Editorial Commentary

^{99m}Tc-sestamibi SPECT/CT—the jury is still out!

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Detection of incidental renal masses has risen over recent decades with the increasing use of cross-sectional imaging in all areas of medicine. Our current challenge as urologists is in risk-stratifying these tumours, so that patients with aggressive disease are treated early with the aim of cure, while those with clinically insignificant disease can avoid invasive tests and treatments and the associated morbidity. This is increasingly relevant as alternative treatments to surgery with varied risk-benefit profiles emerge.

^{99m}Tc-sestamibi single photon emission computed tomography/computed tomography (SPECT/CT) has been presented as a potential solution, with the lipophilic, cationic radiopharmaceutical ^{99m}Tc-sestamibi readily accumulating in cells with high concentrations of mitochondria (1,2), such as renal oncocytomas the most common type of benign renal neoplasm. Further, renal cell carcinomas (RCCs) are relatively deplete of mitochondria and have membrane multi-drug resistance pumps that export ^{99m}Tc-sestamibi from cells (3). Such differences underpin the mechanism by which oncocytomas appear avid and RCCs photopenic on ^{99m}Tc-sestamibi SPECT/CT.

Schober *et al.* are early adopters of ^{99m}Tc-sestamibi SPECT/CT, and we commend them for publishing their real-world experience of using ^{99m}Tc-sestamibi SPECT/CT to inform decision making in select cases (4). ^{99m}Tc-sestamibi SPECT/CT has shown high diagnostic accuracy in several single-centre series for the detection of renal oncocytomas and low grade oncocytic tumours (LOT) (5-10). A recent systematic review and meta-analysis showed 89% sensitivity and specificity for the detection of oncocytomas and LOTs versus other tumour types against a reference standard of histopathology (11).

Schober *et al.* presented retrospective data on 71 patients with 88 renal masses who underwent ^{99m}Tc-sestamibi SPECT/CT over a two-year period in their institution. Patients included had cT1a-cT2a disease, though selection criteria and rationale for ^{99m}Tc-sestamibi SPECT/CT was not reported. Eleven patients (15%) had masses that were exclusively ^{99m}Tc-sestamibi SPECT/CT avid, suggestive of oncocytoma/LOT, of whom 10 (91%) were managed with active surveillance and 1 (9%) with surgery (pathology confirmed oncocytoma). One or more photopenic mass, suggestive of RCC, was present in 60 patients of whom 39 (65%) had surgery, 19 (32%) active surveillance, and 2 (3%) cryoablation. Schober *et al.* therefore demonstrated that patients and clinicians were prepared to use the result of ^{99m}Tc-sestamibi SPECT/CT to guide management decisions for renal tumours.

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Further, Schober *et al.* presented concordance rates between ^{99m}Tc-sestamibi SPECT/CT findings and tumour histotype for the subset of patients who underwent histopathological confirmation of their tumour. Findings were presented using the nomenclature that evolved in this field, since the first published series of ^{99m}Tc-sestamibi SPECT/CT in renal tumours (5), that defined a ^{99m}Tc-sestamibi SPECT/CT avid or "hot" scan suggestive of oncocytoma/LOT as positive, and a photopenic or "cold" scan suggestive of RCC as negative.

In the series, 52 out of 88 masses (59%) had histological confirmation of tumour type from biopsy or surgical resection. Overall, 42/52 were concordant with histology (81%). The main concern presented by authors was that 9/45 tumours appearing 'cold' on ^{99m}Tc-sestamibi SPECT/CT, consistent with RCC, were found to be oncocytoma on histology i.e., false positive for RCC. One case had appeared 'hot' on ^{99m}Tc-sestamibi SPECT/CT and interpreted as an oncocytoma but was found to be a clear cell RCC (ccRCC) on biopsy. Diagnostic accuracy seemed to be particularly poor for patients who underwent biopsy confirmation of their tumour type with 5/8 (63%) of diagnostic samples being discordant, 4/5 being false positives. Schober *et al.* referred to their institutional benign histology rate following surgical resection of 14% and concluded that ^{99m}Tc-sestamibi SPECT/CT did not help patients with benign histology avoid surgery.

Firstly, it is important to consider Schober *et al.*'s findings in the context of being a retrospective case series of non-consecutive patients, exposing the findings to selection bias. The reasons for proceeding with biopsy or surgery in the context of a 'Hot' or 'Cold' ^{99m}Tc-sestamibi SPECT/CT scan were not outlined in the manuscript, and the authors acknowledge that the reduced specificity in their study of 80% compared to other reports using STARD-methodology (12) such as that from Viswambaram *et al.* may lie in patient selection and case mix (8).

The diagnostic accuracy of ^{99m}Tc-sestamibi SPECT/CT may indeed be lower in clinical practice than the original studies suggest. However, we caution against drawing this conclusion from retrospective data, and more studies in this space are needed and planned. The MULTI-MIBI study is currently recruiting with the aim to assess feasibility of a large, multi-centre study of consecutive patients planned to undergo surgery or biopsy, with images acquired and reported by local clinicians, at a range of institutions (13). Central imaging (and pathology) review will also enable assessment of inter-rater and intra-rater agreement on ^{99m}Tc-sestamibi SPECT/CT and standardised histopathology outcomes, which can be nuanced. This work will aim to provide data reflective of how the scan is likely to be delivered in practice, and the training needs for effective implementation.

From our own experience with interpreting ^{99m}Tc-sestamibi SPECT/CT we have learned that the necrotic tissue that forms the stellate scar seen in some renal tumours does not seem to take up ^{99m}Tc-sestamibi radiotracer, and it can therefore be mistaken for a 'cold' lesion.

The prevention of overtreatment of benign renal tumours remains a clinical challenge. Currently, renal tumour biopsy is the only diagnostic tool that can differentiate benign tumours from RCC that is used in clinical practice, yet itself remains underutilised. In the absence of reliable novel alternatives, ^{99m}Tc-sestamibi SPECT/CT holds promise, though we agree with Schober *et al.* that further work is needed to define its utility in real world clinical practice. Ongoing and future research will provide clarity on whether there is a role for ^{99m}Tc-sestamibi SPECT/CT in the diagnostic pathway of renal masses, either as a replacement test, triage test, add-on test, or indeed, at all.

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