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Example of an outstanding review

IOP Publishing editors rate all the reviews we receive on a scale of 1 to 5, with a score of 5 signifying a review of outstanding quality

Manuscript Initial Review

Manuscript Reference
[redacted]

Manuscript Title:
[redacted]

Manuscript Scoring Criteria:
The PMB Referee Report Template was used as a template for this review.

Study Summary

Summary:
In their manuscript [redacted] the authors present their work developing a new mobile gamma camera. This work was very comprehensive, describing the design and construction of the mobile gamma camera, characterization of gamma camera performance, (energy resolution, intrinsic spatial linearity, intrinsic spatial resolution, intrinsic uniformity, system spatial resolution, and system sensitivity), and calibration of the gamma camera to convert the measured data (cps) to activity (MBq) for a thyroid phantom filled with a known, homogenous activity of I-131. The overall result of this work demonstrated that this new mobile gamma camera system: 1) provided improved image quality (namely, spatial resolution) relative to existing high-energy parallel-hole collimators; and 2) can accurately quantify the activity of I-131 in thyroid phantoms. The clinical significance of this work is that accurate quantification of I-131 activity within the thyroid may provide for improved knowledge of the radiation dose received (post-therapy dosimetry) in the thyroid.

Scope:
This manuscript falls within the scope of PMB. The clear medical application of the described mobile gamma camera is imaging the thyroid after therapeutic I-131 NaI therapy. This application is described using computational simulation (Monte Carlo) and experimental physics (design, construction, and testing of a physical bench-top mobile gamma camera using thyroid phantoms).

Originality and significance:
There are numerous prior publications outlining the design, development, and testing of miniature and/or portable gamma cameras using new fabrication techniques (e.g., 3D printed collimators); the authors are certainly familiar with these works as their bibliography cites some prior efforts in this area (e.g., Page 27 Lines 16-21 and Page 28 Lines 5-7).

Thus, the idea of a small, portable gamma camera in and of itself is not novel. However, the application is novel. Most small, portable gamma cameras are aimed to provide qualitative images of radiopharmaceutical uptake, such as in the localization of malignant tissues (for example, see Ortega *et al.*, "Potential role of a new hand-held miniature gamma camera in performing minimally invasive parathyroidectomy." Eur J Nucl Med Mol Imaging 34, 165–169 (2007). https://doi.org/10.1007/s00259-006-0239-7). The device proposed by the authors will provide not just qualitative images of radiopharmaceutical uptake but can also with calibration provide absolute quantification of the amount of activity contained within the thyroid.

Demonstrating a method that improves quantification of I-131 activity in the thyroid after therapy is a significant result that may provide improved patient care by allowing better correlation between thyroidal radiation doses and clinical outcomes. After further research and dosimetry, this may allow clinicians to prescribe custom dosages aimed to maximize the likelihood of disease control on a patient by patient basis, instead of simply administering a generic dosage based on the patient's disease, weight and/or thyroidal uptake. As this is a key component of the theragnostic movement that is rapidly becoming more mainstream, this is a very timely manuscript.

Finally, due to the small form factor and (assumed) lower cost of this device relative to a typical gamma camera, it is possible the proposed gamma camera system could be used outside of the typical nuclear medicine department (for example, within a private practice endocrinology clinic that does not have space or financial support for a standalone gamma camera). This is a compelling positive, as such a mobile gamma camera system may allow patients better access to personalized dosimetry for thyroidal disease treated with I-131.

Scientific rigor:
The methods of this manuscript are thoroughly detailed; in the opinion of this reviewer, if someone possessed this portable gamma camera, they would be able to replicate these research efforts based on the manuscript methods.

The gamma camera design was adequately explained, except for two items:

1. A discussion on shielding the device from extrathyroidal activity was not included (see Minor Concern 1).
2. An indication for why the collimator used was chosen (see Minor Concern 2).

The methods used for the characterization of the mobile gamma camera performance followed (with some modification) existing formalism (NEMA NU-1). Because there were some changes from the NEMA formalism in testing this new mobile gamma camera system (which was expected due to the new system design), the authors should note that comparison of their camera's performance cannot be directly compared to that of typical gamma cameras (see Minor Concern 3). One major gamma camera performance metric not characterized in this work was the system dead time and how that may affect activity quantification (see Major Concern 1).

Two thyroid phantoms filled with known I-131 activities were imaged with the new system; these images were used to assess the effectiveness of the calibration factor. The activity used in both phantoms was approximately constant; it is not clear why a range of activities was not used (see Major Concern 2).

A final major concern was a lack of discussion on several limitations of this device, and how those limitations may be corrected in a final clinical version of this manuscript (see Major Concern 3).

Writing:
The work is well-written and clearly communicated, with several minor concerns regarding writing (see Minor Concerns 4-6).

Length:
This manuscript is long, at about 26 pages of content and 4 pages of references. This is due to study itself; the authors designed and developed a new gamma camera, evaluated a large number of performance characteristics for the gamma camera, developed a method to quantify absolute activity, and imaged two thyroid phantoms to test their method of activity quantification. I do not have any areas I would suggest being removed.

Figures and tables:
The figures and tables were largely clear and useful to the text. There were several minor concerns (see Minor Concerns 7-10).

Title:
The title is sufficient. It was noted that one of the key words may not be suitable for this manuscript (see Minor Concern 11).

Abstract:
The abstract generally describes the work of the manuscript well and is sufficient.

Conclusion:
The conclusion summarizes the work well and describes how the proposed device may improve patient care through improved thyroidal imaging and activity quantification following I-131 therapy. There were several limitations that should be addressed in this section (see Major Concern 3), but otherwise, the conclusion is sufficient and provides closure to the work.

References:
In general, the references are reasonably up to date, appropriate, and consistently formatted. There are a number of older references, but that is expected with regard to the subject matter (thyroid therapy with I-131 is a technique that is many decades old). The authors do provide some examples of citing their own work (e.g., FANTHY5y and FANTHY15y phantom development), but these references are required for this manuscript and do not demonstrate any bias.

There were two references that have newer editions; the authors are encouraged to review these references and potentially update their bibliography with the newer versions (see Minor Concerns 12-13).

Major Concerns:
This section identifies and describes major concerns, if any, of the study.

1. On Page 4 Lines 19-25 the authors mention the final device design will have a maximum counting capability > 200 kCPS and that the high counting capability of the camera will reduce the effect of dead time on activity estimates. The authors correctly identify that the high energy emissions from I-131 (637 and 723 keV photons) will have a large effect on dead time (Page 4 Lines 47-52). The authors mention on Page 7 Lines 31-35 that the detector electronics have been adjusted to avoid any dead time. The authors also indicate that this current gamma camera system is limited to a maximum count rate of 5 kCPS (Page 26 Lines 25-26).

   A major concern identified is that the dead time of this system has not been quantified, and also that the effects of dead time on the calibration factor (CPS/MBq) have not been discussed. Dead time is an important characteristic in gamma camera systems and should be characterized if possible. The maximum counting rate of this test system was fairly low at 5 kCPS (Page 26 Lines 25-26); did this low maximum count rate preclude the measurement of dead time and count losses? Was it verified that at this low maximum count rate the effects of dead time were negligible? Is there an estimated thyroidal activity that will saturate the detector and make the device unusable? It would greatly strengthen this manuscript to include these details, and thus a report of the dead time, count losses as a function of activity, maximum count rate, and the effect these parameters have on the determining the activity in the thyroid should be provided **if and only if** the current rendition of this device can provide this data. If the current rendition of this device **cannot** provide meaningful data regarding the dead time, it should be explained why.

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2. On Page 12 Line 59 it is specified the thyroid phantoms were filled with approximately 50 MBq I-131. It is not clear why only one activity was chosen to demonstrate the effectiveness of the system. Demonstrating that this device can effectively measure the activity within a thyroid for a range of activities would greatly strengthen this manuscript. If there was a reason that a range of activities was not tested, this should be elaborated upon.

3. Several limitations of this study were discussed in the conclusion such as more work being required to evaluate:
   a. activity quantification in small thyroidal tissues (e.g., remnants as discussed on Page 25 Lines 33-37)
   b. extrathyroidal activity increasing scatter (Page 25 Lines 37-41)
   c. the size of the detector being a limiting factor for enlarged thyroid glands (Page 25 Lines 41-45)
   d. design of a new detector for treatment planning, presumably through development of a different collimator specific for I-123 NaI (Page 25 Lines 53)
   e. different 3D printing methods to reduce voids in the tungsten collimators (Page 25 Line 55-Page 26 Line 11);
   f. crystal thickness and edge-packing (page 26 Lines 13-23);
   g. low system maximum count rate (Page 26 Lines 25-30).

There are several other limitations that should also be discussed, which include:

a. a difficulty/inability to quantify activity uptake in metastatic thyroidal disease located outside the thyroid bed, which is possible using whole body imaging on a typical gamma camera. Note is mentioned on Page 24 Lines 54-56 that this camera may be used for imaging other organ systems and/or metastatic disease outside the thyroid bed. This camera appears geometry dependent and limited in terms of FOV, and it is not clear how such imaging will be possible for ectopic or metastatic disease
b. the accuracy of I-131 thyroidal activity quantification on planar gamma cameras and/or SPECT/CT is using methods similar to what is outlined in this manuscript, including a direct quantitative comparison using the data in Figure 11 (Page 22 Lines 1-36).
c. The long image acquisition time. The activity in the thyroid phantom was 50 MBq which is approx. 1.3 mCi (Page 12 Line 59), and the views required 25 minutes (Page 13 Lines 14). For three views (AP, PA, and lateral) this is 75 minutes of imaging (not including the time to reposition the device). The authors should identify if this imaging time will be reduced with improvements to the system to allow for clinical imaging (e.g., much shorter patient table times). It is noted on Page 25 Lines 17-22 that image acquisition times may be reduced with higher thyroid activities to 5-10 minutes with thyroidal activities of approx. 5-20 mCi with approx. 50% uptake. This would be a good improvement in imaging time but may still result in very long scans (e.g., 1% uptake from a 100 mCi I-131 thyroid cancer remnant ablation).

Minor Concerns:
This section identifies and describes minor concerns of the study.

1. This device was tested using two thyroid phantoms (FANTHY5y and FANTHY15y, described on Page 12 Lines 37-54). All of the activity being imaged during these phantom studies was located within the thyroid. It is not clear how extrathyroidal I-131 activity (e.g., activity in bladder) will affect camera performance. The authors do comment that there may be huge scattering background from extrathyroidal activity (Page 25 Lines 37-41) but do not comment on the potentially large amounts of primary radiation that may bypass the collimator and impact the crystal from extrathyroidal activity. It would be useful for the authors to comment on the gamma camera hardware (current or proposed) that will be designed to shield the scintillator from extrathyroidal primary and scattered radiation.
2. Page 6 Lines 54-56: It is stated that a given collimator design was finally chosen, but it is not clear why this design was chosen. It would be useful if the authors could indicate in the text what design criteria were used (e.g., designed for what spatial resolution and sensitivity? Was it 2 mm spatial resolution (FWHM) and 1.24E-05 sensitivity as identified on Page 7 Line 5?)
3. Page 8 Line 20 – Page 12 Line 32: The various performance metrics were measured using methods similar to those outlined in NEMA NU-1 but with various differences (e.g., for intrinsic integral uniformity, a Gaussian 3x3 filter is used instead of a standard 9-point filter, it is not clear if edge pixels were removed, the number of detected events per pixel was greater than 8000 rather than 10000, etc.). The authors should indicate there was a divergence from typical NEMA formalism that may preclude a direct comparison of the proposed mobile gamma camera with existing technology.
4. Page 3 Line 47: There were numerous typographical errors including the one identified at this location (the word “ordinary” appears to be used incorrectly; should this word be “data” or “images”?). The majority of these errors will be corrected upon acceptance, but it is still recommended the authors thoroughly review their manuscript for grammatical and typographical errors.
5. Page 6 Line 27 and Page 15 Line 12: The 10 mm thick $CeBr_3$ crystal is referred to as 1 cm thick (example: page 15) and 10 mm thick (example: page 6) throughout the text. It is recommended the authors refer to this thickness consistently as either 1 cm or 10 mm.

6. Page 6 Line 5: The units Msamples/s are used. Would a sampling rate of 2 MHz make more sense? (Units of kHz are used when referring to counting rates on Page 26 lines 25-30)
7. Page 14 Lines 5-40: It would be useful to include a color bar that relates color to pixel intensity to the top right and bottom images (similar to Figure 7). It would useful to either include a spatial scale or indicate that the full FOV to allow the reader to gauge the size of the thyroid phantom for the top right and bottom images. It would be useful to add the directionality of the views (e.g, label sides as "A" or "P") for the top right and bottom images.
8. Page 17 Lines 18-43: Units (or the % symbol) should be added to the color bars for clarity. Additionally, it would be easier to interpret these results if the scales were matched for the same images measured using different crystals (for example, images c and f should both use the same color bar scale).
9. Page 18 Lines 39-42 and Page 19 Lines 5-57: The caption of Figure 5 states the 6 mm crystal data is on the right and the 10 mm crystal data is on the left. On Page 18 Lines 39-42 the authors indicate light distortion is stronger at the crystal edges using the 10 mm crystal. However, in Figure 8 it appears the right image (Figure 8.b) has stronger distortion at the image edges. Is Figure 8.b the 6 mm crystal as described in the caption? Or is this effect due to mismatched scales? Additionally, the scales should be matched to provide the same scale for similar images (e.g., it is difficult to compare resolution using Figures 8.c and 8.d because the scales are not matched).
10. Page 22 Lines 5-36: It is not clear why the phantom appears symmetric in the mobile gamma camera images but appears to be rotated in the typical gamma camera images. Is this due to the superior positioning of the mobile gamma camera?
11. Page 1 Lines 52-54: One of the key terms is "Image-guided treatment planning." This manuscript discusses the possibility of using this new gamma camera for treatment planning, but the subject of the manuscript is in the determination of activity within the thyroid after an I-131 NaI therapy has been administered. It may be useful to select another keyword that more accurately describes the manuscript contents.
12. Page 26 Lines 43-45: NEMA NU-1 2012 was cited. NEMA NU-1 2018 is now available. This version provides guidance on evaluating SPECT and gamma camera systems that are not typical gamma cameras consisting of a NaI(Tl) slab coupled to PMTs. It is recommended the authors review this newer version and identify if the newer version may be more appropriate to cite.
13. The Sorenson text has much more recent additions (with Cherry as the first author). This text was cited to provide evidence that typical gamma cameras have IU and DU of approximately 3% (Page 16 Lines 50-54). The newer version of the text provides the same evidence, and so this should be updated in the bibliography.

Conclusion:

In this manuscript, the authors presented their work in developing a new mobile gamma camera. The key strengths of this work are that the authors fully quantified the performance of this new system (except for dead time) and developed a method to covert measured counts in the thyroid to I-131 activity within the thyroid. With future work, a finalized version of this device may allow for improved knowledge of thyroid dose in patients undergoing I-131 NaI therapies; this improved knowledge may be correlated to clinical outcomes and allow for personalized dosimetry in the future.

The key weaknesses of this paper are identified in the major concerns (e.g., lack of dead time quantification, lack of activity quantification over a range of activities in the thyroid phantom, and a lack of discussion on several important limitations).

The recommendation for this manuscript is <u>revision to address the concerns prior to publication</u>. This manuscript will be suitable for publication in PMB if the major and minor concerns are addressed. This is a very interesting topic and I hope that the authors perform these revisions to strengthen their manuscript. I believe that this new mobile gamma camera is laying the groundwork for important future work.