Peer Review File

Article Information: https://dx.doi.org/10.21037/tau-23-623

Reviewer A

99mTc-sestamibi (MIBI) is a well-known tumour imaging agent in breast, lung, and kidney cancer. The Author should better describe the reason of 99mTc-MIBI uptake in the tumour. Arbab AS et al investigated the kinetics, cellular uptake, and intracellular distribution of 99mTc-MIBI confirming that most 99mTc-MIBI accumulates inside the mitochondria. Its retention within tumour cell mitochondria is related to perfusion and to the electrical gradient, reflecting cell viability.

1. Arbab AS, Koizumi K, Toyama K, Araki T. Uptake of technetium-99m-tetrofosmin, technetium-99m-MIBI and thallium-201 in tumor cell lines. J Nucl Med. 1996 Sep;37(9):1551-6. PMID: 8790217.

2. Arbab AS, Koizumi K, Toyama K, Arai T, Araki T. Ion transport systems in the uptake of 99Tcm-tetrofosmin, 99Tcm-MIBI and 201Tl in a tumour cell line. Nucl Med Commun. 1997 Mar;18(3):235-40. doi: 10.1097/00006231-199703000-00007. PMID: 9106777

3. Moretti JL, Hauet N, Caglar M, Rebillard O, Burak Z. To use MIBI or not to use MIBI? That is the question when assessing tumour cells. Eur J Nucl Med Mol Imaging. 2005 Jul;32(7):836-42. doi: 10.1007/s00259-005-1840-x. PMID: 15902437.

- Can alternative therapies be further commented on?

Reply 1: We thank the reviewer for their suggestion. We have included a paragraph explaining the mechanism of action of ^{99m}Tc-sestamibi SPECT/CT including the suggested references.

Changes in the text:

Page 1 line 10-16: ^{99m}Tc-sestamibi 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 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 renal cell carcinomas photopenic on ^{99m}Tc-sestamibi SPECT/CT.

Reply 2: We thank the reviewer for this suggestion. The focus of our editorial is ^{99m}Tc-sestamibi SPECT/CT as a diagnostic tool to risk stratify renal tumours. While risk stratification will affect decision making and counselling for treatment, the breadth of 'alternative therapies' (by which we understand surgery, ablation, stereotactic radiotherapy and active surveillance) is increasingly nuanced. We include in the first paragraph a line acknowledging that alternative treatments for

surgery may be chosen based on risk-stratification, but consider more detailed discussion beyond the scope of this article.

Changes in the text:
Page 1 line 7-8: This is increasingly relevant as alternative treatments to surgery with varied risk-benefit profiles emerge.

Reviewer B

Discrimination of benign versus malignant incidental renal masses is an unmet clinical need, and we have high expectations for SPECT/CT with 99mTc-sestamibi, perhaps even exceeding the real benefits that this technique will actually be able to provide.

In my opinion, the editorial proposed is very relevant and well conducted. the language is fluent. Just a couple of typo errors to fix:
- page 2 line 30: "firstly, it important consider ..."
- page 2 line 39: "However, we would caution against ..."

Comment 1:
Reply 1: We thank the reviewer for their positive comments. We have corrected the identified typos.
Changes in the text:
- Page 2 line 7: “firstly, it is important to consider…”
- Page 2 line 16 –> No typo identified. Removed ‘would’.