Ultrasound and Technetium-99m Sestamibi Scintigraphy Diagnostic Performance as Preferred Localization Techniques in Patients with Primary Hyperparathyroidism: A Literature Review

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ABSTRACT

Introduction: Primary hyperparathyroidism (PHPT) is a medical problem whose definitive management is surgery. Preoperative imaging studies for identifying the solitary parathyroid adenoma are a requirement for focused parathyroidectomy in patients with PHPT. There are various imaging modalities for the localization study. Nevertheless, up until now, the gold standard for parathyroid imaging has still not been established. Accurate parathyroid imaging is needed in PHPT cases to support the success of focused parathyroidectomy and prevent increasing patient morbidity due to bilateral neck exploration.

Aims and objectives: It is very important for this study to investigate the positive predictive value (PPV) and sensitivity of sestamibi and ultrasonography as preoperative localization techniques.

Materials and methods: Literature search has been carried out on Cochrane, PubMed, and the ScienceDirect database site, using a combination of Medical Subject Headings (MeSH) search terms and keywords: “parathyroidectomy,” “primary hyperparathyroidism,” “parathyroid adenoma,” “ultrasound,” “ultrasonography,” “radionuclide imaging,” “sestamibi,” “sensitivity and specificity,” and “predictive values of tests.” A literature search was conducted to look for previous publications, about the sensitivity and positive predictive value of ultrasonography as a technique of localizing preoperative compared with sestamibi in localizing parathyroid adenomas in patients with PHPT. After research articles have been obtained, a selection and examination of journals according to the inclusion and exclusion criteria was conducted.

Results: A total of 192 studies were obtained, which are Cochrane (0) study, PubMed (33) studies, and ScienceDirect (159) studies. After screening, 13 studies are selected for review. According to the studies, ultrasonography has a sensitivity of 55–100% and PPV 74–100%. Ultrasonography has a wide range of sensitivity because it is highly operator-dependent depending the expertise of the operator. Ultrasonography by radiologists has a sensitivity of 55–94.6% and PPV 74–97.2%, while ultrasonography by a surgical specialist has a sensitivity of 83–93.2% and PPV 80–85.1%. Sestamibi has a sensitivity of 64–93.3% and PPV 70.5–100%. Limitation of sestamibi includes poor spatial resolution causing low precision in anatomic localization, and there is the use of ionizing radiation. While SPECT/CT has similar sensitivity in localizing parathyroid adenomas located on the retrothyroid and ectopic sites (sensitivity 86.7% and 81.5%; PPV 98.1% and 100%). The study has found that adding ultrasonography to the SPECT/CT examination increased sensitivity, but decreased PPV.

Conclusion: Ultrasound examination is very dependent on the operator so that sensitivity varies, influenced by the expertise and experience of the operator in each institution. Ultrasonography can be used as the main modality in localization studies in patients with PHPT in areas that do not have nuclear radiology facilities.

Keywords: Parathyroidectomy, Primary hyperparathyroidism, Radionuclide imaging, Sestamibi, Ultrasonography.

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is a medical problem whose definitive management is surgery.¹–³ Preoperative imaging studies for identifying the solitary parathyroid adenoma are a requirement for focused parathyroidectomy in patients with PHPT.³ However, there is no universally accepted algorithm for imaging the parathyroid gland, and the choice of imaging is influenced by the preferences of the surgeons. Previous studies have yielded varying sensitivities of parathyroid imaging modalities.⁴,⁵

Both ultrasonography and sestamibi have advantages and disadvantages. Noninvasive, rapid ultrasonography can evaluate lesions in the thyroid gland, but there are limitations in evaluating mediastinal parathyroid glands.⁶,⁷ Sestamibi can detect ectopic and posterior glands that are not detected on ultrasonographic examination, but the radiation used can increase cancer risk.⁴ Besides, there are only 17 hospitals in Indonesia that have nuclear radiology facilities.⁸

Until now there has been no standard or algorithm for parathyroid imaging. Ultrasonography is a publicly available...
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modality, both in urban and rural areas, while scintigraphy is only available in certain hospitals. Accurate parathyroid imaging is needed in PHPT cases to support the success of focused parathyroidectomy and prevent increasing patient morbidity due to bilateral neck exploration. Therefore, it is necessary to study the sensitivity and PPV of ultrasonography and sestamibi as preoperative localization techniques.

Aims and Objectives
To determine the sensitivity and positive predictive value (PPV) of ultrasonography and sestamibi preoperative localization techniques for localizing parathyroid adenomas in patients with PHPT.

Materials and Methods
A literature search was carried out to look for previous publications, which raised research questions about the sensitivity and positive predictive value of ultrasonography as a technique of localizing preoperative compared with sestamibi in localizing parathyroid adenomas among patients with PHPT. The study was conducted at Division of Surgical Oncology, Department of Surgery, Cipto Mangunkusumo Hospital, in December 2018–February 2019. After the research question (“how is ultrasound sensitivity and PPV as preoperative localization techniques compared with sestamibi in localizing parathyroid adenomas in patients with PHPT?”) and the person, intervention, comparison, outcome (PICO) components were identified, a search and selection of literature on Cochrane, PubMed, and Science Direct database was conducted. This was done by using a combination of Medical Subject Headings (MeSH) search terms and keywords: “parathyroidectomy,” “primary hyperparathyroidism,” “parathyroid adenoma,” “ultrasound,” “ultrasonography,” “radionuclide imaging,” “sestamibi,” “sensitivity and specificity,” and “predictive values of tests.” After research articles from each database have been obtained, a selection and examination of journals according to the inclusion and exclusion criteria was conducted to eliminate article duplication.

Inclusion Criteria
- The study is in the form of meta-analysis, systematic review, randomized controlled trial, case series, and case report.
- In English language.
- Publication within the last 5 years.

Exclusion Criteria
- Publication in the form of correspondence, editorial, and commentary.
- Not available in the full-text format.

Result and Discussion
From the literature review, a total of 192 studies were obtained, which are Cochrane (0) study, PubMed (33) studies, and Science Direct (159) studies. After selecting the studies based on the inclusion and exclusion criteria, 10 studies from PubMed and 6 studies from Science Direct were selected. After that, the reviewer conducted a duplicate studies screening, which resulted in one study that was similar from both PubMed and Science Direct, resulting in 15 studies were selected for review. All literature is available in the full-text format; literature downloads are carried out, and assessment is carried out. The summary of the diagnostic performance on ultrasonography and sestamibi based on the literatures reviewed can be seen in Tables 1 to 6.

Based on studies obtained in the literature review, ultrasonography has a sensitivity of 55–100% and PPV 74–100%. Ultrasonography has a wide range of sensitivity in the 13 studied literature. Ultrasonography is highly operator-dependent, so the sensitivity varies, influenced by the expertise and experience of the operator in each institution. The lowest sensitivity, PPV, and ultrasound accuracy (55, 74, and 48%) were obtained in the study of Ryan et al. (2017), where ultrasonographic examinations were carried out in four radiology departments by different radiology specialists. This results in significant interexaminer variability and explains the low sensitivity in this study.9

Al-Kurd et al. (2018) state that the ultrasound performed by an experienced surgeon is superior to other modalities in determining the correct adenoma localization, and has the highest sensitivity and accuracy (93.2% and 80.1%) compared to other inspection (p < 0.001). The superiority of ultrasonography by experienced surgical specialists compared to ultrasonography by radiology specialists who may be inexperienced with PHPT patients can be due to several factors. First, the surgical specialists generally accept patients after ultrasound examination of radiology specialists and sestamibi were made, which leads to bias due to these results. In addition, ultrasound performed by a surgical specialist generally focuses only on the parathyroid and thyroid glands, while radiologists typically examine the entire structure of the neck soft tissue. Finally, surgeons are generally more willing to take risks and regard a borderline-looking structure as an adenoma, whereas radiology specialists are reluctant to include uncertainty in official radiology reports.10

The study of Uslukay et al. shows that ultrasonography performed in a team consisting of surgical specialists and radiology specialists can produce sensitivity, PPV, and accuracy up to 100%. However, the drawback of this study is the small sample size (30 people).11

Of the 13 literatures that included ultrasonography as one of the modalities of localization of surgery, 7 are done by radiologists, 1 is done by endocrine surgeons, 1 is done by radiologists and surgeons, 1 is done by collaboration between radiologists and surgeons, while 2 literatures do not mention specifically the operator of the ultrasound. Ultrasonography by radiologists has a sensitivity of 55–94.6% and PPV 74–97.2%, while ultrasonography by a surgical specialist has a sensitivity of 83–93.2% and PPV 80–85.1%. Ultrasonography performed by trained ultrasonographers produces low sensitivity (58%). Therefore, ultrasound sensitivity and PPV are influenced by the expertise of the operator.

Sestamibi has a sensitivity of 64–93.3% and PPV 70.5–100%. Limitation of sestamibi includes poor spatial resolution causing low precision in anatomic localization, and there is the use of ionizing radiation. In addition, the presence of benign thyroid nodules can reduce sestamibi sensitivity and follicular cell thyroid neoplasms can cause false accumulation of sestamibi.12

In this study, 10 literatures analyzed sestamibi as a localization study of parathyroidectomy. In the literature with a sample size <100 people, sensitivity (85–93.3%) and PPV (91–100%) sestamibi are relatively high. However, in the literature with a sample size of
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≥100 people, sensitivity (64–83.3%) and PPV (70.5–92%) sestamibi decreased.

The Scattergood et al. (2018) study found that the sensitivity of the combination of ultrasonography and sestamibi was higher compared to ultrasonography alone (81% and 70%).\textsuperscript{13} Likewise with the research of Frank et al. (2017), the sensitivity of a combination of sestamibi and ultrasonography (96–100%) is higher than ultrasonography (69–92%) or sestamibi alone (90%).\textsuperscript{14}

Table 1: Sensitivity, specificity, predictive value, and ultrasound accuracy\textsuperscript{9–21}

| Author, year            | N     | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|-------------------------|-------|-----------------|-----------------|---------|---------|--------------|
| Scattergood et al., 2018| 184   | 70              | 57              | 92      | 19      | 68           |
| Al-Kurd et al., 2018    |       |                 |                 |         |         |              |
| • Radiology             | 397   | 70.5            |                 | 84.6    | 62.5    |              |
| • Surgery               | 221   | 93.2            |                 | 85.1    | 80.1    |              |
| Argirò et al., 2018     | 46    | 89.1            | 97.5            | 93.2    | 95.6    |              |
| Ryan et al., 2017       | 129   | 55              |                 | 74      |         | 48           |
| Frank et al., 2017      |       |                 |                 |         |         |              |
| • 3D                    | 52    | 84–92           |                 |         |         |              |
| • 2D                    | 52    | 69–71           |                 |         |         |              |
| Keutgen et al., 2016    | 24    | 100             |                 |         |         | 92           |
| Coelho et al., 2016     | 55    |                 |                 |         |         | 89           |
| Seyednejad et al., 2016 | 24    | 58              |                 | 100     | 58      |              |
| Medas et al., 2016      | 212   | 62.4            |                 | 92.6    |         |              |
| Ibrahim and Elsadawy, 2015 | 40  | 94.6           | 66.6            | 97.2    | 92.5    |              |
| Uslukaya et al., 2015   | 30    | 100             |                 | 100     | 100     |              |
| Kluijfhout et al., 2015 | 54    | 63.2            |                 |         |         | 78.3         |
| Hughes et al., 2014     | 1644  | 83              |                 |         |         | 80           |

Table 2: Sensitivity, specificity, predictive value, and accuracy of sestamibi\textsuperscript{12–16,18–22}

| Author, year            | N     | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|-------------------------|-------|-----------------|-----------------|---------|---------|--------------|
| Scattergood et al., 2018| 184   | 64              | 57              | 92      | 17      | 64           |
| Al-Kurd et al., 2018    | 376   | 83.3            |                 | 70.5    |         | 70.5         |
| Argirò et al., 2018     | 46    | 83.6            | 98.3            | 95      | 93.7    |              |
| Frank et al., 2017      | 52    | 90              |                 |         |         |              |
| Keutgen et al., 2016    | 28    | 85              |                 |         |         |              |
| Coelho et al., 2016     | 47    |                 |                 |         |         |              |
| Medas et al., 2016      | 180   | 78.9            |                 | 89.9    |         |              |
| Ibrahim and Elsadawy, 2015 | 40  | 89.5           | 100             | 100     | 90      |              |
| Uslukaya et al., 2015   | 30    | 93.3            |                 | 100     | 93.3    |              |
| Hughes et al., 2014     | 1165  | 66              |                 |         |         | 88           |

Table 3: Sensitivity, specificity, predictive value, and accuracy of the combination of ultrasonography and sestamibi\textsuperscript{12–14,19,21}

| Author, year            | n     | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|-------------------------|-------|-----------------|-----------------|---------|---------|--------------|
| Scattergood et al., 2018| 184   | 81              | 71              | 95      | 33      | 80           |
| Argirò et al., 2018     | 46    | 93.4            | 98.3            | 95      | 98.3    |              |
| Frank et al., 2017      |       |                 |                 |         |         |              |
| • 3D                    | 52    | 100             |                 |         |         |              |
| • 2D                    | 52    | 96              |                 |         |         |              |
| Ibrahim and Elsadawy, 2015 | 40  | 97.3           | 100             | 100     | 97.5    |              |
| Hughes et al., 2014     | 920   |                 |                 |         |         | 92           |

Table 4: SPECT sensitivity, specificity, predictive value, and accuracy\textsuperscript{22}

| Author, year            | n     | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|-------------------------|-------|-----------------|-----------------|---------|---------|--------------|
| McCoy et al., 2018      |       |                 |                 |         |         |              |
| • Solitary gland        | 539   | 91              |                 | 85      |         | 77           |
| • Multiglandular        | 94    | 49              |                 | 37      |         | 22           |
Double-phase parathyroid imaging using 99mTc-MIBI and SPECT/CT is one of the reliable and accurate methods for assessing parathyroid adenoma surgery. This examination is better for preoperative identification and localization if compared to ultrasonography, CT, and MRI.\(^\text{23}\)

The Koberstein et al. (2016) study found that localization of parathyroid adenomas located on the retrothyroid and ectopic sites had similar sensitivity and PPV using SPECT/CT (sensitivity 86.7% and 81.5%; PPV 98.1% and 100%). In addition, the probability of precise localization increases with increasing serum PTH.\(^\text{23}\)

McCoy et al. (2018) concluded that SPECT/CT provides a more reliable operating guide than SPECT alone. Although the two imaging techniques are not adequate predictors for multiglandular disease, SPECT/CT is 60% more accurate (36% and 22%), with higher sensitivity and PPV compared to SPECT alone in identifying multiglandular disease (68% and 49% sensitivity; PPV 53% and 37%).\(^\text{22}\) Ryan et al. (2017) stated that ultrasound and SPECT/CT are only 37% suitable in localizing adenomas.\(^\text{22}\)

Ryan et al. (2017) stated that ultrasound has a sensitivity of 64–93.3% and PPV of 70.5–100%. Ultrasound examination is very dependent on the operator so that sensitivity varies, influenced by the expertise and experience of the operator in each institution.

Ultrasoundography can be used as the main modality in localization studies in patients with PHPT in areas that do not have nuclear radiology facilities.

**Conclusion**

- Ultrasonography has a sensitivity of 55–100% and PPV of 74–100%.
- Sestamibi has a sensitivity of 64–93.3% and PPV of 70.5–100%.
- Ultrasound examination is very dependent on the operator so that sensitivity varies, influenced by the expertise and experience of the operator in each institution.
- Ultrasonography can be used as the main modality in localization studies in patients with PHPT in areas that do not have nuclear radiology facilities.

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