Peer Review File

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Reviewer A

This manuscript written by Himam Murad reported the utility of 18F-Fluoromethylcholine-positron emission tomography in detecting the localization enlarged parathyroid gland. This imaging modality should contribute to the progress of the preoperative imaging for PHPT. Although well-described, several points should be addressed.

#1

Was 18F-FCh-PET-CT performed only for the patients who had inconclusive results on Tc99m-sentamibi/SPECT-CT? If patients who had conclusive findings on Tc99m-sentamibi/SPECT-CT also underwent 18F-FCh-PET-CT, the information about the consistency between Tc99m-sentamibi/SPECT-CT and 18F-FCh-PET-CT would be important to emphasize the performance of 18F-FCh-PET-CT

We realize that the manuscript is unclear on what the indications for 18-FCh-PET-CT were. 18F-FCh-PET-CT was done when US and/or Tc99m-sentamibi/SPECT-CT were negative or inconclusive, or when there was discrepancy in their results, i.e. discordant findings, or when there was suspicion of multiglandular disease. We have included a more precise definition and the text has been revised, please see page 4, line 91-93.

#2

The definition of inconclusive results in Tc99m-sentamibi/SPECT-CT was unclear. In fact, in Table 3, four of nine patients had positive glands in Tc99m-sentamibi/SPECT-CT. Is this situation inconclusive? If Tc99m-sentamibi/SPECT-CT indicate at least one diseased gland, I assume that it is conclusive. Please clarify this point.

The definition is now stated at the corresponding paragraph. Please see page 4, line 103-105 and page 5, line 118-120.

#3

Patients with familial diseases such as MEN and HPT-JT was included in this study. Total parathyroidectomy plus auto-transplantation might be considered to such the patients regardless of the numbers of enlarged glands. Furthermore, multiple enlarged glands suggest the familial diseases, hence genetic test for MEN1 might be considered. Please clarify the inclusion or exclusion criteria regarding this point.

We did not include patients with known hereditary disease, such as MEN1 or HPT-JT. However, we did not explicitly test for these conditions in the absence of clinical suspicion. No patient in this study had, as far as we knew, MEN1 or HPT-JT. Text has been clarified, please see page 4, line 90-91 and page 8, line 188-189.

Reviewer B

In this original manuscript by Murad et al., authors report the results from a retrospective study in a cohort of 52 patients suspected of primary hyperparathyroidism (PHPT) in whom 34 underwent surgery after TEP-choline localization. They found great performances of TEP-choline in identifying diseased glands, especially in multiglandular disease patients. As a TEP-choline believer, I find these results important to report but I have a few comments/questions authors should address.

A. MAJOR COMMENTS

1. My most major concern is the same in most studies about TEP-choline: recruitment bias. Only patients in which surgery was performed were included in the analysis. I mean, patients were screened by US, then Sestamibi, then TEP-choline: should the latter be negative (which is a failure), patients did not go to surgery and therefore were not taken into account for diagnostic performances. I would strongly suggest authors include all the patients in which TEP-choline has been performed in their analysis: patients who did not go to surgery should be considered, as in intention-to-treat analysis, as a failure of this technique. They should compare TEP-choline to Sestamibi and to US, as well as to surgery. The overall performances of all of these techniques should dramatically decrease, but will reflect the reality patients (and physicians) face in the real-world. Patients and physicians do not need >98% accurate assays: they need data reflecting their day-to-day findings.

We totally agree with the reviewer on this point and that's why we created two study cohorts, where all patients who underwent 18-FCh-PET-CT were included in cohort I, regardless if they were operated or not, and only those who were operated were included in cohort II. At the same time, it's worth mentioning that not all patients who were not operated were due to non-diagnostic Choline PET examinations. In fact, 9/18 non-operated patients were not operated due to other reasons (comorbidities, patient refusal, etc.) in spite of positive localization on Choline PET, But, yes we agree with you at this can be regarded as failure in the intention to treat process. We are aware of this problem and regard it as a limitation as stated in the manuscript.

2. The other very important point has been made by the authors themselves: imaging is way too often performed BEFORE the positive diagnosis for PHPT. Especially with such an expansive and hard to access technique, this should be avoided. What were the diagnosis criteria for PHPT? This is a very tricky point: did the authors only include hypercalcemic patients? this does not seem to be the case as some of them appeared to exert ionized calcium concentration at 1.24 mM, which is very hard to interpret as PHPT. Authors should report biological findings before and after surgery: how could one tell some normocalcemic PHPT is cured by surgery just looking at blood calcium concentration after surgery? This is a major point when assessing performances of surgery or imaging in PHPT.

We agree that so-called “normocalcemic pHPT” is controversial, and it is difficult to ascertain cure in those patients. Regarding the diagnostic criteraia for pHPT in our study, we have revised the text, please see page 4, line 87-88.

B. MINOR COMMENTS

1. I don't get what should be considered as 'inconclusive' for US or Sestamibi. Authors should be more explicit about those criteria.

We realise that the manuscript is unclear, please see also answer to comments #1 and #2 from Reviewer 1. The text has been changed, please see page 4, line 103-105 and page 5, line 118-120.

2. How experienced were the surgeons? I mean, performances of PHPT surgery greatly depend on the experience of the surgeon, as well as US imaging depends on the experience of the one performing it.

We agree that this is an important point. We have tried to clarify this issue, please see page 4, line 100-102.

3. I totally disagree with authors: the patient with FHH who underwent surgery did probably not take advantage of this surgery. It appears that histopathology was 'hyperplasia' which is barely a thing. Surgery should not have been performed and I am not convinced that these glands were really pathological. Performing imaging in this very patient has been detrimental. Was any 24h calciuria assessment performed before surgery?

We agree with the reviewer that patients with FHH usually do not benefit from surgery. However. This particular patient was investigated many years ago at another center due to hypercalcemia, and FHH was verified. At that point, sestamibi/SPECT CT was performed and showed suspected enlarged parathyroid gland. No surgery was done. The patient was referred to us 4 years later with symptomatic hypercalcemia and a very high ionized serum calcium (1.63mmol/l) and PTH at 13.2pmol/l. We suspected that the patient might have both FHH and PHPT that is why Choline PET was done and showed double adenoma. The decision to operate was made in an attempt to lower the serum calcium to a lower acceptable level. Surprisingly enough, histopathology showed parathyroid adenoma of chief cell type of both removed lesions.

Reviewer C

The authors assessed the diagnostic performance of [18F]FCH PET/CT in patients with primary hyperparathyroidism. Their results are in line with the current literature, and the study does not add more data to our knowledge; nevertheless, since this instrumental examination is going to be introduced in everyday clinical practice, more "hard data" concerning its excellent diagnostic performance are needed (mainly to resolve the current issues regarding its reimbursement from national services worldwide).

Here are my comments:

General: radionuclides and tracers should be reported as stated by EANM guidelines (https://www.eanm.org/content-eanm/uploads/2019/12/EANM_GUIDANCE-_TRACER_NOMENCLATURE-1.pdf).
The reporting of radionuclides throughout the text has been revised as stated by EANM guidelines.

Introduction: line 62: the authors state that "4D-CT is less precise". I would write that it is less accurate and I would specify from what.
We agree that this sentence could be clarified. We have changed the text, please see page 3, line 62-66.

Line 63: the authors write: "in many patients." What kind of patients? Please add a percentage from the reference.
We refer to patients with PHPT, this has been clarified, please see page 3, line 66.
We agree with the authors that it is an advantage to be specific whenever possible. However, the rate of non-conclusive ("double/triple negative") patients differs between institutions and reports, due to different patient populations, and different sensitivities of different imaging techniques used. This is why we do not state a specific percentage, since this number differs a lot between institutions.

Along the text, authors refer to PET/CT using the word "method." Please rephrase with "instrumental examination."
We understand and appreciate your suggestion. After discussion with other authors, we prefer to keep the present term for now, but leave the final decision on that to Mr. Editor in Chief to choose the appropriate term.

Methods: I miss the data concerning SPECT, PET and CT acquisition parameters.
Thanks for pointing this out. These parameters have been added, please see page 5, line 106 – 131.

Line 102: please rephrase PET/CT camera with PET/CT tomograph.
We have rephrased accordingly, please see page 5 line 124.

Results: na.

Discussion: line 210, please rephrase oncocytic thyroid cancer with oncocytic thyroid nodules.
We have changed the text according to suggestion, please see page 10, line 240.
Concerning false positive findings in FCH PET for pHPT:

1 study observed which nodules were more likely to have an increased uptake (Ciappuccini R, Licaj I, Lasne-Cardon A, Babin E, de Raucourt D, Blanchard D, Bastit

V, Saguet-Rysanek V, Lequesne J, Peyronnet D, Grellard JM, Clarisse B, Bardet S. 18F-Fluorocholine Positron Emission Tomography/Computed Tomography is a Highly Sensitive but Poorly Specific Tool for Identifying Malignancy in Thyroid Nodules with Indeterminate Cytology: The Chocolate Study. Thyroid. 2021 May;31(5):800-809. doi: 10.1089/thy.2020.0555. Epub 2020 Dec 23. PMID: 33183159; PMCID: PMC8110014.).

1 study reported the incidence of false positive findings due to thyroid nodules (Rizzo A, Racca M, Cauda S, Balma M, Dall'Armellina S, Dionisi B, Mossetti C, Bruna MC, Freddi M, Palestini N. 18F-fluorocholine PET/CT semi-quantitative analysis in patients affected by primary hyperparathyroidism: a comparison between laboratory and functional data. Endocrine. 2023 May;80(2):433-440. doi: 10.1007/s12020-022-03280-9. Epub 2022 Dec 10. PMID: 36495390).
Please cite both the studies and compare the obtained results with theirs.
We agree that these two studies are important and cite them on page 10 line 241-242. They are now included as references nr 20 and 24.