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PICTORIAL REVIEW

^{99m}Tc -sestamibi SPECT/CT for the characterization of renal masses: a pictorial guide

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ABSTRACT

In parallel to the increased utilization of cross-sectional imaging, the incidence of small renal masses has steadily risen in recent years. At the present time, anatomical imaging techniques are limited in their ability to differentiate benign from malignant renal masses. Moreover, renal mass biopsy has a high non-diagnostic rate, poor negative-predictive ability, and carries potential risks as well as substantial costs. As a result, benign renal masses are often unnecessarily resected for the false presumption of cancer. ^{99m}Tc -sestamibi single photon emission computed tomography/computed tomography (SPECT/CT) is a molecular imaging test that allows for the differentiation of benign renal oncocytomas and hybrid oncocytoma/chromophobe tumours apart from malignant renal cell carcinomas on the basis of differences in mitochondrial content as well as multidrug resistant pump expression. Herein, we review the principles of ^{99m}Tc -sestamibi SPECT/CT administration and image interpretation for the purpose of renal mass characterization.

INTRODUCTION

Due to the increasing use of abdominal cross-sectional imaging for a variety of indications, the incidence of renal masses has been steadily rising in recent decades.¹ However, currently utilized imaging techniques are often unable to distinguish between renal cell carcinoma (RCC) and benign solid renal masses such as oncocytomas, fat-poor angiomyolipomas, and metanephric adenomas.² The most common benign renal mass is the oncocytoma, comprising over 10% of all renal masses.³ Because of the inability to reliably identify RCC on the basis of cross-sectional imaging, an estimated 5,600 benign lesions are unnecessarily excised each year in the USA alone.⁴

One method to distinguish benign from malignant renal masses is percutaneous biopsy. While this method has improved in accuracy and safety in recent years, limitations remain. Renal biopsy has a non-diagnostic rate ranging from 8 to 14%.^{5–7} In addition, biopsy carries a poor negative-predictive value, making it difficult for clinicians and

patients alike to have the confidence to forego surgery following a negative biopsy. Furthermore, renal biopsy is less effective when assessing smaller renal masses.⁷ This limitation presents a dilemma because smaller renal tumours are the most likely to be a benign histology.⁴ Furthermore, the invasive nature of renal biopsy presents risk of haematoma, pain, and haematuria.⁵ While renal biopsy can be a useful risk-stratification tool, its diagnostic limitations and potential risks limit its ability to effectively diagnose benign renal masses.

^{99m}Tc -sestamibi single photon emission computed tomography/computed tomography (SPECT/CT) has been proposed as an alternative to renal mass biopsy for distinguishing benign renal oncocytomas apart from RCC. ^{99m}Tc -sestamibi is a lipophilic cation that accumulates in cells with a high content of mitochondria. Because renal oncocytomas are composed of oncocytic cells with numerous densely packed mitochondria,^{8,9} these tumours avidly take up the ^{99m}Tc -sestamibi radiotracer. Likewise,

Figure 1. (a) Axial venous/nephrographic phase contrast-enhanced CT, (b) axial ^{99m}Tc -sestamibi SPECT, and (c) axial ^{99m}Tc -sestamibi SPECT/CT fusion images of a normal kidney. Note uniformly high radiotracer uptake throughout the renal parenchyma. SPECT, single photon emission CT.

RCC tumours do not concentrate the ^{99m}Tc -sestamibi radiotracer for two principle reasons. First, most RCCs are relatively devoid of mitochondria.^{8,10} A notable example is the clear cell subtype of RCC (ccRCC) which has optically clear cytoplasm owing to a paucity of mitochondria.¹¹ Second, many RCCs express multi-drug resistant pumps that actively shuttle the ^{99m}Tc -sestamibi out of the cells, leading to a low concentration of radiotracer within malignant lesions.^{12–14} As a result of these differences, oncocytomas take up significant amounts of radiotracer and appear “hot” on ^{99m}Tc -sestamibi SPECT, whereas RCC tumours demonstrate low radiotracer uptake and appear “cold” on the scan.

After a successful pilot study of ^{99m}Tc -sestamibi SPECT/CT imaging of renal tumours by investigators at Johns Hopkins,¹⁵ this imaging test was more extensively evaluated in a prospective study of 50 solid clinical T_1 renal masses imaged prior to surgical resection.¹⁶ In this study, ^{99m}Tc -sestamibi SPECT/CT had a sensitivity of 87.5% and specificity of 95.2% for diagnosing renal oncocytomas and hybrid oncocytic/chromophobe tumours (HOCTs), a benign renal tumour that histologically has features of oncocytomas and chromophobe RCC.¹⁷ Two falsely-positive tumours were noted and both were of the eosinophilic variant

of chromophobe RCC, a tumour subtype that typically behaves in an indolent fashion and can likely be safely observed.¹⁸ A secondary analysis of this study illustrated that incorporating ^{99m}Tc -sestamibi SPECT/CT into the pre-operative work-up of renal lesions significantly augmented confidence in characterizing renal masses as benign or malignant.¹⁹

Following these reports, investigators at the Karolinska University Hospital in Stockholm, Sweden found similar results in a study of 27 patients with 31 tumours imaged with ^{99m}Tc -sestamibi SPECT/CT prior to either surgery or biopsy. In this study, 11/12 (91.6%) oncocytomas and 3/3 (100%) HOCTs were identified with this imaging test, with only two false positives (one papillary RCC that was described as having “slight” uptake and one angiomyolipoma).²⁰

Given the ability of ^{99m}Tc -sestamibi SPECT/CT to accurately differentiate renal oncocytomas from malignant tumours, clinicians at the Johns Hopkins Hospital now routinely use this test in clinical practice to aid in the risk stratification of patients presenting with an indeterminate renal mass. Additionally, a number of other centres have either begun utilizing or have

Figure 2. (a) Sagittal arterial/corticomedullary phase contrast-enhanced CT, (b) sagittal ^{99m}Tc -sestamibi SPECT, and (c) sagittal ^{99m}Tc -sestamibi SPECT/CT fusion images of a predominantly exophytic photopenic (*i.e.* “cold”) tumour (white and black arrow heads) with uptake markedly less than the adjacent normal renal parenchyma. This lesion was resected and was found to be a clear cell RCC. RCC, renal cell carcinoma; SPECT, single photon emission CT.

Figure 3. (a) Axial late arterial/corticomedullary phase contrast-enhanced CT, (b) axial ^{99m}Tc -sestamibi SPECT, and (c) axial ^{99m}Tc -sestamibi SPECT/CT fusion images of an intensely “hot” tumour (white and black arrow heads) with uniformly high radiotracer uptake that is visually above the level of uptake of the surrounding renal parenchyma. This lesion was resected and was found on surgical pathology to be an oncocytoma. This is the most characteristic appearance on ^{99m}Tc -sestamibi SPECT/CT for an oncocytoma with a large, avidly-enhancing component. SPECT, single photon emission CT.

expressed interest in adopting this imaging modality (personal communications to the authors). Because the literature with renal ^{99m}Tc -sestamibi SPECT/CT remains limited to small studies with a total of less than 100 patients, a guide to the accurate interpretation of these scans based on pathologic correlation is needed in order to facilitate clinical implementation of this test. It is for this reason that we undertook the compilation of this pictorial essay.

Herein, we summarize the keys to administering and interpreting ^{99m}Tc -sestamibi SPECT/CT for the purpose of characterizing indeterminate renal masses.

PROTOCOL AND IMAGE ANALYSIS

Indications for ^{99m}Tc -sestamibi SPECT/CT imaging include the evaluation of indeterminate solid renal masses greater than 1.5 cm. Assessment is occasionally difficult with tumours 1.5–2 cm in size, especially for endophytic masses, given the

intrinsic spatial resolution images of SPECT and normal high background renal uptake.

Preceding the scan, patients are kept *nil per os* for 4–6 h in an effort to limit the amount of radiotracer that has been excreted through the hepatobiliary pathway. In clinical practice, we have seen varying success with this approach and the amount of uptake in the bowel can potentially interfere with the assessment of very anterior renal masses. 925 MBq (25 mCi) of ^{99m}Tc -sestamibi is administered intravenously followed by a 75-min break allowing for radiotracer dissemination and uptake. The SPECT/CT acquisition is then performed as previously described by Rowe et al 2015.¹⁵

Regarding image analysis, this can be practically carried out with any software package able to handle nuclear medicine fusion data [the authors have used both a Mirada Medical Workstation

Figure 4. (a) Axial arterial/corticomedullary phase contrast-enhanced CT, (b) axial ^{99m}Tc -sestamibi SPECT, and (c) axial ^{99m}Tc -sestamibi SPECT/CT fusion images demonstrating a tumour [white arrow head in (a)] with heterogeneous uptake. Portions of the tumour have radiotracer uptake similar to renal parenchyma [white arrows in (b, c)] and other portions are distinctly low in uptake [arrows in (b, c)]. This is another uptake pattern that suggests a benign or indolent lesion, and this tumour was found to be an HOCT upon resection. HOCT, hybrid oncocytic/chromophobe tumour; SPECT, single photon emission CT.

Figure 5. (a) Coronal venous/nephrographic phase contrast-enhanced CT, (b) coronal ^{99m}Tc -sestamibi SPECT, and (c) coronal ^{99m}Tc -sestamibi SPECT/CT fusion images of a large renal mass (white and black arrow heads) with a stellate central scar. This pathology proven oncocytoma demonstrates the typical pattern seen in the context of the presence of a central scar, with predominantly peripheral radiotracer uptake and relative photopenia in the scar. SPECT, single photon emission CT.

(Oxford, UK) and a HERMES Medical Solutions Hybrid Recon Oncology Workstation (Stockholm, Sweden)]. We recommend a qualitative approach for the vast majority of studies, and the principles of image interpretation are discussed below. However, in select cases, quantitative measurements may be of diagnostic assistance. To calculate a relative tumour uptake value, locate

the areas of highest tumour uptake within the renal mass as well as within the ipsilateral normal renal parenchyma. Place spherical volumes at both of these locations to determine maximum uptake within each sphere, and the uptake value is calculated as maximum uptake of tumour divided by maximum uptake of normal parenchyma. Higher uptake values are more suggestive

Figure 6. (a) Axial arterial/corticomedullary phase contrast-enhanced CT, (b) axial ^{99m}Tc -sestamibi SPECT, and (c) axial ^{99m}Tc -sestamibi SPECT/CT fusion images of another pathology-proven oncocytoma (white and black arrow heads). Note that this oncocytoma demonstrates radiotracer uptake that is visually slightly less than the adjacent normal kidney, however there is still uptake distinctly within the mass. Compare to Figure 2, where the clear cell RCC had no discernable uptake that could be considered to be within the mass. SPECT, single photon emission CT.

Figure 7. (a) Axial venous/nephrographic phase T_1 weighted fat saturation contrast-enhanced MRI, (b) axial ^{99m}Tc -sestamibi SPECT, and (c) axial ^{99m}Tc -sestamibi SPECT/CT fusion images showing another uptake pattern that can be seen with this imaging modality. The partially endophytic/partially exophytic mass [white arrow head in (a)] demonstrates radiotracer uptake in the endophytic portion of the lesion while the exophytic portion is photopenic. This mass was found to be an oncocytoma following resection. SPECT, single photon emission CT.

of oncocytoma/HOCTs, although there is no strict cut-off value that we have found to be generally applicable.

IMAGE INTERPRETATION

The basis of the ^{99m}Tc-sestamibi scan is that oncocytomas and HOCTs have high radiotracer uptake, whereas RCCs have low uptake. Normal renal parenchyma also demonstrates high avidity for ^{99m}Tc-sestamibi (Figure 1), and thus the most common pattern seen with oncocytomas is uptake similar to surrounding parenchyma. In contrast, RCCs typically have lower uptake relative to surrounding parenchyma and thus appear as photopenic “punched out” lesions or defects on the SPECT image (Figure 2). Tests are considered positive for an oncocytoma or HOCT when the tumour has high radiotracer uptake, and negative when the mass has low uptake more suggestive of RCC. While this description implies a relatively simple binary read-out, the relatively high uptake of oncocytomas and HOCTs can manifest in one of a few stereotypic patterns including (1) uniformly high tumour uptake (Figure 3), (2) variable tumour uptake with areas of high uptake (Figure 4), (3) peripheral uptake with central photopenia (Figure 5), (4) definite tumoral uptake but at a level below surrounding renal parenchyma (Figure 6), and (5) uptake that is predominantly in the endophytic portion of a partially endophytic/partially exophytic lesion (Figure 7). The uniting theme among these patterns is that if any portion of the tumour

has a moderate to high level of radiotracer uptake, the lesion is likely an oncocytoma or HOCT. Likewise, tumours should only be considered definitively malignant if the entirety of the mass is photopenic. The following examples demonstrate what normal anatomy, malignant lesions, cysts, and various oncocytomas look like with CT, SPECT, and SPECT/CT fusion images.

CONCLUSION

The aim of this guide is to allow for proper implementation of ^{99m}Tc-sestamibi SPECT/CT of renal tumours. While these images can be read with relative facility, understanding the various presentations of oncocytomas/HOCTs vs malignant tumours will allow for better accuracy and reliability in interpreting scans and will reduce any potential learning curve. Adding the ^{99m}Tc-sestamibi scan to the workup of the renal mass improves ability to characterize renal lesions and will hopefully decrease the number of benign renal masses excised in the future.

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