

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

Diani Kartini¹, Sonar S Panigoro², Ciputra Linarydy³

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, 15 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.

World Journal of Endocrine Surgery (2020): 10.5005/jp-journals-10002-1284

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.^{4,6,7} 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

^{1–3}Department of Surgery, Cipto Mangunkusumo Hospital, Universitas Indonesia, Jakarta, Indonesia

Corresponding Author: Ciputra Linarydy, Department of Surgery, Cipto Mangunkusumo Hospital, Universitas Indonesia, Jakarta, Indonesia, Phone: +628158709821, e-mail: d.kartini@gmail.com, linarydy.c@gmail.com

How to cite this article: Kartini D, Panigoro SS, Linarydy C. Ultrasound and Technetium-99m Sestamibi Scintigraphy Diagnostic Performance as Preferred Localization Techniques in Patients with Primary Hyperparathyroidism: A Literature Review. *World J Endoc Surg* 2020;12(1):9–13.

Source of support: Nil

Conflict of interest: None

Until now there has been no standard or algorithm for parathyroid imaging. Ultrasonography is a publicly available

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 ScienceDirect (159) studies. After selecting the studies based on the inclusion and exclusion criteria, 10 studies from PubMed and 6 studies from ScienceDirect were selected. After that, the reviewer conducted a duplicate studies screening, which resulted in one study that was similar from both PubMed and ScienceDirect, 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 lateralization, 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 Uslukaya 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, 1 is done by trained ultrasonographers, 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

Table 1: Sensitivity, specificity, predictive value, and ultrasound accuracy⁹⁻²¹

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^{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		96		
Coelho et al., 2016	47			91		
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^{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 accuracy²²

Author, year	n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
McCoy et al., 2018						
• Solitary gland	539	91		85		77
• Multiglandular	94	49		37		22

≥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%).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%).¹⁴

Table 5: SPECT/CT sensitivity, specificity, predictive value, and accuracy^{9,11,17,22,23}

Author, year	n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
McCoy et al., 2018						
Solitary gland	647	96		90		83
Multiglandular	108	68		53		36
Ryan et al., 2017	161	73		87		67
Seyednejad et al., 2016	24	90		90		75
Koberstein et al., 2016	88	85.1		98.7		84.1
Retrothyroid	88	86.7	96.4	98.1	77.1	89.8
Ectopic	88	81.5	100	100	92.4	94.3
Kluijfhout et al., 2015	63	80.3		93		

Table 6: Sensitivity, specificity, predictive value, and accuracy of the combination of USG and SPECT/CT^{9,11}

Author, year	n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Ryan et al., 2017	119	66		46		38
Kluijfhout et al., 2015	54	84.2		77.4		

Double-phase parathyroid imaging using 99m Tc-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.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.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%).²² Ryan et al. (2017) stated that ultrasound and SPECT/CT are only 37% suitable in localizing adenomas.²² Kluijfhout et al. (2015) found that adding ultrasonography to the SPECT/CT examination increased sensitivity, but decreased PPV.¹¹

Ultrasonography, if performed by a trained operator, can produce an equivalent or higher sensitivity and PPV compared to sestamibi so that it can be used as the main modality in localization studies in patients with PHPT. This can especially be applied 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.

REFERENCES

1. Pallan S, Khan A. Primary hyperparathyroidism: update on presentation, diagnosis, and management in primary care. *Can Fam Physician* 2011;57(2):184–189.
2. Tay Y-KD, Yeh R, Kuo JH, et al. Pre-operative localization of abnormal parathyroid tissue by 99mTc-sestamibi in primary hyperparathyroidism using four-quadrant site analysis: an evaluation of the predictive value of vitamin D deficiency. *Endocrine* 2018;60(1):36–45. DOI: 10.1007/s12020-018-1528-1.
3. Wilhelm SM, Wang TS, Ruan DT, et al. The American association of endocrine surgeons guidelines for definitive management of primary hyperparathyroidism. *JAMA Surg* 2016;151(10):959–968. DOI: 10.1001/jamasurg.2016.2310.
4. Kuzminski SJ, Sosa JA, Hoang JK. Update in parathyroid imaging. *Magn Reson Imaging Clin N Am* 2018;26(1):151–166. DOI: 10.1016/j.mric.2017.08.009.
5. Mihai R, Simon D, Hellman P. Imaging for primary hyperparathyroidism—an evidence-based analysis. *Langenbeck's Arch Surg* 2009;394(5):765–784. DOI: 10.1007/s00423-009-0534-4.
6. Cheung K, Wang TS, Farrokhyar F, et al. A meta-analysis of preoperative localization techniques for patients with primary hyperparathyroidism. *Ann Surg Oncol* 2012(2):577–583. DOI: 10.1245/s10434-011-1870-5.
7. Udelsman R, Åkerström G, Biagini C, et al. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop. *J Clin Endocrinol Metab* 2014;99(10):3595–3606. DOI: 10.1210/jc.2014-2000.
8. Syarifah F, Daftar Rumah Sakit yang Gunakan Teknologi Nuklir untuk Kanker. <https://www.liputan6.com/health/read/2453125/daftar-rumah-sakit-yang-gunakan-teknologi-nuklir-untuk-kanker>. Published March 7, 2016. Accessed January 15, 2019.
9. Ryan S, Courtney D, Moriariu J, et al. Surgical management of primary hyperparathyroidism. *Eur Arch Oto-Rhino-Laryngol* 2017;274(12):4225–4232. DOI: 10.1007/s00405-017-4776-4.
10. Al-Kurd A, Levit B, Assaly M, et al. Preoperative localization modalities in primary hyperparathyroidism: correlation with postoperative cure. *Surgery* 2018;164(1):130–136. DOI: 10.1016/j.surg.2018.02.016.
11. Kluijfhout WP, Borel IHM, Valk GD, et al. Enabling minimal invasive parathyroidectomy for patients with primary hyperparathyroidism using Tc-99m-sestamibi SPECT-CT, ultrasound and first results of 18F-fluorocholine PET-CT. *Eur J Radiol* 2015. 3–9.

12. Argirò R, Diacinti D, Sacconi B, et al. Diagnostic accuracy of 3T magnetic resonance imaging in the preoperative localisation of parathyroid adenomas: comparison with ultrasound and 99mTc-sestamibi scans. *Eur Radiol* 2018;(11). DOI: 10.1007/s00330-018-5437-8.
13. Scattergood S, Marsden M, Kyrimi E, et al. Combined ultrasound and sestamibi scintigraphy provides accurate preoperative localisation for patients with primary hyperparathyroidism. *Ann R Coll Surg Engl* 2018. 1–6.
14. Frank SJ, Goldman-yassen AE, Koenigsberg T, et al. Sensitivity of 3-dimensional Sonography in preoperative evaluation of parathyroid hyperparathyroidism. *J Ultrasound Med* 2017;36(9):1897–1904. DOI: 10.1002/jum.14245.
15. Keutgen XM, Nilubol N, Agarwal S, et al. Reoperative surgery in patients with multiple endocrine neoplasia type 1 associated primary hyperparathyroidism. *Ann Surg Oncol* 2016;23(Suppl 5):701–707. DOI: 10.1245/s10434-016-5467-x.
16. Coelho MCA, Beuren AC, Lopes CB, et al. Role of imaging tests for preoperative location of pathologic parathyroid tissue in patients with primary hyperparathyroidism. *Endocr Pr* 2016;22(9):1062–1068. DOI: 10.4158/EP151137.OR.
17. Seyednejad N, Healy C, Tiwari P, et al. Dual-energy computed tomography: a promising novel preoperative localization study for treatment of primary hyperparathyroidism. *Am J Surg* 2016;211(5):839–845. DOI: 10.1016/j.amjsurg.2016.01.003.
18. Medas F, Erdas E, Longheu A, et al. Retrospective evaluation of the pre- and postoperative factors influencing the sensitivity of localization studies in primary hyperparathyroidism. *Int J Surg* 2016;25:82–87. DOI: 10.1016/j.ijssu.2015.11.045.
19. Ibrahim EAG, Elsadawy ME. Combined Tc-99m sesta MIBI scintigraphy and ultrasonography in preoperative detection and localization of parathyroid adenoma. *Egypt J Radiol Nucl Med* 2015;46(4):937–941. DOI: 10.1016/j.ejrnm.2015.07.006.
20. Uslukaya O, Gumus M, Tasdemir B, et al. Improvement of minimally invasive parathyroidectomy outcomes by real time ultrasonography performed by a surgeon and radiologist team. *Med Ultrason* 2015;17(3):315–321. DOI: 10.11152/mu.2013.2066.173.oky.
21. Hughes DT, Sorensen MJ, Miller BS, et al. The biochemical severity of primary hyperparathyroidism correlates with the localization accuracy of sestamibi and surgeon-performed ultrasound. *J Am Coll Surg* 2014;219(5):1010–1019. DOI: 10.1016/j.jamcollsurg.2014.06.020.
22. McCoy KL, Ghodadra AG, Hiremath TG, et al. Sestamibi SPECT/CT versus SPECT only for preoperative localization in primary hyperparathyroidism: a single institution 8-year analysis. *Surg* 2018;163(3):643–647. DOI: 10.1016/j.surg.2017.10.064.
23. Koberstein W, Fung C, Romaniuk K, et al. Accuracy of dual phase single-photon emission computed tomography/computed tomography in primary hyperparathyroidism: correlation with serum parathyroid hormone levels. *Can Assoc Radiol J* 2018;67(2):115–121. DOI: 10.1016/j.carj.2015.06.002.