

Peer Review File

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Reviewer A

Comment 1: Title – single gland disease is more commonly used than “solitary PHPT.” Suggest something along the lines of “Preoperative localization of single gland disease in primary hyperparathyroidism: a comparative study of...”

Reply: Thank you for your comment. We have modified our text as advised.

Changes in the text: Page 1, Line 1

Comment 2: Abstract – suggest using the ‘single gland disease’ terminology rather than ‘solitary PHPT.’

Reply: Thank you for your comment. We have modified our text as advised.

Changes in the text: Page 3, Line 55, 57

Comment 3: Highlight box – for key finding #1, the modalities are for localizing parathyroid adenoma(s) in PHPT not for ‘localizing PHPT’ as currently written. For what is known and what is new, the fact that parathyroid CT outperforms other modalities is not new; see PMID 30193297 for a discussion of some of this pre-existing evidence.

Reply: Thank you for your advice. We revised the text for key finding #1 as advised.

In addition, we also agree with your opinion that parathyroid CT may outperform other imaging modalities, which is not a novel finding, as previously discussed in PMID 30193297. Therefore, in the sentence “This study revealed that 4D CT outperformed US and 99mTc-sestamibi SPECT in sensitivity and specificity for PHPT localization, maintaining accuracy even when US and 99mTc-sestamibi SPECT yield negative results,” we have removed the phrase “This study revealed that” and simply presented the information about 4D CT. and we have revised and cited the relevant content in the

Discussion section.

Changes in the text: Page 4, Line 77

Comment 4: Introduction – in paragraph 3 discussing the imaging modalities, suggest mentioning and citing the American College of Radiology’s Appropriateness Criteria document on this topic (PMID 34794597)

Reply: We appreciate the reviewer’s suggestion to include and cite the American College of Radiology’s Appropriateness Criteria document (PMID 34794597). In accordance with Reviewer B’s recommendation to move this paragraph from the Introduction to the Discussion section, we have revised and cited the relevant content in the Discussion section.

Changes in the text: Page 5, Line 95-99. & Page 10, Line 221-232

Comment 5-1: Methods – In the patients section, again would use ‘single gland disease’ to describe the selected patient population rather than solitary PHPT. Also, why exclude patients with MGD? Parathyroid CT is also known to be relatively better in this group, and it would likely increase the (very small) sample size. SGD vs MGD is not known pre-operatively and so the selected cohort methodology of this study does not match real-world clinical practice.

Reply: Thank you for your comment. We have modified our text as advised.

In addition, the incidence of PHPT in South Korea appears to be lower than that in Western countries, with an incidence of approximately 1 per 1,000 people (0.1%) (PMID 29732354). As a result, the number of parathyroidectomies performed is also significantly lower compared to Western countries. Therefore, cases of primary hyperparathyroidism with multiple gland disease (MGD) are rare in South Korea. In our study, the chart review did not identify any cases of MGD due to its rarity in South Korea, and thus, these cases were not included in the analysis.

Changes in the text: Page 5, Line 105 & Page 6 line 110 / Page 12, Line 293-295

Comment 5-2: In the sestamibi section, the images were acquired “at” 20 and 120 minutes rather than “for”

Reply: Thank you for your comment. We have modified our text as advised.

Changes in the text: Page 6, Line 129

Comment 5-3: In the parathyroid CT section, some justification for the 4th post-contrast phase should be provided. This was the original description in 2006, but since this time most places have gone to 3 or fewer phases. Two phases vs 4 phases is discussed but no mention is made of the most common 3 phase protocol. See reference 10 for evidence of the 3-phase protocol being most common.

Reply: Thank you for your advice. In this study, we adopted the 4-phase protocol for 4D CT, originally described in 2006, as the optimal number of post-contrast phases is undetermined, and additional phases can enhance sensitivity. However, as the reviewer noted, the 3-phase protocol is now the most commonly used approach. Given its lower radiation exposure and the minimal difference in sensitivity between the 3-phase and 4-phase protocols, we consider the 3-phase approach may be more advantageous. We have added these considerations to the limitations section of our manuscript.

Changes in the text: Page 13, Line 300-303

Comment 5-4: In the surgery section (and later), the “hyperplasia” term is no longer preferred in the setting of PHPT (see Erickson et al summary of WHO 2022 update; PMID 35175514). It may still be the case that this outdated language is appropriate in the context of this retrospective study, but some acknowledgement of the fact that MGD in PHPT is now recognized to be multiple adenomas and that “hyperplasia” is best reserved for secondary hyperparathyroidism would be appropriate. Also, were there any mechanisms to ensure that these patients truly had SGD (i.e., that the single parathyroidectomies were biochemically successful)? These mechanisms could include intraoperative PTH and/or normocalcemia at 6-month follow-up.

Reply: We sincerely appreciate the reviewer’s insightful comment regarding the terminology of “hyperplasia” in the context of PHPT. We acknowledge that the updated

WHO 2022 classification (Erickson et al., PMID: 35175514) recommends reserving “hyperplasia” for secondary hyperparathyroidism and that it is no longer considered an appropriate term for single-gland disease in PHPT. However, in our retrospective study, the term “hyperplasia” was used in accordance with the historical terminology prevalent at the time, and this updated consensus has not yet been universally adopted worldwide. Consequently, at our institution, “hyperplasia” continues to be used in diagnostic histopathological findings. Furthermore, our study focuses on single-gland disease rather than multiglandular disease. Therefore, we have chosen to retain the term “hyperplasia” in our manuscript and kindly ask for your understanding on this matter.

In addition, we agree with the reviewer’s suggestion regarding the need to confirm that these patients truly had single-gland disease. In the Results section, we had initially noted that postoperative PTH and calcium levels decreased in all patients. However, to provide further clarity, we have now explicitly stated that, at the 6-month follow-up, all patients' PTH and calcium levels were within the normal range. This additional information confirms the biochemical success of the single parathyroidectomies.

Changes in the text: Page 8, Line 184-185

Comment 6-1: In the patients section, see comment above re: ‘hyperplasia.’

Reply: Thank you for your comment. We have chosen to retain the term “hyperplasia” in our manuscript. We kindly ask for your understanding on this matter.

Comment 6-2: In the incorrect localization section, what is the definition of ‘huge goiter.’ I am not aware of this as a medical term appropriate for use in scientific writing.

Reply: Thank you for your comment. We acknowledge that “huge goiter” is not a precise medical term appropriate for scientific manuscripts. In the revised manuscript, we have replaced “huge goiter” with “large thyroid nodule” to ensure more appropriate terminology.

Changes in the text: Page 9, Line 210

Also in the incorrect localization section, a more correct interpretation of the finding related to sestamibi false negatives and gland volume would be that “Tumor volumes were significantly smaller among patients with false negative sestamibi studies compared to patients with true positive sestamibi studies.”

Reply: Thank you for your comment. We have modified our text as advised.

Changes in the text: Page 10, Line 215-216

Also, the formula for estimating volume should be provided in the Methods.

Reply: Thank you for your comment. We have added the formula for estimating volume to the Method section as advised.

Changes in the text: Page 7, Line 159-161

Comment 7-1: Discussion – First sentence would more appropriately be “Various methods have been proposed for the localization of parathyroid adenoma(s) in patients...”

Reply: Thank you for your comment. We move this paragraph from the Discussion to the Introduction section, so we have modified as your advised in the Introduction section.

Changes in the text: Page 5, Line 95

Comment 7-2: As mentioned earlier, comparison to results from 3 phase protocols published in the literature would be appropriate, which may even support these protocols as better than 4 phase (i.e., similar performance without the additional radiation).

Reply: Thank you for your advice. We agree with you, so we have mentioned it in the limitations section.

Changes in the text: Page 13, Line 300-303

Comment 7-3: In the paragraph beginning “US is a noninvasive...” it would be more appropriate to say that an advantage is that US can “guide” rather than “perform” FNA, etc.

Reply: Thank you for your comment. We have modified our text as advised.

Changes in the text: Page 11, Line 260

Comment 7-4: In the final paragraph, the authors seem to suggest that iodinated contrast reactions are more common in patients with impaired renal function. Allergic reactions to iodinated contrast and so-called “contrast induced nephropathy” are separate issues. I am not aware of any data suggesting that patients with renal disease are more likely to have an allergic reaction. Suggest revising accordingly.

Reply: Thank you for your advice. We have revised our text as advised. We acknowledge that allergic reactions to iodinated contrast media and contrast-induced nephropathy are distinct concerns. So, we revise the final paragraph to clarify this distinction and ensure our wording does not suggest a greater risk of allergic reactions in patients with renal disease.

Changes in the text: Page 12, Line 282-285

Comment 7-5: A limitations section is needed, of which there are many. I have mentioned some above, and the authors can likely think of others.

Reply: Thank you for your comment. We added a new subsection about limitations.

Changes in the text: Page 12-13, Line 291-311

Comment 8: Conclusion – Again, would use single gland disease terminology rather than solitary PHPT.

Reply: Thank you for your comment. We have modified our text as advised.

Changes in the text: Page 13, Line 318

Comment 9: References – see comments above re: some references to potentially incorporate/add.

Reply: Thank you for your comment. We added some references.

Changes in the text: Page 14

Reviewer B

Comment 1: The introduction is well-contextualized but could be more concise. Detailed explanations about imaging methods for localization could be shifted to the discussion section, making the introduction more objective and focused.

Reply: Thank you for your comment. We agree that it can be made more concise and focused. In accordance with your recommendation, we have shifted the detailed explanations of imaging methods for localization to the Discussion section and retained only a concise overview in the Introduction section.

Changes in the text: Page 5, Line 95-99. & Page 10, Line 221-232

Comment 2-1: Patients: Clarify whether only patients undergoing their first surgery were included. Localization tests typically have reduced sensitivity and specificity in reoperative cases. This distinction is essential for interpreting the results.

Reply: Thank you for your insightful comment. All patients included in this study underwent parathyroid surgery for the first time, and we have explicitly noted this in the manuscript for clarity.

Changes in the text: Page 6, Line 106

Comment 2-2: Neck Ultrasonography (US): Specify whether all ultrasounds were performed by the same endocrinologist. If so, include their years of experience. This is crucial since US is operator-dependent. Explain how blinding was implemented. Was US performed first, or was the endocrinologist blinded to the results of the other imaging modalities and clinical records?

Reply: Thank you for your comment. We have modified our text as advised.

Changes in the text: Page 6, Line 116-120

Comment 2-3: Tc-99m-Sestamibi SPECT: Indicate whether a single nuclear medicine physician interpreted all SPECT scans. Include their level of experience and whether they were blinded to the results of US and 4D CT.

Reply: Thank you for your suggestion. We have added our text as advised.

Changes in the text: Page 7, Line 137-140

Comment 2-4: Four-Dimensional Computed Tomography (4D CT): Similar to SPECT, clarify if a single radiologist analyzed all 4D CT scans, their experience, and whether they were blinded to other imaging results.

Reply: Thank you for your comment. We have modified our text as advised.

Changes in the text: Page 7, Line 149-151

Comment 2-5: General Concerns about Imaging: Were all imaging tests performed at the same institution? If not, clarify if external reports were included and how these were standardized.

Reply: Thank you for your advice. All imaging tests were performed at the same institution (our institution)

Comment 2-6: Surgery: Specify the criteria used to define correct localization during surgery. Was it based solely on the side (right/left), or was the exact location within the neck considered?

Reply: Thank you for your insight comment. The results from the three imaging modalities were combined to determine preoperative localization (right/left, upper/lower), and surgery was performed using a minimally invasive approach. In ambiguous cases, the CT scan was rechecked intraoperatively to confirm the anatomical location, and the final localization was then decided accordingly. We hope this clarifies

our criteria for defining correct localization during surgery and appreciate your valuable feedback.

Comment 2-7: Statistical Analysis: Mention if a normality test was conducted before comparing data. Describe the statistical methods used for calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. These details should appear under "Statistical Analysis" rather than "Surgery." Include information about confidence interval (CI) calculations, as these are presented in the results.

Reply: Thank you for your comment. We have added our text as your advised and we have shifted the statistical methods used for calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy to the Statistical Analysis section. We hope this addition meets your expectations and adds value to our study.

Changes in the text: Page 8, Line 166-175

Comment 3-1: Thyroidectomy: Lines 176-177 mention that thyroidectomy was performed in 12 patients. Was this exclusively due to preoperatively diagnosed thyroid diseases, or was it also necessary due to challenges in localizing the parathyroid gland or suspicion of intrathyroidal parathyroid?

Reply: Thank you for your insight comment. All patients who underwent concomitant surgery had coexisting diseases, and this information has been added to revised manuscripts. We hope this addition meets your expectations and adds value to our study.

Changes in the text: Page 8, Line 181-183

Comment 3-2: Line 192 uses the term "correlation" incorrectly. It refers to a "comparison," which has a different statistical meaning.

Reply: Thank you for your suggestion. We have modified our text as advised.

Changes in the text: Page 9, Line 203

Comment 3-3: Additional Data Presentation: Consider including a table listing all 41 cases, showing whether each imaging method (US, 4D CT, and SPECT) correctly localized the lesion and comparing this to the surgical findings. This would enhance transparency and could be supplementary material if not included in the main manuscript.

Reply: Thank you for your insightful suggestion. We agree with you that. So, we have created a table summarizing this data and included it as supplementary material. We hope this addition meets your expectations and adds value to our study.

Comment 3-4: The description of results appears biased toward 4D CT. While the manuscript highlights instances where US and SPECT failed, no details are provided about cases where 4D CT was incorrect. Similarly, cases where SPECT succeeded after US failure (and vice versa) are not discussed. Including these would provide a more balanced perspective.

Reply: Thank you for your comment. We have modified our text as advised.

Changes in the text: Page 10, Line 218-219

Comment 3-5: Analyze the combined performance of two imaging modalities, as clinical practice often employs both (e.g., US + SPECT or SPECT + 4D CT). This could provide valuable insights for clinical decision-making.

Reply: Thank you for your insightful suggestion. We agree with you that. So, we have created a new table and included it to the Result section. We hope this addition meets your expectations and adds value to our study.

Changes in the text: Page 9, Line 194-201 & Table 3

Comment 4-1: Bias Toward 4D CT: The discussion and conclusion overemphasize the superiority of 4D CT. However, the CI analysis suggests that the observed differences may not be statistically significant due to the small sample size. Acknowledge this limitation.

Reply: Thank you for your insightful comment. We agree with your observation that the small sample size may limit the statistical significance of the observed differences in the performance of 4D CT, as reflected in the confidence interval analysis. We have acknowledged this limitation in the revised manuscript's limitations section. We appreciate your feedback in helping us improve the clarity and objectivity of our study.

Changes in the text: Page 12, Line 291-293

Comment 4-2: Limitations of SPECT: Lines 261-263 attribute SPECT's poor performance in small-volume lesions to functional limitations. Provide a potential explanation for this finding.

Reply: Thank you for your comment. We have modified our text as advised and added some references.

Changes in the text: Page 12, Line 272-276

Comment 4-3: Comprehensive Analysis: Expand the discussion to cover the advantages and limitations of each imaging modality, supported by data from the literature. Discuss the practical use of combined modalities and highlight the need for experienced radiology teams for interpreting 4D CT.

Reply: Thank you for your valuable comment. We have added some references. And we agree with your observation. In the revised manuscript, we have discussed and acknowledged them as limitations of our study.

Changes in the text: Page 13, Line 307-311

Comment 4-4: Study Limitations: Emphasize that the findings reflect a single-institution sample and may not generalize to other settings. Highlight potential biases due to methodology (e.g., lack of blinding, external imaging reports) and stress the need for multicenter studies to validate the results.

Reply: Thank you for your comment. We added a new subsection about limitations.

Changes in the text: Page 12-13, Line 291-311

Comment 5: Conclusion - Conclude that 4D CT performed well in the observed cases, particularly where US and SPECT had limitations. However, emphasize that the CIs do not allow for definitive conclusions about its superiority. Larger multicenter studies are required to better define the role of 4D CT, especially in cases where other imaging methods fail.

Reply: Thank you for your comment. We have modified our text as advised.

Changes in the text: Page 13, Line 314-318