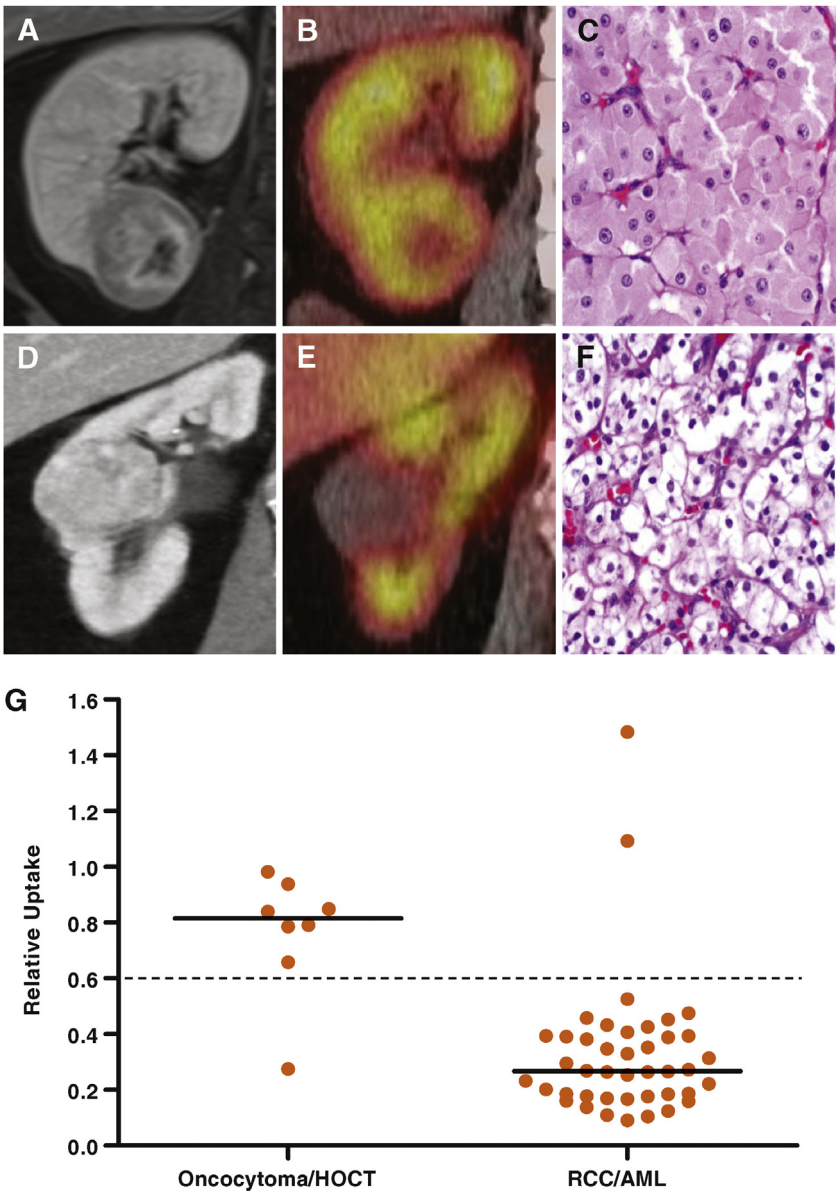

Fig. 1 – (A) Coronal T1-weighted postcontrast magnetic resonance imaging, (B) coronal fused technetium-99m (^{99m}Tc)-sestamibi single-photon emission computed tomography/x-ray computed tomography (SPECT/CT), and (C) hematoxylin and eosin (H&E) histologic image from a patient with an oncocytoma. Note that the enhancing cellular periphery of the tumor in panel 1A corresponds to high radiotracer uptake in panel 1B, whereas the hypoenhancing central stellate scar demonstrates relative photopenia on SPECT/CT. This oncocytoma was classified as positive for radiotracer uptake. (D) Coronal venous/nephrographic-phase postcontrast computed tomography, (E) coronal fused ^{99m}Tc-sestamibi SPECT/CT, and (F) H&E histologic image from a patient with clear cell renal cell carcinoma. The entirety of the tumor appears as a photopenic defect on SPECT/CT and was classified as negative for uptake. (G) Average relative uptake values of imaged tumors. The oncocytomas and hybrid oncocytic/chromophobe tumors consistently accumulated radiotracer at a ratio of >0.6 relative to the ipsilateral normal renal parenchyma. Notably, the two ^{99m}Tc-sestamibi avid outliers in the RCC/angiomyolipoma group were both chromophobe RCCs.
AML = angiomyolipoma; HOCT = hybrid oncocytic/chromophobe tumor; RCC = renal cell carcinoma.

Table 1 – Distribution of tumor histologies and SPECT/CT results

Histologic type	Central pathology review, *n* (%[a])	Positive on ^{99m}Tc-sestamibi SPECT/CT, *n* (%[b])
Oncocytoma	6 (12)	5 (83.3)
HOCT	2 (4)	2 (100)
Clear cell RCC[c]	26 (52)	0
Papillary RCC[d]	8 (16)	0
Chromophobe RCC	4 (8)	2 (50)
Clear cell papillary RCC	2 (4)	0
Unclassified RCC	1 (2)	0
AML	1 (2)	0
Oncocytoma plus HOCT	8 (16)	7 (87.5)
RCC plus AML	42 (84)	2 (4.8)

^{99m}Tc = technetium-99m; AML = angiomyolipoma; HOCT = hybrid oncocytic/chromophobe tumor; RCC = renal cell carcinoma; SPECT/CT = single-photon emission computed tomography/x-ray computed tomography.
[a] Denominator is the total number of tumors (*n* = 50).
[b] Denominator is the number of tumors of the specified histologic type.
[c] Grade 3–4 tumors: 16 (61.5%).
[d] Grade 3–4 tumors: 4 (50%).

(ie, "cold") (Fig. 1D–1F) for radiotracer uptake and quantified the maximum radiotracer uptake within the tumor and ipsilateral normal renal parenchyma. Relative radiotracer uptake was calculated as the ratio of tumor to parenchymal uptake, and the mean across the four reads was calculated for each tumor. Following surgical resection, two blinded genitourinary pathologists (A.S.B., J.I.E.) collaboratively reviewed all cases to determine tumor histology, and this served as the standard to which SPECT/CT results were compared. A more detailed description of the study methods can be found in Supplement 1.

In total, 50 patients participated in this study. Supplementary Table 1 provides details of the study cohort. On final surgical pathology, 6 (12%) tumors were classified as renal oncocytomas and 2 (4%) as HOCTs. With the exception of 1 (2%) angiomyolipoma, all other tumors were RCCs (82%). Table 1 details the histologic types of resected tumors. Notably, 26 (52%) tumors were classified as clear cell RCC and 8 (16%) as papillary RCC, with 1 papillary RCC (12.5% of papillary RCCs) being subclassified as the oncocytic variant. Among cases of clear cell and papillary RCC, 20 (58.8%) were nucleolar grade 3–4.

Following blinded review of the SPECT/CT scans, values for inter- and intraobserver agreement were calculated (Supplementary Table 2). This analysis revealed nearly perfect agreement for all comparisons (range of κ values: 0.93–1.00). Only 1 (2%) tumor required reconciliation at the intraobserver level.

^{99m}Tc-sestamibi SPECT/CT correctly identified 5 of 6 (83.3%) oncocytomas and 2 of 2 (100%) HOCTs, resulting in an overall sensitivity of 87.5% (95% confidence interval [CI], 47.4–99.7%) (Table 1). Only two tumors were falsely positive on SPECT/CT (both chromophobe RCCs), resulting in a specificity of 95.2% (95% CI, 83.8–99.4%). On *post hoc* analysis, a relative uptake value of 0.6 was found to correctly classify tumors (Fig. 1G).

Consistent with the findings of our earlier pilot study [5], we found that ^{99m}Tc-sestamibi SPECT/CT allowed for the sensitive and specific detection of renal oncocytomas. In addition, ^{99m}Tc-sestamibi SPECT/CT allowed for the diagnosis of HOCTs, a subtype of renal tumor that histologically resembles both oncocytoma and chromophobe RCC but behaves in a benign fashion [7]. These data demonstrate the potential utility of this nuclear imaging test for the preoperative assessment of indeterminate renal tumors, possibly sparing patients with a positive test further invasive procedures.

A concern about a test that aims to identify benign tumors is that a false-positive finding may result in inaction on the part of the physician, placing the patient at risk for undertreatment. The results of our study, however, show nearly perfect specificity of ^{99m}Tc-sestamibi SPECT/CT, with only two tumors being incorrectly classified as positive, resulting in specificity of 95.2%. Interestingly, both false-positive lesions were chromophobe RCCs, an RCC subtype that has a largely indolent clinical course. In fact, proposed biopsy-based treatment algorithms recommend active surveillance as the management of choice for small chromophobe tumors [8]. This is further supported by data from our institution's own active surveillance program, in which no case of chromophobe RCC has crossed over to require an intervention [9]. Moreover, in a contemporary systematic review of the active surveillance literature, no case of chromophobe RCC has been reported to have metastasized while on surveillance [10]. Consequently, although in our study we classified these tumors as falsely positive, from a practical standpoint, a test that can identify renal oncocytomas, HOCTs, and chromophobe RCCs offers a tremendous leap forward in our current ability to noninvasively risk-stratify patients presenting with an indeterminate renal mass.

A limitation of our study is the relatively small sample size of only 50 tumors. Given this, the CIs associated with the observed values for sensitivity and specificity are fairly wide. In addition, not all RCC subtypes/variants were adequately sampled, for example, no case of clear cell RCC with eosinophilic features or any tumor type with sarcomatoid components was imaged. These tumors are potentially aggressive, and more fully evaluating their imaging characteristics with this test will be of value. Lastly, we feel it is critical to image a larger number of chromophobe RCCs so as to better understand the performance of this test with respect to these tumors.

In summary, ^{99m}Tc-sestamibi SPECT/CT is a promising imaging test for the differentiation of oncocytomas and HOCTs from other renal tumor histologies. This test offers the potential to spare a substantial number of patients unnecessary invasive procedures such as biopsy, ablation, and surgery, each with its attendant risk of complications. Prior to clinical implementation, however, larger numbers are needed to more precisely define the sensitivity and specificity of this test and its exact place in the diagnostic armamentarium.

Author contributions: Mohamad E. Allaf had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gorin, Rowe, Epstein, Javadi, Allaf.
Acquisition of data: Gorin, Rowe, Baras, Solnes, Ball, Pierorazio, Pavlovich, Epstein, Javadi, Allaf.
Analysis and interpretation of data: Gorin, Rowe, Baras, Solnes, Ball, Pierorazio, Pavlovich, Epstein, Javadi, Allaf.
Drafting of the manuscript: Gorin, Rowe.
Critical revision of the manuscript for important intellectual content: Gorin, Rowe, Baras, Solnes, Ball, Pierorazio, Pavlovich, Epstein, Javadi, Allaf.
Statistical analysis: Gorin, Rowe.
Obtaining funding: Gorin, Allaf.
Administrative, technical, or material support: None.
Supervision: Epstein, Javadi, Allaf.
Other (specify): None.

Financial disclosures: Mohamad E. Allaf certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This study was supported by a mini grant from the National Kidney Foundation of Maryland and by generous donations to The James Buchanan Brady Urological Institute.

Acknowledgment statement: The authors acknowledge Jason Hong, Tina Wlajnitz, and Brooke Sroka for their outstanding support in coordinating this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2015.08.056.

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