Manuscript

Case presentations:

Our first patient (P1) is a 69-year-old male with a 4 year history of a progressively enlarging left renal upper pole mass; contrast-enhanced CT demonstrated a 3.4cm lesion in 2017, increasing in size on sequential cross sectional imaging to 6.0cm as of March 2021. A biopsy was performed in 2020 when the tumour measured 5.6cm, and demonstrated cells in a solid nest and trabeculae pattern, with eosinophilic cytoplasm, hyperchromatic nuclei and inconspicuous nucleoli. Immunohistochemistry was cd117, e-cadherin (incomplete) and CD10 positive, CK7 & vimentin negative, consistent with a diagnosis of oncocytoma[1]. ^{99m}Tc-sestamibi SPECT-CT showed increased uptake within the tumour, consistent with the histological diagnosis of oncocytoma (Figure 1). As the mass continues to enlarge, and the patient remains keen for non-surgical active treatment, cryotherapy is being considered as an alternative treatment option.

The second patient (P2) is a 59-year-old male with a presentation of a 5.2cm right renal mass demonstrated on CT. Following clinic consultation, the patient declined a biopsy and elected for surgical excision of the lesion. ^{99m}Tc-sestamibi SPECT-CT showed absence of uptake in the renal mass (Figure 2). Following this, a robot assisted radical nephrectomy was performed, and recovery was uneventful. Surgical histology confirmed the tumour to be an eosinophilic clear cell renal cell carcinoma.

Both patients were consented for inclusion in our pilot trial of ^{99m}Tc-sestamibi SPECT-CT for differentiating between malignant renal cell cancer (RCC) and benign oncocytoma.

^{99m}Tc-sestamibi SPECT-CT:

Historically up to 30% of patients undergoing surgery for small renal masses have been found to have benign lesions, the most common being oncocytoma[2,3]. Surgical intervention for suspected RCC, involving either radical or partial nephrectomy, is associated with a 5% risk of ≥ Clavien 3 complication and a 0.5% thirty-day mortality rate[4,5]. An analysis of the British Association of Urological Surgeons (BAUS) nephrectomy dataset from 2013 – 2016, showed that 1202 patients had had surgery for an oncocytoma, of which 20.2% had in-hospital complications. Of these 48% were Clavien–Dindo grade ≥III (4% of the total cohort), including five deaths within 60 days of surgery[6].

Oncocytoma and RCC both present in a similar demographic (males > female, in the 6th-7th decade) and with similar radiological features. The 'central stellate scar' sign on CT said to be characteristic of oncocytomas is only present in around a third of cases[6] and can also be seen in renal cell carcinoma and is thus unreliable. Although renal tumour biopsy (RTB) is becoming more acceptable, uptake and access is not uniform across the NHS due to persisting clinician concerns regarding biopsy track seeding, bleeding and non-diagnostic rates[8]. Many patients therefore only discover their tumour is benign following surgery.

A non-invasive diagnostic test which could reliably differentiate between RCC and oncocytoma with a high degree of specificity would be an important tool to help patients avoid potentially unnecessary surgery and the associated risks.

Recent work by Gorin & colleagues at Johns Hopkins [9] demonstrates the potential of a nuclear medicine ^{99m}technetium sestamibi single photon emission computed tomography –computed tomography (^{99m}Tc-sestamibi SPECT-CT) scan (used traditionally in imaging parathyroid adenoma and the heart) in differentiating between renal oncocytoma and RCC. Oncocytomas are composed of cells which are mitochondria dense and therefore take up ^{99m}Tc-sestamibi after intravenous injection. In contrast, malignant renal masses have relatively reduced density of mitochondria compared to normal renal tissue. RCC is also known to express multidrug resistance (MDR) transmembrane pumps which are thought to promote excretion of ^{99m}Tc-sestamibi from the cytoplasm. These two factors lead to the relative dearth of ^{99m}Tc-sestamibi uptake in RCC compared to surrounding healthy tissue [9].

A recent systematic review included 4 articles with a total of 117 lesions[10]. The pooled and weighted sensitivity and specificity values of ^{99m}Tc-sestamibi SPECT-CT for distinguishing renal oncocytoma versus other renal lesions were 92% (95% CI 72-98%) and 88% (95% CI 79-94%), respectively, and 89% and 67%, respectively, for renal oncocytoma versus ChrRCC[10]. High diagnostic accuracy of ^{99m}Tc-sestamibi SPECT-CT could see it adopted as an add-on or replacement test to RTB. In a recent systematic review of 9 studies including 205 RTBs the positive predictive value of RTB for oncocytoma was reported to be 67% [11].

We present the first two cases using ^{99m}Tc-sestamibi SPECT-CT in the imaging of renal tumours in our pilot single centre study (ISRCTN23705289). To our knowledge this is the first published description of this modality to evaluate renal masses in the NHS setting.

Methods:

The pilot study has HRA/NHS REC approval (Ref 20/YH/0279), Administration of radioactive substances advisory committee (ARSAC) approval (Ref AA-466) and is registered on the ISRCTN registry (ISRCTN23705289).

All participants provided written informed consent. As it was not our usual practice to require patients to fast when ^{99m}Tc-sestamibi scans are performed for other indications, we removed the fasting element described in previous studies. 900 MBq of ^{99m}Tc-sestamibi was delivered intravenously 75 minutes prior to scanning. A SPECT-CT of the abdomen and pelvis with the heart positioned at the top of the field of view was performed on a BOLD camera (Siemens, Erlangen, Germany). Acquisition parameters are detailed in Supplementary Table 1. Participant experience feedback was assessed at 24 hours and 2 weeks following the scan via telephone. Reconstructed SPECT-CT images were visualised using Hermes software (Hermes Medical Solutions, Stockholm, Sweden). The regions of interest (ROI) were delineated by hand. ROIs were drawn within the tumour and in normal cortex of the kidney, and the maximum number of counts from within each ROI were used to calculate the tumour to background ratio.

Figure 1: Patient 1 (P1). Coronal fused ^{99m}Tc-sestamibi SPECT-CT (1A) demonstrates an intensely ^{99m}Tc-stestamibi avid area, corresponding to the left upper pole renal mass seen on coronal low dose CT (1B). This lesion was shown to be oncocytoma on hematoxylin and eosin (H&E) histology from previous renal mass biopsy (1C).

Figure 2: Patient 2 (P2). Coronal fused ^{99m}Tc-sestamibi SPECT-CT shows a photopenic region in the right kidney (2A), corresponding to the right interpolar renal mass seen on coronal low dose CT (2B). Subsequent surgical histology revealed an eosinophilic clear cell RCC on H&E image (2C). ^{99m}Tc-sestamibi is also excreted in the small bowel, as seen in image 2B.

Results:

^{99m}Tc-sestamibi tracer uptake in patient P1 (Figure 1A) with previously biopsy confirmed oncocytoma was greater than in the cortex of the kidney, with a tumour to background ratio of 1.6. In contrast, patient P2 (Figure 1D) demonstrated a right interpolar renal mass photopenic relative to normal kidney; tumour to background ratio 0.14. These findings are consistent with published thresholds of relative radiotracer uptake ratio of >0.6 (for oncocytoma) and ≤0.6 (RCC) from Gorin et al [9].

Patient experience feedback has been excellent with no concerns.

Discussion:

We report on our initial experience of the first 2 cases of using ^{99m}Tc-sestamibi SPECT-CT imaging to characterise renal masses in the UK.

Patient demographics, clinical findings and traditional CT/MRI radiographic features are largely similar between RCC and oncocytoma. Pre-surgical biopsy remains a useful tool pre-operatively, however uptake is low, in part due to inherent clinician bias and patient concerns. A large heterogenous mass poses a diagnostic challenge, in differentiating malignant RCC, from oncocytomas, hybrid oncocytoma/chromophobe tumours, and chromophobe tumours with oncocytic or eosionophilic elements. The main limitation of 99mTc-sestamibi SPECT-CT is that it is potentially less able to differentiate oncocytoma from hybrid oncocytic-chromobobe tumours (HOCT) and chromophobe RCC. In the previously mentioned systematic review, the specificity of 99mTc-sestamibi SPECT-CT for detecting tumours on the oncocytoma-chromophobe RCC spectrum was 96% (95% CI 84–99%)[10]. A 99mTc-sestamibi SPECT-CT demonstrating avid uptake therefore indicates a renal mass which could be considered as at best oncocytoma, and at worst an indolent form of RCC, which may also benefit from active monitoring, especially when considering personalised management options in the context of tumour size, patient wishes, and specific co-morbidities.

To conclude, initial experience indicates that this non-invasive procedure (with a camera time of 35 minutes and total scan time of around 2 hours) is acceptable to patients and may have less impact on NHS resources compared to either diagnostic biopsy in the interventional radiology department or surgery for kidney tumours subsequently found to be oncocytomas. We note that Su and colleagues demonstrated ^{99m}Tc-sestamibi to represent a cost effective approach in the monitoring of small renal masses[12] , though further work is needed to characterise the full financial impact of either strategy within the NHS. The role of 99mTc-sestamibi SPECT-CT in the diagnostic pathway for renal masses, either as an add-on, alternative or triage test for confirmatory biopsy remains to be established. Removal of the fasting requirement described in the other studies has the potential to minimise inconvenience to patients, and has not impacted on the uptake and interpretation of ^{99m}Tc-sestamibi scans thus far in our limited experience. However, further validation is planned with blood glucose levels assessed prior to scanning in future studies. The pilot study is recruiting well and will provide insights into whether the use of ^{99m}Tc-sestamibi is feasible and acceptable in the NHS setting. Since

^{99m}Tc-sestamibi SPECT-CT is routinely used in the NHS already for investigation of other pathologies, and nuclear medicine facilities are widely available and accessible, there is potential for ease of scaling up to improve the care of patients with renal masses across the United Kingdom.

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Declaration of conflicts of interest:

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Supplementary table 1: SPECT parameters used for image acquisition in figures 1A and 2A

Matrix: 128x 128	Degrees of Rotation: 180
Zoom: 1	Detector Configuration: 180
No of views: 60	Orbit: Non circular
Camera Pre-set: Tc-99m-NMG	Mode: step and shoot
Detectors: Both	Attenuation Correction: Off
Orientation: Head out	Study Based set-up: Off
Patient Position: Supine	Time per view: 28 sec
Rotation Direction: CW	Starting Angle: 0

Supplementary table 2: CT reference values used for image acquisition in figures 1B and 2B

kV	130
Coll	16 x 1.2
Slice thickness (mm)	2
mAs	65
Rotation Time (s)	0.6

Pitch	1.2
Safire	3
Dose Mode	On
CareDose	4D
Care KV	Yes