

A review of ^{99m}Tc-sestamibi SPECT/CT for renal oncocytomas: A modified diagnostic algorithm

Mitchell P Wilson*, Prayash Katlariwala, Jonathan Abele, Gavin Low

Department of Radiology and Diagnostic Imaging, University of Alberta, Edmonton, Alberta, Canada.

SUMMARY ^{99m}Tc-sestamibi SPECT/CT is a promising nuclear medicine imaging investigation for benign renal lesions such as renal oncocytomas. The purpose of this article is to *i*) review the current literature on ^{99m}Tc-sestamibi SPECT/CT, *ii*) to review to current application of ^{99m}Tc-sestamibi SPECT/CT for indeterminate renal lesion imaging, and *iii*) to discuss present limitations and areas for future research. The literature has been reviewed up to April 2022 for articles relating to the application of ^{99m}Tc-sestamibi SPECT/CT for benign renal lesions including a recently published systematic review and meta-analysis performed by the authors. One study evaluating ^{99m}Tc-sestamibi SPECT alone and five studies evaluating ^{99m}Tc-sestamibi SPECT/CT have been performed to date. ^{99m}Tc-sestamibi SPECT/CT demonstrates high sensitivity and specificity for detecting benign renal lesions, particularly renal oncocytomas. ^{99m}Tc-sestamibi SPECT/CT demonstrates near-perfect specificity for benign and low-grade renal lesions. The optimal quantified threshold ratio for tumor-to-background renal parenchyma radiotracer uptake for a positive result is > 0.6. In this article, we propose a modified diagnostic algorithm for small enhancing renal masses measuring 1-4 cm in which suspected benign lesions after conventional imaging are considered for ^{99m}Tc-sestamibi SPECT-CT. In this algorithm, positive studies can be monitored with active surveillance rather than requiring invasive biopsy and/or targeted therapy.

Keywords oncocytoma, RCC, renal, SPECT, sestamibi, surveillance

1. Introduction

The incidence of renal lesions has shown rapid growth in recent previous decades with an increasing number of surgical resections performed but no corresponding reduction in mortality (1). The rising incidence of incidental benign renal lesions on imaging is believed to play a considerable role in this result (2,3). Renal oncocytomas (RO) represent a particularly challenging benign renal lesion to differentiate from renal cell carcinomas (RCC) on imaging and frequently require surgical resection. In one study of nearly 3,000 surgically resected renal tumors, ROs accounted for 73% (274/376) of the surgically resected benign renal lesions (4).

One interesting histopathological feature previously found in ROs is a robust presence of mitochondria. In electron microscopy studies, the frequent presence of mitochondria in ROs has been a particularly distinguishable feature compared to chromophobe renal cell carcinomas (ChrRCC), a lesion which is essentially indistinguishable from RO on conventional imaging

(5,6). This histopathological difference is believed to be exploited in ^{99m}Tc-sestamibi imaging, as sestamibi is a lipophilic cation which has been shown to accumulate in cells with high density mitochondria (7). Gormley *et al.* were the first group to hypothesize the potential application of ^{99m}Tc-sestamibi imaging with a pilot SPECT imaging study in 1996 (8). In their study, they performed ^{99m}Tc-sestamibi SPECT imaging on 6 patients including one oncocytoma, one renal cyst, one angiomyolipoma one cystic RCC and two solid RCCs. Of these patients, only the renal oncocytoma was shown to have a relative tumor-to-background renal parenchyma uptake of > 1 with a ratio of 1.44, nearly 0.6 greater than the next highest lesion.

Further exploration of ^{99m}Tc-sestamibi imaging remained relatively quiescent until 2015 when Rowe *et al.* published the first pilot study evaluating ^{99m}Tc-sestamibi SPECT/CT with 6 patients (3 renal oncocytomas and 3 RCCs), which showed complete differentiation of the relative tumor uptake between the groups (ROs 0.85-1.78 versus RCCs 0.21-0.26) (9). Since then, four additional studies have been

published in title or conference abstract format (10-13). One additional study has been posted on the Cochrane Central Register of Controlled Trials but remains unpublished to date (14). A systematic review and meta-analysis evaluating the diagnostic accuracy of 99mTc-sestamibi SPECT/CT in benign renal lesions such as renal oncocytomas has been recently published (15). The purpose of this article is to *i*) review the current literature on 99mTc-sestamibi SPECT/CT, *ii*) to review to current application of 99mTc-sestamibi SPECT/CT for indeterminate renal lesion imaging, and *iii*) to discuss present limitations and areas for future research.

2. Diagnostic performance for benign renal lesions

Five studies evaluating the diagnostic performance of 99mTc SPECT/CT for benign renal lesions with a total of 148 lesions are summarized in Table 1. A total of 31 ROs were included in reviews to date with 29 (94%) demonstrating positive sestamibi uptake. An additional 6 lesions were hybrid oncocytic/chromophobe tumors (HOCT), all of which were positive for sestamibi uptake. Only 3 of 8 (38%) ChrRCCs were positive for uptake and 2/98 (2%) of all other renal cell carcinomas (RCC) were positive for sestamibi uptake. A recent meta-analysis demonstrated a sensitivity and specificity of 92% (95% CI: 72-98%) and 88% (95% CI: 79-94%) respectively for RO versus other renal lesions and 86% (95% CI: 66-95%) and 90% (95% CI: 80-95%) for benign versus malignant lesions when HOCTs were considered malignant (15). The positive and negative likelihood ratios for benign versus malignant lesions were 8.6 (95% CI: 4.1-17.9) and 0.16 (95% CI: 0.06-0.42) respectively.

There is no clear consensus regarding the characterization of HOCTs. The 2013 Vancouver Classification of Renal Neoplasia by the International Society of Urological Pathology (ISUP) characterized HOCTs as a subcategory of ChrRCCs given the presence of some morphologic characteristics of ChrRCCs (16). However, the group also recognized that this characterization is not clear as in some cases such as patients with oncocytomatosis, HOCTs may in

fact represent a morphologically distinct category and not a progressive spectrum between ROs and ChrRCCs. In 2016, the World Health Organization (WHO) significantly revised their fourth edition of the WHO "blue book" classification of urinary system and male genital organ tumors (17). In this most recent version, no specific classification of HOCTs as malignant is made. Gorin *et al.*'s group have chosen to consider HOCTs as benign renal lesions, citing a study following four HOCTs for 44 months without progression (10,18). Their group has recently performed a meta-analysis of 167 patients including unpublished data from their institution in which they characterize ROs and HOCTs together as benign lesions with a sensitivity and specificity of 86.6% (95% CI: 77.3-93.8%) and 89.1% (95% CI: 82.6-94.2%) respectively for 99mTc-sestamibi SPECT/CT (19). When HOCTs were characterized as benign lesions in a published meta-analysis, the sensitivity, specificity, and positive predictive value for benign renal lesions became 88% (29/33), 95% (80/84), and 88% (29/33) respectively (15).

Despite electron microscopy studies demonstrating a distinct difference in number of mitochondria between oncocytomas and ChrRCCs, 99mTc-sestamibi SPECT/CT is currently not specific at sub-classifying the two lesion types. This evaluation is limited however, by a small available sample size to date. ChrRCCs are also known to represent a more indolent form of RCC with better long-term prognosis than other RCC subtypes (20). Some authors have even argued that biopsy proven ChrRCC < 2 cm and deep (> 5 mm depth) 2-4 cm ChrRCCs should be managed with active surveillance rather than surgery (21). Of the 5 sestamibi positive malignant renal lesions noted to date, at least 3 are ChrRCC with a third not subtyped and the fourth representing a papillary RCC. No clear cell RCCs have demonstrated sestamibi uptake on published articles to date.

3. Threshold value for a positive result

Three of five published studies have used semi-quantitative analysis demonstrating an optimal cut-

Table 1. Summary of patients in diagnostic performance studies evaluating 99mTc-sestamibi SPECT/CT for benign renal lesions

Authors (Ref.)	No. RO (No. positive)	No. AML (No. positive)	No. HOCT (No. positive)	No. ChrRCC (No. positive)	Other RCC (No. positive)	No. MA (No. Positive)	Lymphoma (No. Positive)
Gorin (10)	6 (5)	1 (0)	2 (2)	4 (2)	37 (0)		
Rowe (9)	3 (3)				3 (0)		
Sistani (11)	7 (7)		1 (1)	2 (1)	21 (0)		
Tzortzakakis (12)	12 (11)	1 (1)	3 (3)	2 (0)	11 (1)	1 (0)	1 (0)
Zhu (13)	3 (3)	1 (1)		Unclear*	26 (1)		
Total	94% (29/31)	67% (2/3)	100% (6/6)	38% (3/8)	2% (2/98)	0% (0/1)	0% (0/1)

RO: renal oncocytoma; AML: angiomyolipoma; HOCT: hybrid oncocytic/chromophobe tumors; ChrRCC: Chromophobe RCC; RCC: renal cell carcinoma; MA: metanephric adenoma. *, Conference abstract with no details of renal cell carcinoma subtypes provided.

off tumor-to-background renal parenchyma ratio of 0.6 (9,10,13). Tzortzakakis *et al.* utilized a visual analysis resulting in a sensitivity of 88% (15/17) and a specificity of 93% (13/14) for benign versus malignant renal lesions when HOCTs were considered benign (12). However, their group did recommend a more quantitative method of analysis to improve evaluation. A secondary analysis of Gorin *et al.*'s patients showed that quantitative analysis demonstrates a slightly increased but potentially clinically important differentiation between benign and malignant lesions, especially with lesions demonstrating an uptake ratio near the 0.6 cut-off (22). When quantitative methods are utilized, studies have shown excellent to near-perfect intra-observer and inter-observer agreement for diagnosis of a positive result with 99mTc-sestamibi SPECT/CT (10,23). Tzortzakakis *et al.* recently demonstrated that the intra-class correlation coefficient for SUVmax measurements by the same reader was 97-99% and 87-89% between readers for solid renal tumors. Strong agreement is likely at least partially related to large differences between tumor-to-renal parenchyma ratios between negative and positive results. Only a small proportion of the renal lesions evaluated to date have demonstrated ratios between 0.6-0.8.

4. Current application for indeterminate renal lesions

The literature currently demonstrates that 99mTc-sestamibi SPECT/CT is both sensitive and specific for identifying benign renal lesions at a cut-off tumor-to-renal parenchyma ratio of 0.6. The test becomes very specific when HOCTs are also characterized as benign renal lesions. Although the test is not good at differentiating ROs from ChrRCCs, very few non-ChrRCCs have demonstrated positive uptake on this examination, supporting a very high specificity for benign and low-grade renal lesions.

99mTc-sestamibi SPECT/CT is currently applicable for indeterminate renal lesions which are considered for active surveillance rather than surgical resection. In one retrospective study evaluating the added value of 99mTc-sestamibi SPECT/CT to conventional cross-sectional imaging, preoperative sestamibi imaging was shown to improve the confidence of a conventional imaging diagnosis in nearly 30% of cases (14/48) (24). In their study, the area under the curve increased from 0.60 for conventional imaging alone to 0.85 after combining conventional imaging with 99mTc-sestamibi SPECT/CT. Another review has supported this argument, suggesting that applying 99mTc-sestamibi SPECT/CT in indeterminate renal lesions < 4 cm will increase the number of patients undergoing active surveillance rather than unnecessary intervention (25). Therefore, we propose an imaging pathway in which small enhancing renal masses measuring 1-4 cm suspected to represent benign lesions after conventional

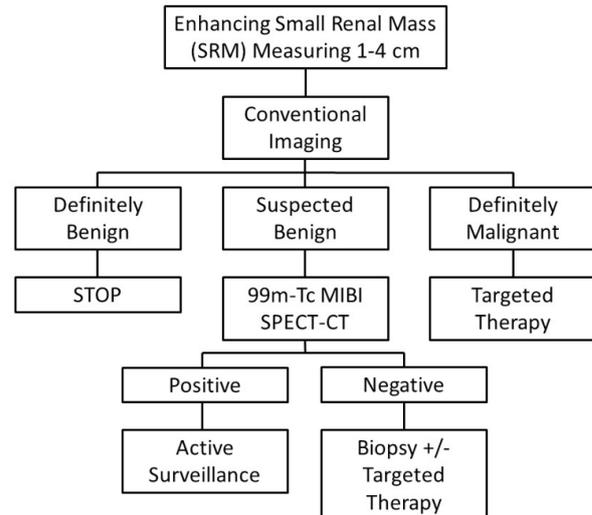


Figure 1. Proposed imaging pathway with integration of 99mTc sestamibi for small enhancing renal masses measuring 1-4 cm being considered for active surveillance.

imaging be considered for 99mTc-sestamibi SPECT/CT. In this pathway, lesions which demonstrate positive uptake have a high specificity for benignity and can be monitored with active surveillance rather than biopsy and/or targeted therapy. The proposed imaging pathway is demonstrated in Figure 1.

5. Limitations and future research

The main limitation to date is a small sample size with only 148 lesions described in the literature. Given that the acquisition technique was similar amongst studies and the diagnostic criteria for most studies was also similar, variability amongst studies is lower than is typically seen in diagnostic accuracy studies. Specific imaging acquisition techniques for each study are demonstrated in Table 2. More studies from different institutions will help improve confidence in the diagnostic performance of this examination, particularly for patients eligible for active surveillance rather than intervention with our proposed pathway.

In addition to studies evaluating performance alone, subgroup analysis will aid in better characterizing which situations this study is best applied. For example, smaller lesions (< 1.5 cm) are generally known to have lower sensitivity on SPECT imaging due to limits in spatial resolution and partial volume averaging (26). Understanding differences in performance dependent on size will assist in knowing the minimum size criteria for 99mTc-sestamibi SPECT/CT application. Only two studies describe the mean lesion size, identifying an average lesion of 3.1 cm, although these are not subcategorized by positive and negative results. Tzortzakakis *et al.* report the number of tumors by size range noting that 19% (6/31) of their lesions were

Table 2. SPECT/CT acquisition details for individual studies

Authors (Ref.)	SPECT/CT Brand	Dose MIBI (MBq)	SPECT/CT Post Injection Timing (min)	Collimator Energy	Matrix Size	Projection Timing (sec)	Range of Projection	CT kV	CT mAs	CT Slice Thickness (mm)
Gorin (10)	Siemens*	925	75	NR	NR	NR	NR	NR	NR	NR
Rowe (9)	Siemens*	925	75	Low	64 × 64	28	180 degrees @ 30 Intervals	130	90	3
Sistani (11)	GE**	1110	60 - 90	NR	NR	NR	NR	NR	NR	NR
Tzortzakakis (12)	Siemens*	925 ± 25	60 - 90	Low	128 × 128	NR	NR	130	Modulated	5
Zhu (13)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

*Siemens Symbia, 16 Slice SPECT/CT; **GE Discovery, 16 Slice SPECT/CT; NR: Not Reported.

between 1-1.5 cm but do not clearly define which of these were positive or not. They did not include any lesions < 1 cm.

Another area for subgroup analysis would be specifically evaluating the diagnostic performance for other non-oncocytoma benign renal masses. For example, prior studies analyzing the ultrastructure of AMLs have identified numerous mitochondria in these lesions as well (27). In studies reported to date, 2/3 angiomyolipomas have demonstrated positive uptake. Lipid poor AMLs are another difficult lesion to diagnose with conventional imaging, and if this test can subclassify these lesions, there may be additional value in using this examination in specific circumstances such as T2 hypointense indeterminate renal lesions (28).

Finally, an area currently being explored by the Johns Hopkins group is the utilization of 99mTc-sestamibi SPECT/CT in dual-tracer SPECT imaging (29). Several agents targeting the transmembrane protein carbonic anhydrase IX (CAIX) have been developed, including 124I-girentuximab, which has been trialed in a large multicenter study of 195 patients with PECT/CT (REDECT Trial) demonstrating a sensitivity of 86.2% (95% CI: 75.3-97.1) and specificity of 85.9% (95% CI: 69.4-99.9) for clear cell RCC, statistically better than the comparator contrast-enhanced CT ($p = 0.005$) (30). This combined tracer would have the potential to differentiate indeterminate renal lesions into benign renal lesions such as oncocytoma, but also further characterize 99mTc-sestamibi SPECT/CT negative lesions into clear cell RCC or other. The Johns Hopkins group has developed an 111In-labeled SPECT radiotracer-targeting CAIX and are currently investigating a dual-tracer SPECT study with 99mTc-sestamibi in a single center prospective trial (29,31).

6. Conclusion

Current literature has shown that 99mTc-sestamibi SPECT/CT is both sensitive and specific for benign and low-grade renal lesions such as oncocytomas and hybrid oncocyctic/chromophobe tumors. We propose a diagnostic algorithm with the use of 99mTc-sestamibi SPECT/CT for small enhancing renal masses measuring 1-4 cm suspected to be benign, where studies with positive uptake can be monitored with active surveillance rather than undergo an invasive diagnostic and/or therapeutic procedure. Future studies evaluating the diagnostic performance of 99mTc-sestamibi SPECT/CT for indeterminate renal lesions with subgroup analysis and dual-tracer studies will continue to refine specific applications in indeterminate renal lesions.

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**Address correspondence to:*

Mitchell P Wilson, Department of Radiology and Diagnostic Imaging, University of Alberta, 2B2.41 WMC, 8440-112 Street NW, T6G 2B7, Edmonton, Alberta, Canada.
Email: mitch.wilson@ualberta.ca

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