Original Article

The impact of sestamibi scan on clinical decision-making for renal masses: An observational single-center study

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ABSTRACT

Introduction: We aimed to determine whether sestamibi scan changes management of renal masses.
Methods: All patients undergoing sestamibi scan for renal masses between 2008 and 2022 at a single center were retrospectively reviewed. Data were gathered on patient demographics, pre- and postoperative creatinine, sestamibi scan parameters, and cross-sectional imaging characteristics. Outcomes included whether the patient underwent renal mass biopsy or surgical resection and the final pathological diagnosis if tissue was obtained from biopsy or resection. Data regarding postbiopsy as well as postoperative complications were also collected. The odds ratio (OR) for surgery or biopsy based on sestamibi result was calculated.
Results: Forty-three patients underwent sestamibi scan from 2008 to 2022, with 10 scans consistent with oncocytoma and 33 with nononcocytoma. The mean tumor size at initial presentation was 4.0 ± 1.8 cm with a median RENAL score of 7 (range: 4–11). For patients with sestamibi scans negative for oncocytoma, the OR for surgery was 12.5 (95% confidence interval [CI]: 2.1–71.2, $P = 0.005$), and the OR for biopsy was 0.04 (95% CI: 0.005–0.39, $P = 0.005$). Conversely, for patients with sestamibi scans positive for oncocytoma, the OR for surgery was 0.28 (95% CI: 0.03–2.4, $P = 0.24$) and the OR for biopsy was 24.0 (95% CI: 2.6–222.7, $P = 0.005$). Creatinine at the last follow-up was similar between patients with positive and negative sestamibi scans. No patients experienced complications from surgery or biopsy. The median follow-up was 19 months (range: 2–163).
Conclusions: A sestamibi scan positive for oncocytoma led to increased use of renal mass biopsy for confirmation. Sestamibi scans that were negative for oncocytoma were more likely to result in surgical resection without biopsy.

INTRODUCTION

The incidence of small, incidentally detected renal masses has continued to increase over the past decades. According to the 2021 American Urological Association (AUA) guidelines and the 2022 European Association of Urology (EAU) guidelines for the management of renal masses, options for differentiation of malignant and benign renal masses include cross-sectional imaging and renal mass biopsy.[1-3] The 2020 American College of Radiology (ACR) guidelines only recommend ultrasound, magnetic resonance imaging, or computed tomography (CT) with or without contrast, depending on contraindications to contrast administration. The ACR guidelines do not recommend routine biopsy.[4]

Benign tumors are reported to be postoperatively diagnosed in 15–20% of partial and radical nephrectomy specimens with a higher incidence in smaller masses.[5,6] Specifically, oncocytomas are the most common benign renal mass and often masquerade as malignant renal masses with a reported

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incidence of 10% of all renal masses <7 cm and 3%–4% of surgically resected lesions.[7-9] While cross-sectional imaging is able to diagnose cystic and solid renal masses, it is unable to reliably distinguish benign and malignant solid tumors.[10,11] Renal mass biopsy has an excellent positive predictive value (PPV) of over 90% for the diagnosis of malignancy, but the nondiagnostic rate and negative predictive value (NPV) are both relatively poor at approximately 14% and 80%, respectively.[1-3] The preoperative diagnosis of benign renal masses, especially oncocytoma, remains an area needing improvement.

Histologically, oncocytomas have been uniquely found to have high numbers of mitochondria, and 99mTc-sestamibi has a specific and high uptake in cells with high-density mitochondria.[12] Sestamibi scan has shown promising utility in identifying oncocytoma and can potentially decrease the need for invasive procedures for both diagnosis of renal masses, such as renal mass biopsy, and treatment of renal masses, such as surgery or ablation. Prior studies have shown an 86%–92% sensitivity and 67%–95% specificity of sestamibi in identifying oncocytoma.[13-16] However, the clinical utility and implications of sestamibi results have not been fully studied. Indeed, sestamibi remains an experimental imaging modality in the 2021 AUA guidelines and is not mentioned in the 2022 EAU guidelines.[1-3] From a radiology standpoint, the 2020 ACR guidelines only mention sestamibi for renal masses under "special imaging considerations" but do not include it as a recommended imaging modality.[4] We aimed to describe the clinical use and utility of sestamibi in the diagnosis and treatment of renal masses in our practice.

METHODS

All patients undergoing sestamibi scan for renal masses between 2008 and 2022 at a single center were included for retrospective review. Patients were excluded if their sestamibi scan was performed for indications other than evaluation of a renal mass. This study was performed under institutional review board approval; due to the retrospective and de-identified nature of the data, a waiver of consent was granted. Data were gathered on patient demographics, sestamibi scan parameters, and cross-sectional imaging characteristics including size, RENAL nephrometry score, contrast enhancement, and central scarring. Outcomes included whether the patient underwent renal mass biopsy or surgical resection and the final pathological diagnosis if tissue was obtained from biopsy or resection.

Patients were selected for sestamibi based on physician judgment. Patients underwent sestamibi if they had a previous history of oncocytoma or familial syndrome; had a mass that was suspicious for oncocytoma on cross-sectional imaging; or were older, unhealthy, or not a good surgical candidate. Patients were selected for renal mass biopsy based on current guidelines as well as clinical judgment based on the size of the mass (<3 cm); growth kinetics (>0.5 cm/year); age, functional status, and comorbidities of the patient; and appearance and radiology interpretation on cross-sectional imaging and sestamibi scan.[1,2]

All scans were performed according to standard protocol: 75 min after the administration of 25mCi of Tc99m sestamibi, a single-photon emission computed tomography (SPECT)/CT of the kidneys was performed. Initial clinical radiological read was performed by seven separate nuclear medicine specialists. For the purposes of this study, images were re-reviewed both subjectively and quantitatively by an experienced nuclear medicine radiologist (MT) with 20 years of experience, with a region of interest placed on the lesion and on background renal cortex and interpretation based on prior literature.[11,14] Generally, a tumor-to-background ratio of ≥60% was used to identify sestamibi-positive lesions; however, some subjective clinical judgment was used in the setting of the presence of central scarring as described in prior literature.[11,14] For all scans, the initial clinical radiology interpretation was concordant with the re-reviewed interpretation for the study. However, some lesion signal counts were slightly changed or retrospectively added for the purposes of this data collection. The radiologist was aware of patient clinical characteristics and cross-sectional imaging results during a review of the scans but was unaware of pathology results.

Patients on surveillance for renal masses followed the same surveillance protocol, regardless of sestamibi or biopsy result. Repeat cross-sectional imaging was performed at 6 months and annually thereafter with either cross-sectional imaging or renal ultrasound.

Statistical analysis to determine baseline differences between the groups was performed using Student's *t*-test and Chi-squared or Fisher's exact analysis. The sensitivity, specificity, NPV, and PPV of sestamibi scan were computed for biopsy-proven or surgery-proven cancer. The odds ratio (OR) for surgery or biopsy based on sestamibi result was calculated.

RESULTS

Demographics and diagnostic value of sestamibi

There were 2223 patients who underwent surgical intervention for a localized renal mass during the study period. Of these, we identified 43 patients who underwent sestamibi scan from 2008 to 2022. Of these, 33 sestamibi scans were negative for oncocytoma, and 10 scans were consistent with oncocytoma.

Table 1 shows demographics and radiographic findings. There were no significant differences in baseline characteristics between patients who were positive or negative for

oncocytoma on sestamibi. The median follow-up for the cohort was 19 months (range: 2–163). Radiographically, only the lesion signal counts on sestamibi scan and the ratio of signal to cortical counts on sestamibi scan were different between the groups [Table 1]. There was no difference in other radiographic findings [Table 1].

Sestamibi was found to have a 100% specificity (95% confidence interval [CI]: 87%–100%) and PPV for the diagnosis of oncocytoma in this cohort [Table 2]. Conversely, the sensitivity of sestamibi in ruling out oncocytoma was only 50% (95% CI: 23%–77%), with NPV of 79% (95% CI: 69%–86%) [Table 2], and the area under the receiver operating characteristic curve was 0.7 [Supplemental Figure 1]. When considering whether sestamibi scan was reliable in diagnosing cancer when negative for oncocytoma, the sensitivity and specificity were 100% (95% CI: 82%–100%) and 44% (95% CI: 20%–70%), respectively, with a PPV of 68% (95% CI: 58%–76%) [Table 2].

Clinical utility of sestamibi and outcomes

The median time from initial diagnosis of a renal mass on cross-sectional imaging to sestamibi scan was 2 months (range: 0–141) in patients with scans negative for oncocytoma and 8 months (range: 0–61) in patients with scans positive for oncocytoma ($P = 0.9$).

For patients with sestamibi scans negative for oncocytoma, the OR for surgery was 12.5 (95% CI: 2.1–71.2, $P = 0.005$), and the OR for biopsy was 0.04 (95% CI: 0.005–0.39, $P = 0.005$). Conversely, for patients with sestamibi scans positive for oncocytoma, the OR for surgery was 0.28 (95% CI: 0.03–2.4, $P = 0.2$) and the OR for biopsy was 24.0 (95% CI: 2.6–222.7, $P = 0.005$) [Table 1]. Creatinine at the last follow-up was similar between patients with positive and negative sestamibi scans [Table 1].

For patients with sestamibi scan negative for oncocytoma, 25 (76%) underwent surgery, and 18 (72%) had cancer on pathologic specimens. The final pathology for patients with surgically resected cancer was primarily pT1a clear cell renal cell carcinoma in 13 patients. Other pathology included papillary in one patient, chromophobe in two patients, and unclassified renal cell carcinoma in two patients. Of the remaining seven patients who underwent resection for benign masses, four were found to have oncocytoma, and three had other benign tumors. In addition to the four patients found to have oncocytoma on surgical resection, three additional patients had biopsy-proven oncocytoma for a total of seven patients with oncocytoma in the group with a negative sestamibi scan. There were no complications from biopsy or surgery in any patients. No patients had recurrence or progression of cancer on follow-up. Only one patient died of unrelated causes.

Table 1: Demographics by sestamibi scan result

Variable	Overall (*n*=43)	Sestamibi negative for oncocytoma (*n*=33)	Sestamibi positive for oncocytoma (*n*=10)	*P*
Male, *n* (%)	32 (74.4)	23 (69.7)	9 (90.0)	0.2
Mean age (years)	63	61	68	0.09
Known history of oncocytoma	4 (9.3)	3 (9.0)	1 (10)	1
Known familial syndrome	1 (2.3)	0	1 (10)	0.2
Mean creatinine at diagnosis (mg/dL)	1.0±0.28	1.0±0.28	1.1±0.25	0.4
Mean creatinine at last follow-up (mg/dL)	1.2±0.39	1.2±0.38	1.1±0.42	0.5
Mean creatinine change from diagnosis to follow-up (mg/dL)	0.15±0.28	0.19±0.28	0.01±0.15	0.09
Mean tumor size (cm)	4.0±1.8	3.9±1.8	4.7±1.9	0.2
Median RENAL score (range)	7 (4–11)	7 (4–11)	8.5 (5–10)	0.9
Background cortex signal counts on sestamibi	1829	2023	1344	0.5
Lesion signal counts on sestamibi	694	392	1694	<0.001
Ratio of signal to cortex on sestamibi	0.51	0.28	1.25	<0.001
Growth rate (cm/year)	0.24	0.31	0.13	0.4
Tumor characteristics on CT, *n* (%)				
Heterogeneity	25 (81)	20/24 (83)	5/7 (71)	0.6
Contrast enhancement	34/34 (100)	26/26 (100)	8/8 (100)	1
Central scarring	4/29 (14)	3/23 (69)	1/6 (17)	1
Smooth margins	22/30 (73)	18/23 (78)	4/7 (73)	0.3
Biopsy performed, *n* (%)	18 (42)	8 (24)	8 (80)	0.02
Surgery performed, *n* (%)	27 (63)	25 (75)	2 (20)	0.002

CT = Computed tomography

Table 2: Diagnostic outcomes of sestamibi scan

Outcome	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Sestamibi detection of oncocytoma	50	100	100	79
Compared to biopsy pathology	58	100	100	38
Compared to surgery pathology	33	100	100	84
Sestamibi detection of cancer	100	44	68	100
Compared to biopsy pathology	100	57	14	100
Compared to surgery pathology	100	25	76	100

Of the 10 patients with sestamibi scan positive for oncocytoma, 7 were shown to have biopsy- or pathology-proven oncocytoma. The remaining three patients underwent surveillance without pathologic confirmation and did not have evidence of growth requiring intervention.

Finally, of the 14 patients who underwent biopsy but did not undergo surgery, 7 (50%) had a sestamibi scan suggestive of oncocytoma, and 8 (57%) had a biopsy showing oncocytoma. Of the eight with biopsy-proven oncocytoma, only five had a sestamibi scan suggestive of oncocytoma. The median follow-up for the 14 patients who underwent biopsy but did not undergo surgery was 46 months (range: 2–167 months). Growth kinetics were available for 10 patients, with an average growth of 0.9 mm/year (range: –11–8 mm/year). No patient in this group has undergone surgery at the time of this manuscript, and no patient has developed concern for metastatic disease. One patient in this cohort with sestamibi negative for oncocytoma but with biopsy showing oncocytoma subsequently developed a new renal mass and remains on surveillance. The biopsy-proven oncocytoma has not changed in size.

DISCUSSION

In this retrospective study, we evaluated the utility of sestamibi scan in the evaluation and treatment of renal masses in clinical practice. The diagnostic value of sestamibi was found to be like prior reports in the literature, with high specificity and PPV.[13,16] A sestamibi scan negative for oncocytoma was only somewhat useful in predicting cancer on final biopsy or resection pathology. In our series, sestamibi was better at predicting benign renal masses than other characteristics on cross-sectional imaging such as contrast enhancement, growth rate, or central scarring. Overall, in our study, a positive sestamibi scan reliably predicted masses that could be safely managed with surveillance. This is similar to other studies in the literature, which have previously shown that sestamibi accurately characterizes benign or low-grade renal lesions and that masses identified as benign on sestamibi can be safely managed with surveillance.[13,14,17,18]

In this study, patients with sestamibi scan positive for oncocytoma were all found to either have biopsy- or surgically proven oncocytoma or proceeded with surveillance with no growth of the mass requiring intervention. However, there were seven patients with false-negative sestamibi scan, with the final pathology showing oncocytoma. On re-review of these seven scans by an experienced nuclear MT, only two were found to have an explainable error; both masses, while hot, were close to a larger cyst that was cold on sestamibi, which attenuated the positive signal. This is a common error that has been addressed in the literature: masses should be considered positive if any portion of the tumor is positive.[11] For the purposes of this retrospective study, we have reported the original read in this manuscript. The other scans had no clear radiographic or clinical reason for the false-negative read.

In our practice, a sestamibi scan that was positive for oncocytoma led to increased use of renal mass biopsy for confirmation. Sestamibi scans that were negative for oncocytoma were more likely to result in a decision for surgical resection without biopsy. There were no adverse outcomes from any management decision in our small population. These results suggest that the combination of sestamibi scan and renal mass biopsy may help better inform treatment decisions for small renal masses. While renal mass biopsy has been shown to have good PPV in predicting cancer, its weakness is its nondiagnostic rate and unreliable NPV; renal mass biopsy does not reliably diagnose benign masses.[1,2] On the contrary, sestamibi scan in our series and in others has shown to reliably predict benign oncocytomas, when positive.[13,14,16] Therefore, the combination of renal mass biopsy, which accurately diagnoses cancer, and sestamibi, which accurately diagnoses benign oncocytomas, is a promising method of identifying masses safe for surveillance. These findings add to a cost-effectiveness analysis performed by Su *et al*. in 2021, where a predictive model comparing sestamibi, renal mass biopsy, and surgery showed that sestamibi with confirmatory biopsy both avoided invasive treatment for small renal masses while minimizing missed renal malignancy.[18] In this study, the combination of sestamibi with confirmatory biopsy had the greatest cost-effectiveness, with an incremental cost-effectiveness ratio of $18,821/quality-adjusted life years.[18] With the high specificity of sestamibi scan for benign renal tumors and the high specificity of renal mass biopsy for renal malignancy, the combination of these two diagnostic tests shows promise in maximizing the cost-efficacy of the evaluation and treatment of small renal masses.

Limitations

This study is limited by its retrospective nature and small study cohort, which introduces selection bias. Due to the retrospective nature of the data, not all masses had pathology-proven results, limiting the evaluation of the true sensitivity, specificity, PPV, and NPV of sestamibi scan. In this cohort, there were no missed renal malignancies in the group with sestamibi scans positive for oncocytoma. However, in the literature, sestamibi has been previously compared to pathologic results, and the false-positive rate of sestamibi scans is low at approximately 4%. In the setting of false-positive sestamibi results, the masses are often chromophobe renal cell carcinoma, a more indolent form that is more amenable to surveillance.[16] Additionally, this study evaluated patients treated at a high-volume center with ready access to radiologists specialized in nuclear medicine. Although the availability of sestamibi scan and SPECT/CT is reasonably widespread due to its use in cardiac

and parathyroid disease, its use for the evaluation of renal masses can be more specialized. Therefore, the experience we describe in this article may not be generalizable to all practices.

CONCLUSIONS

This study suggests that sestamibi scan affects clinical decision-making in the treatment of renal masses. While our study retrospectively evaluates past practice patterns, a prospective evaluation of alterations in practice patterns regarding sestamibi scan in the evaluation of small renal masses is warranted. Additional studies of the clinical utility of sestamibi scan will allow evidence-based recommendations on its use in the existing guidelines for the evaluation and treatment of renal masses.

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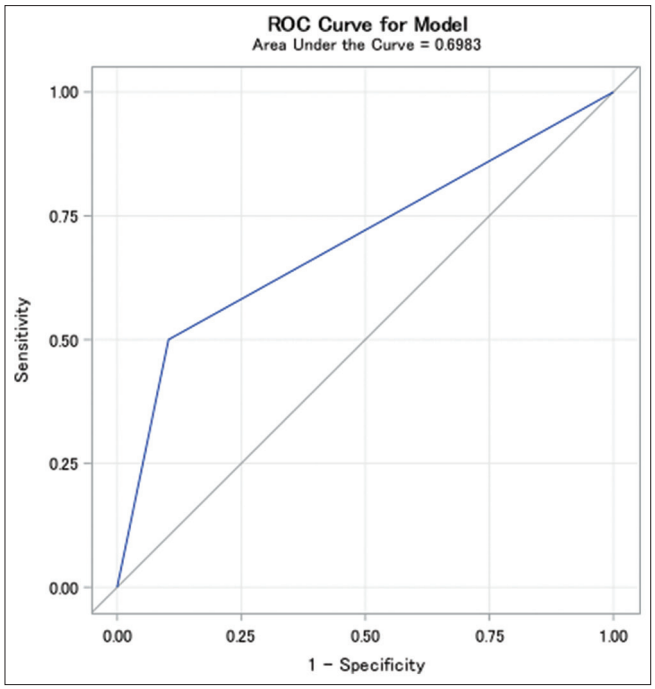

Supplemental Figure 1: Receiver operating characteristic curve for sestamibi scan predicting oncocytoma. Curve is based on whether sestamibi scan was positive in biopsy-proven oncocytoma. Area under the curve was 0.7