

The value of ^{99m}Tc -sestamibi single-photon emission computed tomography-computed tomography in the evaluation and risk stratification of renal masses

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Abstract

Introduction: Differentiation of renal cell carcinoma (RCC) from oncocytoma is a common diagnostic dilemma. A few studies have shown that ^{99m}Tc -sestamibi (MIBI) imaging has the potential to characterize indeterminate renal masses. This comparative study evaluated the utility of MIBI single-photon emission computed tomography-computed tomography (SPECT-CT) in the assessment and risk stratification of renal masses.

Methods: A total of 29 patients with 31 renal masses who had cross-sectional imaging and MIBI SPECT-CT were included. Lesions were categorized as either MIBI-positive or -negative on SPECT-CT. Individual lesion density ranged from 22–56 Hounsfield units (HU) on the non-contrast CT part of SPECT-CT. Quantitative relative MIBI uptake was calculated by measuring tumor to ipsilateral renal parenchymal uptake. The imaging results were correlated with histopathology.

Results: All oncocyctic lesions, including seven oncocytomas and one hybrid oncocyctic chromophobe tumor (100%), were positive on MIBI. One chromophobe RCC showed low-grade MIBI uptake. The remaining RCC subtypes, including 15 clear-cell, four papillary, two mixed clear-cell and papillary, and one chromophobe, were MIBI-negative. The quantitative relative tumor uptake showed statistically significant higher uptake in the low-risk/oncocyctic lesions compared to RCCs.

Conclusions: This study demonstrates that MIBI SPECT-CT is valuable in the characterization of indeterminate renal masses. The combination of MIBI uptake on SPECT and lesion density on non-contrast CT can be used for risk stratification of renal masses. This technique may reduce the need for further imaging (multiphasic CT or magnetic resonance imaging), renal mass biopsy, or surgical resection of low-risk renal masses. Subsequently, more patients could be followed with active surveillance.

Introduction

The incidence of renal cell carcinoma (RCC) has almost doubled in Canada since 1970.¹ This is likely related to the growing incidence of risk factors, such as hypertension and obesity, and higher detection of incidental solid renal masses on routine diagnostic imaging examinations.^{1,2}

The most commonly encountered solid enhancing renal masses include RCC, oncocytoma, and fat-poor angiomyolipoma (AML).³ RCC has several typical and distinct histological subtypes; clear-cell is the most common (75%), followed by papillary (10%) and chromophobe (5%).³ Oncocytoma is a benign renal tumor that has significant imaging overlap with RCC.⁴ The classic central scar is typically found in oversized oncocytomas and is likely due to lesion growth, resulting in central infarction, hemorrhage, and necrosis.⁵ Additionally, a small percentage of lesions may have hybrid pathology, known as hybrid oncocyctic chromophobe tumor (HOCT). As with oncocytomas, HOCT in previous studies showed no regional or metastatic progression during followup.⁶

Due to the overlap in the imaging features between RCC and oncocytoma, many oncocytomas are surgically resected.⁴ Published literature demonstrates that currently, renal masses with features suspicious of malignancy may be overtreated.^{7,8} A study by Frank et al, including 2770 resected renal masses, showed that 12.8% of the lesions were benign, and when further stratified based on size, 25% of lesions smaller than 3 cm were benign.³ Additionally, a recently published study with approximately 900 patients showed that 14% of patients who underwent partial nephrectomy had benign masses, with oncocytoma being the most common benign pathology.⁹

Currently, biopsy is the only reliable method to accurately differentiate between oncocytoma and RCC. Although biopsy has a diagnostic accuracy of 80–90%, 10–20% of cases remain indeterminate, and biopsy of small lesions remains challenging.^{10,11} In addition, some patients, particularly those who are young and healthy, are not willing to accept the risk

of a false-negative biopsy result and may undergo surgery that is ultimately not necessary.¹² As a result of the above factors, there is a need for a non-invasive method to differentiate RCC and oncocytoma and reduce overdiagnosis and overtreatment of renal tumors.

In 1996, ^{99m}Tc-sestamibi was first introduced for its potential in the diagnosis of oncocytoma.¹³ ^{99m}Tc-sestamibi is a lipophilic, cationic molecule taken up by cells with a high concentration of mitochondria, such as myocardium, parathyroid adenoma, and breast cancer.^{14,15} Histologically, oncocytoma contains numerous mitochondria, as does chromophobe RCC. In the latter case, however, the mitochondria are typically abnormal.¹⁶ Clear-cell and papillary RCC have microvilli and lack mitochondria.¹⁶

There have been very few studies investigating the role of ^{99m}Tc-sestamibi single-photon emission computed tomography-computed tomography (MIBI SPECT-CT) in the assessment of renal masses.¹⁷⁻²⁰ The purpose of this study was to evaluate this role further in the Canadian healthcare system, and also define the value of MIBI SPECT-CT in the risk stratification of renal masses.

Methods

A single-site, comparative study was conducted on 29 patients with 31 renal masses between December 2018 and March 2020. The study was approved by the institutional ethics committee. Patients who required further characterization of their renal mass prior to proceeding with treatment (based on the discretion of the treating urologist) were selected to undergo further imaging with MIBI SPECT-CT as part of standard of care.²⁰ All patients provided consent to undergo the imaging investigations, renal mass biopsy, or surgical excision, and all care was funded by the Ontario Health Insurance Plan (OHIP). Data was subsequently collected and analyzed in a retrospective manner.

All patients had a CT scan and renal MIBI SPECT-CT scan. MIBI SPECT-CT imaging was performed 60–90 minutes after the administration of 30 mCi of MIBI on a 16-slice SPECT-CT camera (GE Discovery NM/CT 670). All MIBI SPECT-CT images were reviewed independently by an experienced nuclear medicine specialist and a dual radiology/nuclear medicine resident. A final diagnostic interpretation was made by consensus. The imaging physicians were not blinded to the patient record.

A visual approach was used in the evaluation of the renal masses, as has been previously described by Campbell et al.²⁰ Six patterns of uptake were defined as follows: 0: no uptake; 1: uniformly high uptake; 2: variable tumor uptake with areas of high uptake; 3: peripheral uptake with central photopenia; 4: tumoral uptake but below the level of surrounding renal parenchyma; and 5: uptake in the endophytic portion of the lesion. Ultimately, MIBI scans were

characterized as negative (0: no uptake) and positive (1–5: any pattern of uptake). Additionally, a quantitative relative tumor uptake was calculated by ratio of mean and maximum tumor uptake to ipsilateral renal parenchymal physiological uptake on SPECT (1.5 cm² circular region of interest). The density of lesions was measured by placing a 1 cm² circular region of interest within the mass on the non-contrast CT part of SPECT-CT.

The histopathology of the renal masses was determined through either image-guided percutaneous biopsy or surgical excision with partial or radical nephrectomy. Histopathology results were correlated with MIBI SPECT-CT imaging findings.

Statistical analysis was performed using Microsoft Excel, Version 16.36 (20041300). Descriptive data are presented as median, range, or percentage as appropriate. Univariate analysis was performed using Independent Sample t-test to compare means of continuous variables.

Results

Twenty-nine patients with 31 histopathologically confirmed lesions were included in the study. The information regarding patient demographics and baseline imaging characteristics of renal masses are detailed in Table 1. The results of the MIBI scans and corresponding histopathology are summarized in Table 2.

The pattern of uptake in the nine MIBI positive lesions was as follows: three lesions showed uniformly high uptake; three had variable uptake with areas of high uptake; one had definite uptake but less than ipsilateral renal parenchyma; and two showed uptake in the endophytic portion of lesions. Lesion density ranged from 22–56 Hounsfield units (HU) on the non-contrast CT of the SPECT-CT scans. Selected images of an oncocytoma and an RCC are shown in Figs. 1 and 2.

The mean and maximum relative tumor uptake to ipsilateral renal parenchyma was calculated. The median of “mean relative tumor uptake” was 0.66 in oncocytic lesions and 0.27 in RCC lesions. The median of “maximum relative tumor uptake” was 0.76 and 0.33 in oncocytic and RCC lesions, respectively. The mean and maximum relative tumor uptake were statistically significantly higher in benign/oncocytic lesions compared to RCCs ($p=0.016$ and 0.012 , respectively). It is noteworthy to clarify that lesions were not classified as MIBI-positive or -negative based on quantitative evaluation, and this quantitative relative tumor uptake was calculated to determine if a quantitative cutoff exists to categorize lesions as benign (oncocytic lesions) vs. malignant (RCC).

Of the five Bosniak IV lesions mentioned in Table 1, three were clear-cell RCCs, one was a chromophobe RCC, and one was an oncocytoma. One patient with Birt-Hogg-Dubé syndrome had seven bilateral renal masses that all showed high MIBI uptake. One of the lesions underwent biopsy and was confirmed to be an oncocytoma. The remaining

Table 1. Demographics and characteristics of renal masses

Characteristic	
Age (n=29)	
Median (years)	59.9
Range (years)	30–83
Gender (n=29)	
	n (%)
Female	6 (20.7%)
Male	23 (79.3%)
Renal mass size (n=31)	
Median (cm)	2.9
Range (cm)	1.6–8
<4 cm*	26 (83.9%)
>4cm	5 (16.1%)
Renal mass appearance	
	n (%)
Solid enhancing mass	26 (83.9%)
Bosniak 4 cyst	5 (16.1%)

*Lesions less than 4 cm are defined as small renal masses (SRMs).

Table 2. MIBI SPECT-CT results are correlated with histopathology results

Histopathology	Number of lesions	Positive MIBI scan	Negative MIBI scan
Oncocytoma	7	7 (100%)	–
HOCT	1	1 (100%)	–
Chromophobe RCC	2	1 (50%)	1 (50%)
Clear cell RCC	15	–	15 (100%)
Papillary RCC	4	–	4 (100%)
Mixed papillary and clear-cell RCC	2	–	2 (100%)
Total	31	9	22

Results are expressed as actual number (percentage of total number of lesions with specific histopathology). HOCT: hybrid oncocytic chromophobe tumor; MIBI: ^{99m}Tc-sestamibi; RCC: renal cell carcinoma; SPECT-CT: single-photon emission computed tomography-computed tomography.

lesions were not biopsied, as their imaging features were identical to the biopsied lesion. Only the biopsied lesion was included in the data analysis. One of the patients had an AML in the contralateral kidney with typical imaging characteristics on CT and MRI, which did not show uptake on MIBI scan but was not included in the analysis due to lack of histopathology confirmation.

Discussion

This single-center, comparative study is in alignment with previously published studies regarding the utility of MIBI SPECT-CT in the characterization of solid renal masses. In our study, 100% of oncocytomas (n=7), one HOCT (n=1), and one chromophobe RCC (n=1 of 2) were MIBI-positive. In the study by Gorin et al, 83.3% (5/6) of oncocytomas, 100% of HOCTs (n=2), and 50% of chromophobe RCCs (2/4) showed radiotracer uptake.¹⁷ Another study by Tzortzakakis et al evaluated 31 solid renal lesions and showed MIBI uptake in 91.6% of oncocytomas (11/12), 100% of HOCTs (n=3), one lipid-poor AML, and surprisingly one papillary RCC (1/3).¹⁸ Additionally, in a recently published study including 30 patients with solid solitary renal lesions, all oncocytomas (n=3), one AML, and one RCC (1/26) demonstrated radiotracer uptake.¹⁹



Fig. 1. Selected axial contrast enhanced and non-contrast computed tomography (CT) and fused single-photon emission computed tomography (SPECT)-CT images demonstrate an enhancing mass with indeterminate density on non-contrast CT and increased ^{99m}Tc-sestamibi (MIBI) uptake on SPECT-CT. The biopsy was in keeping with an oncocytoma. Additionally, there is a hyperdense renal cyst posteriorly with density of more than 70 Hounsfield units (HU), most in keeping with a hemorrhagic cyst.

In our study, one chromophobe RCC had false-positive uptake and there were no false-negatives, resulting in a sensitivity of 100% and a specificity of 96% for MIBI in the detection of benign/oncocytic lesions vs. RCCs. A very recent meta-analysis showed sensitivity and specificity of 88% and 95%, respectively, for detecting benign vs. malignant renal lesions when HOCTs were characterized as benign.²¹ In our study, there were two chromophobe RCCs; one showed low-grade uptake (less than ipsilateral parenchyma), and the other showed no uptake (negative). As mentioned earlier, chromophobe RCCs do contain mitochondria similar to oncocytomas but typically the mitochondria are abnormal.¹⁶ This could account for the low-grade uptake in one case. Chromophobe RCC has a better prognosis and a lower risk of tumor progression, metastasis, and mortality compared to clear-cell and papillary RCCs.²²

On quantitative analysis, the mean and maximum relative tumor uptake were found to be higher in the oncocytic lesions than in RCCs; the difference was statistically significant, although we did not find a quantitative cutoff to categorize lesions as benign vs. malignant. This technique was found to be more cumbersome and subject to sampling error, particularly in small lesions, where delineation of the region of interest becomes more difficult. Also, physiological uptake in normal adjacent renal parenchyma and nearby

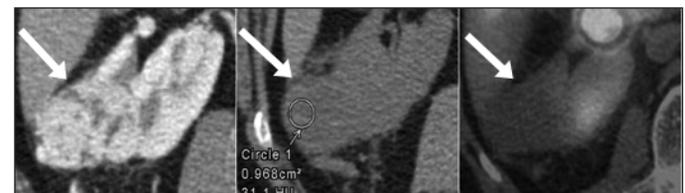


Fig. 2. Selected axial contrast enhanced and non-contrast computed tomography (CT) and fused single-photon emission computed tomography (SPECT)-CT images demonstrate an enhancing mass with indeterminate density on non-contrast CT and no ^{99m}Tc-sestamibi (MIBI) uptake on SPECT-CT. The postoperative histopathology showed a clear-cell renal cell carcinoma.

bowel loops may result in an inaccurate quantitative evaluation of uptake in the renal lesion. We found that qualitative/visual assessment of MIBI uptake within the lesion is easier and more reliable in the classification of tumors.

Although the final result of the MIBI study is a simple binary designation (positive vs. negative), attention to different patterns of uptake is essential to avoid potential pitfalls in interpretation. Background knowledge and familiarity with the cases with heterogenous/non-uniform uptake of radiotracer is essential to limit lesion misclassification. Both oncocytoma and RCC can have cystic, hemorrhagic, or necrotic changes.⁴ These fluid-filled components demonstrate no MIBI uptake due to lack of cellularity, regardless of pathology. So, MIBI uptake should be evaluated in the solid component of lesions (contrast-enhancing component on CT, or the component with a density higher than 20 HU on non-contrast CT). Additionally, blooming artifact from physiological uptake in the adjacent normal renal parenchyma should be differentiated from uptake in the lesion, which may result in a false-positive characterization. This is potentially relevant in very small endophytic lesions and can result in an indeterminate scan.

A “completely characterized renal mass” is defined as a mass with imaging features diagnostic for a specific lesion, such as macroscopic fat in an AML. It may also refer to imaging features allowing a risk assessment and subsequent management recommendation, such as the Bosniak classification for renal cysts.^{23,24} Full characterization of solid renal masses by imaging studies has always been challenging, as there are no specific diagnostic imaging features for malignant lesions. As a result, there has been a need for a molecular imaging technique that can identify low-risk or indolent renal masses and subsequently assist with risk

stratification of renal lesions.⁸ It appears that MIBI uptake is an imaging feature in low-risk renal lesions that aids in the diagnostic workup.

A large study by O’Connor et al reviewing the imaging features of renal masses on non-contrast CT, demonstrated that all lesions with a homogenous density <20 and >70 HU were benign and no further workup was needed.²⁵ This is currently an established criterion and was added to American College of Radiology (ACR) appropriateness criteria. Non-contrast CT is an important part of the renal mass imaging protocol and can demonstrate fat that could be obscured after IV contrast administration.²⁵ These features highlight the value of the non-contrast CT part of the MIBI SPECT-CT study.

In our study, all renal masses had a density of 20–70 HU, which is expected given the selection of lesions with solid components. Thus, all cases were in an indeterminate range of density for risk stratification (benign vs. malignant).

Currently, most “incompletely characterized renal masses” detected incidentally on cross-sectional imaging are referred for detailed evaluation with multiphasic CT or MRI. Presuming that MIBI becomes an established tool in the evaluation of incompletely characterized renal masses, then both the SPECT and CT components of scan have the potential to be used in the characterization and risk stratification of renal masses, as detailed in Fig. 3. As a result, the need for renal mass evaluation with multiphasic CT or costly MRI studies could potentially be curtailed.

Limitations of this study are the small sample size and limited number of less frequent pathologies, such as HOCT and chromophobe RCCs. Also, this study was neither prospective nor blinded.

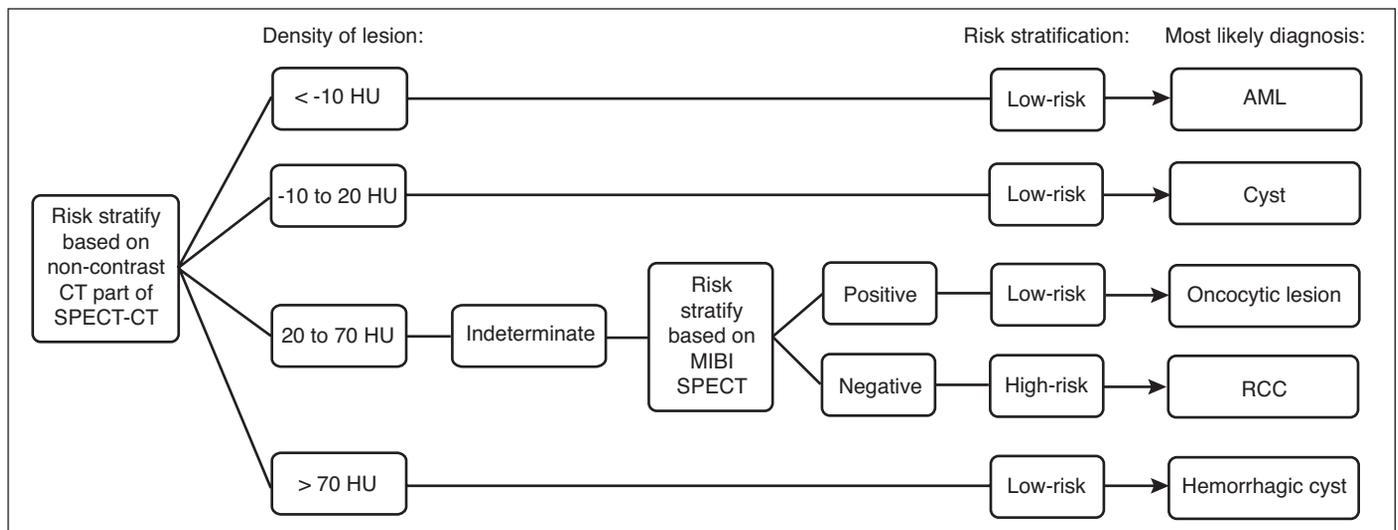


Fig. 3. Risk stratification of renal masses by ^{99m}Tc-sestamibi (MIBI) single-photon emission computed tomography-computed tomography (SPECT-CT). AML: angiomyolipoma; HU: Hounsfield units; RCC: renal cell carcinoma.

Conclusions

Our results demonstrate that MIBI SPECT-CT improves the characterization and risk stratification of renal masses with the potential to replace or reduce the need for invasive biopsy in differentiating benign from malignant renal lesions. Also, MIBI SPECT-CT scan can help to avoid unnecessary renal mass resection and increase the number of patients offered active surveillance as the primary management for their renal mass. Further studies are required to confirm that positive MIBI is a diagnostic imaging feature for low-risk renal lesions.

Competing interests: Dr. Romsa has participated in clinical trials supported by Endocyte and Progenics. Dr. Pautler has been a paid proctor in robotic surgery for Minogue Medical. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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