Accuracy of Choline PET/CT vs. Tc 99m Sestamibi SPECT/CT Parathyroid Imaging in Comparison to Histopathology in the Diagnosis of Parathyroid Adenoma : A Meta-Analysis

Bettina Karmel D. Tecson, MD, Gari P. Danganan, MD, Michele D. Ogbac, MD

Division of Nuclear Medicine, Philippine Heart Center
E-mail address: bettinatecson@gmail.com , gari.danganan@gmail.com , mikaelamci@yahoo.com

ABSTRACT

Introduction:

In the advent of the recently accepted use of Choline in parathyroid PET/CT, we aimed to assess its accuracy in diagnosing parathyroid adenomas in comparison to the Tc 99m Sestamibi SPECT/CT parathyroid imaging, with histopathology as the reference standard.

Objective:

To determine the diagnostic accuracy of Choline PET/CT in comparison to Tc 99m Sestamibi parathyroid imaging in detecting parathyroid adenomas, with histopathology as the reference standard.

Methods:

Cross-sectional studies from 2014 to 2019 were identified through MEDLINE, Pubmed, clinicaltrials.gov, and Google scholar. Our literature search yielded 13 articles, of which only 3 met the set inclusion and exclusion criteria.

Results:

Three published cross-sectional studies were included with a total of population of 157 patients. Choline PET/CT was found to have a pooled sensitivity of 0.99 (0.96 - 1.00), pooled specificity of 0.45 (0.17 - 0.77), positive likelihood ratio of 1.79 (1.1 – 2.9), negative likelihood ratio of 0.03 (0.0 – 0.1), positive predictive value of 96.0% (93.4 - 97.7%) and negative predictive value of 83.3% (39.0 - 97.6%), estimated with 95% CI. Tc 99m Sestamibi SPECT/CT parathyroid imaging had a pooled sensitivity of 0.77 (0.70-0.84), pooled specificity of 0.45 (0.17 - 0.77), positive likelihood ratio of 1.43 (0.8–2.4), negative likelihood ratio of 0.49 (0.2–1.4), positive predictive value of 96.0% (93.4-97.7%) and negative predictive value of 83.3% (39.0-97.6%), estimated with 95% CI.

Conclusion:

Choline PET/CT showed superior sensitivity, negative predictive value and negative likelihood ratio over Tc 99m Sestamibi SPECT/CT parathyroid imaging. The measured specificities, positive predictive values and positive likelihood ratios of both modalities were found to be similar.

Keywords*: Parathyroid adenoma, hyperparathyroidism, Choline PET/CT, Tc 99m Sestamibi SPECT/CT Parathyroid Imaging, histopathology*

INTRODUCTION

Hyperparathyroidism is a condition defined by elevated parathyroid hormone levels due to increased synthesis and release of the hormone with resultant hypercalcemia and hypophosphatemia. Asymptomatic patients are usually diagnosed through incidentally noted abnormalities in routine laboratory examinations.

Primary hyperparathyroidism is most commonly caused by a single hyperfunctioning adenoma (in 85% of cases), which has been shown to be due to somatic mutations with clonal expansion of the mutated cells. Multi-gland hyperplasia and double adenoma occurs in 10% of the cases while parathyroid carcinoma accounts in only 1% of cases. Affected individuals, when symptomatic, often present with severe hypercalcemia, palpable neck masses, bone pains, fractures and renal colic. [1]

Secondary hyperparathyroidism, on the other hand, occurs commonly in patients with renal disease. The patients present with an abnormally low serum calcium and high phosphate levels, which in turn cause a compensatory increase in parathyroid hormone [2].

Normally, two parathyroid glands are each located in the posterolateral aspects of the upper and lower portion of the thyroid lobes, with a total of four parathyroid glands. However, 13%-15% of individuals are found to have a fifth parathyroid gland. Most parathyroid adenomas (80%) are located adjacent to the thyroid while the remainder (20%) are ectopically located in the anterior or posterior mediastinum, within or next to the thymus or along the esophagus or carotid sheath at the level of the carotid bifurcation. Invariable results often cause parathyroid lesions to be missed in surgery. In addition, its small size and location pose difficulty in the interpretation of most imaging modalities for parathyroid gland assessment [3].

In nuclear medicine, parathyroid imaging with SPECT/CT has helped in localizing hyperfunctioning parathyroid glands for surgical removal, contributing to reduction in surgical removal time. These imaging procedures are specifically useful in negative neck explorations and recurrent or persistent elevation of serum calcium after parathyroid gland resection. [4].

Most recently, the use of F18-fluoricholine PET/CT and C11-choline PET/CT, which are used in the diagnosis of recurrent prostate carcinoma, has recently gained popularity in the diagnosis of parathyroid adenomas. Choline radiotracers in PET have been found to accumulate not only in prostate carcinoma, but in other tumors and inflammatory conditions as well, since choline is a physiologic component of the cell membrane.5 With this newly found use of Choline in PET/CT, the aim of this study is to determine the diagnostic accuracy of Choline in PET/CT in comparison to Tc 99m Sestamibi SPECT/CT parathyroid imaging in the diagnosis of parathyroid adenomas, with histopathology as the reference standard.

OBJECTIVES

A. General Objective

To determine the diagnostic accuracy of Choline PET/CT versus Tc 99m Sestamibi parathyroid imaging in detecting parathyroid adenomas, with histopathology as the reference standard.

B. Specific Objectives

To determine the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value and negative predictive value of Choline PET/CT versus Tc 99m Sestamibi Parathyroid imaging.

MATERIALS AND METHODS

Ethical Considerations

This study has been granted exemption status by the institutional ethical review board of Philippine Heart Center.

Criteria for Considering Studies for the Review

Types of Studies

Cross-sectional studies on patients with clinical hyperparathyroidism were selected. Only studies that directly compared choline PET/CT and Tc 99m Sestamibi parathyroid scintigraphy for parathyroid localization were included.

Population Characteristics

Trials included patients ranging from 21–72 years old with hyperparathyroidism, which was defined as clinical evidence of primary hyperparathyroidism, i.e. those with elevated serum levels of parathyroid hormone (PTH) and/or calcium. Aforementioned patients must have undergone both choline PET/CT and Tc 99m Sestamibi parathyroid imaging and subsequently had surgery and histopathology for confirmation of lesion histopathology.

Diagnostic Test of Interest

The diagnostic accuracy of Choline PET/CT and Tc 99m Sestamibi SPECT/CT Parathyroid Imaging were evaluated.

Reference Standard

Histopathology after surgical resection was used as the reference standard.

Search Strategy for Identification of Studies

MEDLINE, Pubmed, clinicaltrials.gov, and google scholar literature search of cross-sectional studies assessing accuracy of Choline PET/CT in comparison to Tc 99m Sestamibi Parathyroid imaging for localization of parathyroid adenoma was done. Studies from 2014 to 2019 were retrieved for meta-analysis using both free-text and medical subject heading (MeSH) search method. Only published articles were selected based on certain inclusion and exclusion criteria.

Methods of the Review

Validity Assessment

Methodological quality for each study was assessed independently by 2 authors using the critical appraisal form for assessment of diagnostic studies. In cases of disagreement, a third party (adviser) was asked to help resolve the issue.

Data Extraction

Data on measures of diagnostic accuracy for each study was extracted and placed in the data extraction form for articles evaluating diagnosis.

Data Analysis

All meta-analysis was performed using Review Manager 5.3 (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Sensitivity, specificity and likelihood ratios (95% confidence intervals), were computed using MetaDisc 1.4. Heterogeneity was identified by visual inspection of the forest plots and by using a standard x^2 with a significance level of 0.05.

RESULTS

Search Outcome

A chart showing the flow of the search for eligible studies is shown in Figure 1. Of the 12 published articles retrieved, only 3 directly compared the diagnostic accuracy of Choline PET/CT against Tc 99m Sestamibi SPECT/CT Parathyroid Imaging. Nine studies were excluded due to at least one of the following: 1) Data acquisition was ongoing, 2) head-to-head comparison of Choline PET/CT and Tc 99m Sestamibi SPECT/CT Parathyroid imaging was note done, 3) not all patients with Tc 99m Sestamibi SPECT/CT Parathyroid imaging underwent Choline PET/CT (only equivocal cases). Only three studies fit the inclusion and exclusion criteria, published by Beheshti et al (2018) [6], Thanseer et al (2017) [7] and Orevi et al (2014)[8], as detailed in Table 1.

Quality Assessment

Quality of the studies included in the meta-analysis were appraised according to patient selection, index test, reference standard, as well as flow and timing using the revised Quality Assessment diagnostic accuracy Studies tool (QUADAS-2) (Figure. 2). A high risk of bias was demonstrated in index test interpretation in two of the studies due to lack of blinding. High risk of bias was also noted with regards to study flow and timing in two of the studies due to long time interval between index test performance and histopathology.

Data of the three studies selected were then subjected to statistical analysis and evaluation using the techniques of meta-analysis.

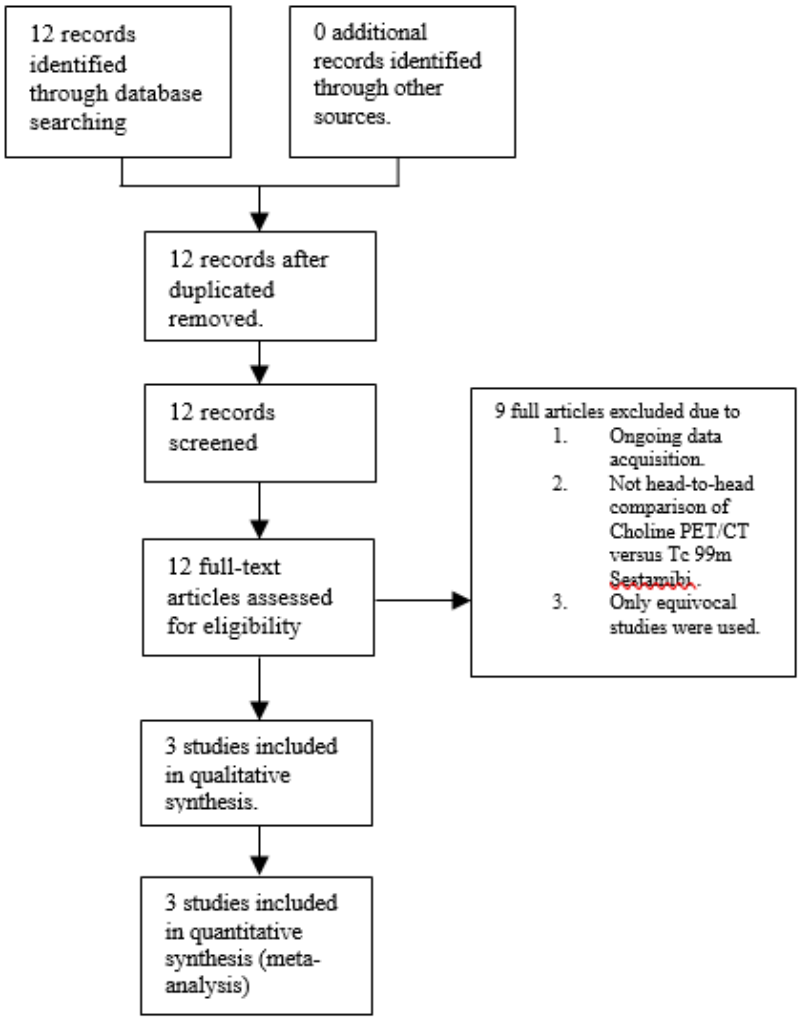

FIGURE 1. Flow chart of the search for eligible studies

TABLE 1. Study and patient characteristics

Study author	Year	Country	Type of PET/CT	Type of SPECT/CT Gamma Camera	No. Patient	Age (yrs) (mean ± SD)	%Male	Ca^{++} serum values (mmol/L)	PTH serum values (pg/mL)
Beheshti et. al.[5]	2018	Austria	PET/CT - Discovery 710; GE Healthcare, with extended field-of-view full-ring high-resolution LSO PET component, 128-slice spiral CT component	SPECT/CT scanner - Symbia T2 or T6; Siemens Healthineers	76	57.4 ± 12.5	21%	Mean: 2.78 ± 0.34	Mean: 196.5 ± 236.4
Thanseer et. al.[6]	2017	India	PET/ CT scan - GE Discovery 710 and STE-16; GE Healthcare, Milwaukee, Wis	Dual- headed gamma camera - Symbia T16; Siemens, Erlangen, Germany	54	47.7 ± 14	30%	Mean: 2.97 ± 0.3	Median: 171.5
Orevi et. al. [7]	2014	Israel	Discovery ST PET/CT system - GE Medical System, Milwaukee, WI	Not specified	27	55 (21-72)	35%	Mean: 2.8 (2.4-3.11)	Mean: 149.5 (33.8-496)

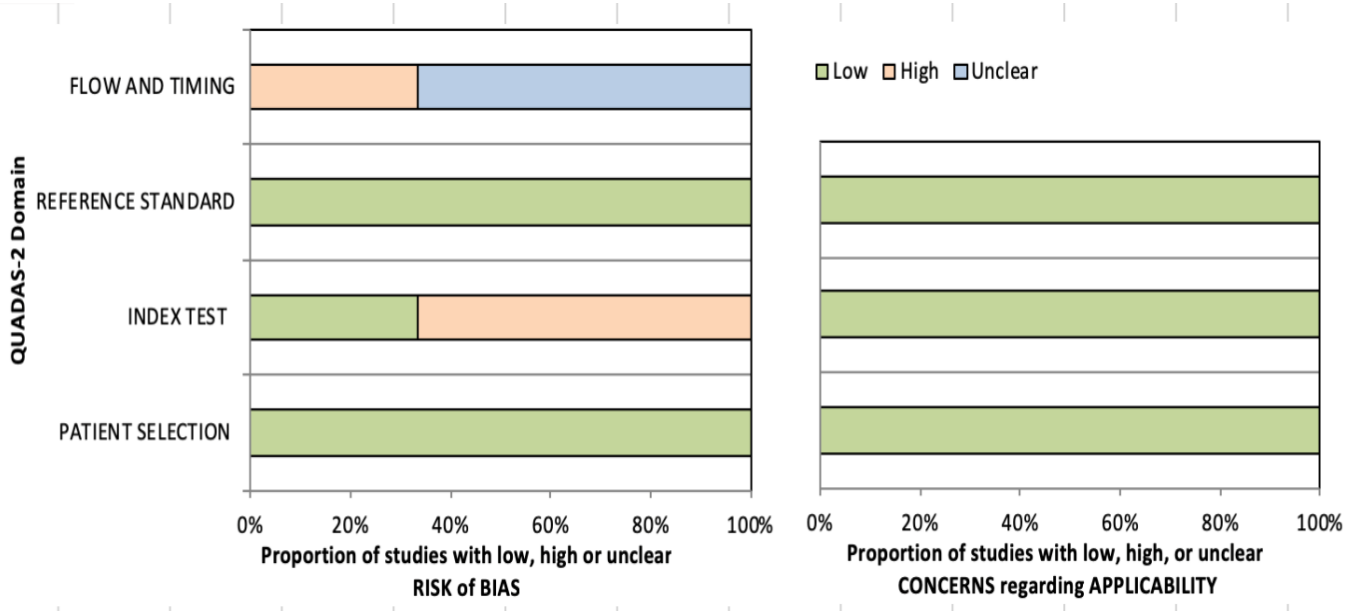

FIGURE 2. QUADAS-2 results summarizing the proportion of low, high, and unclear risk of bias and applicability concerns

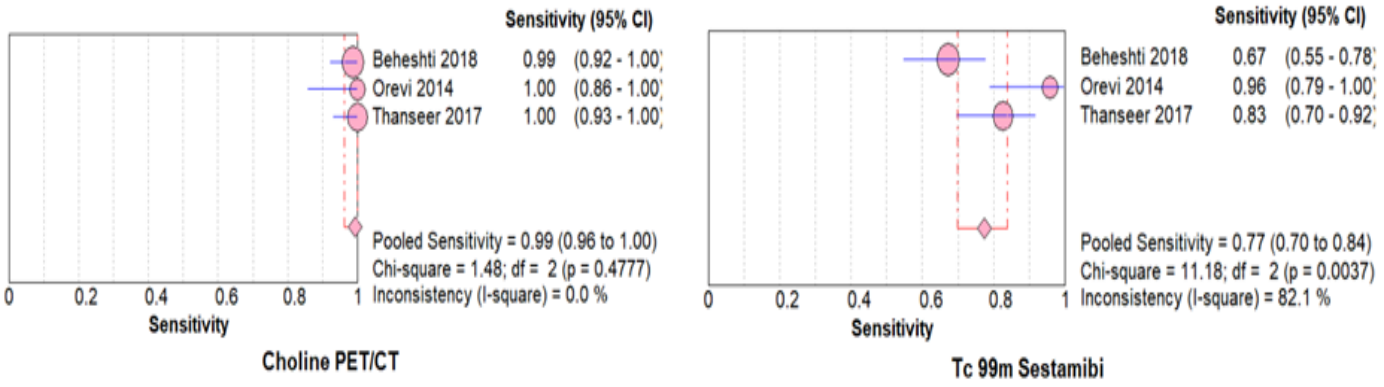

FIGURE 3. Forest plot of sensitivity of Choline PET/CT and Tc 99m Sestamibi Parathyroid imaging studies with pooled sensitivity, Q-statistic of the chi-squared, and I-squared results.

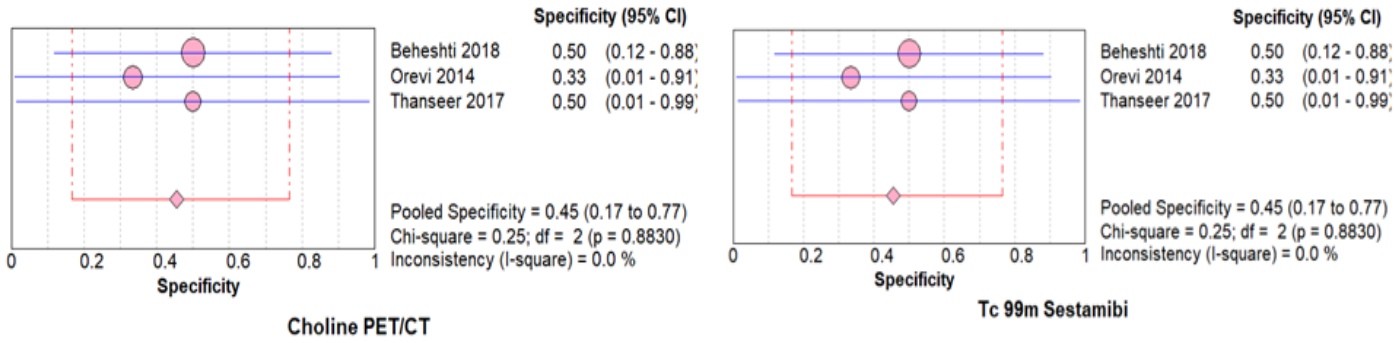

FIGURE 4. Forest plot of sensitivity of Choline PET/CT and Tc 99m Sestamibi Parathyroid imaging studies with pooled specificity, Q-statistic of the chi-squared, and I-squared results.

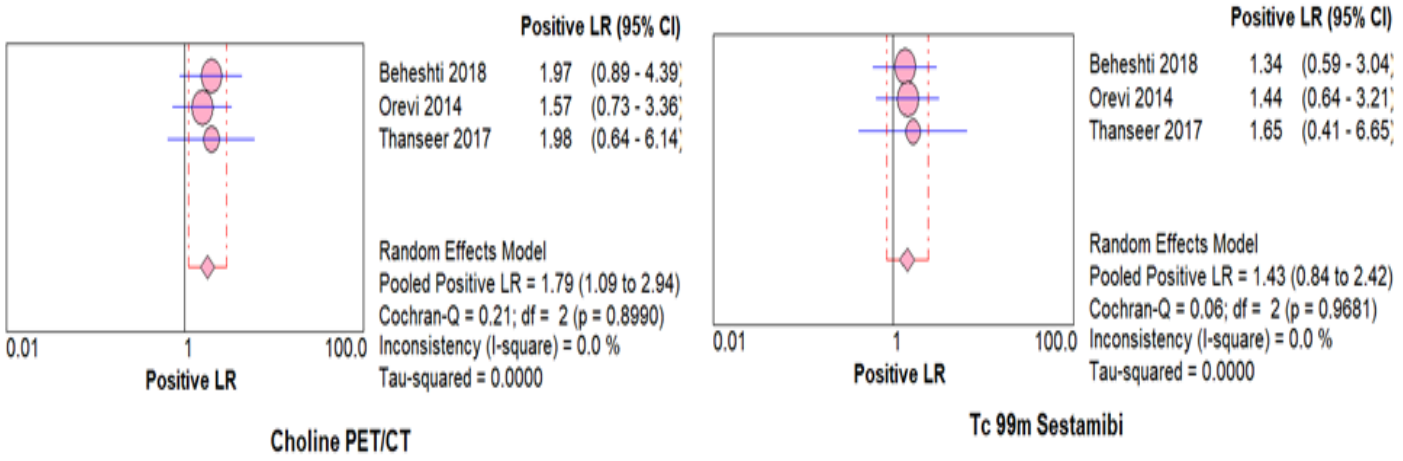

FIGURE 5. Forest plot of Forest plot positive likelihood ratio of Choline PET/CT and Tc 99m Sestamibi Parathyroid imaging with pooled positive likelihood ratio, Q-statistic of the chi-squared, and I-squared results.

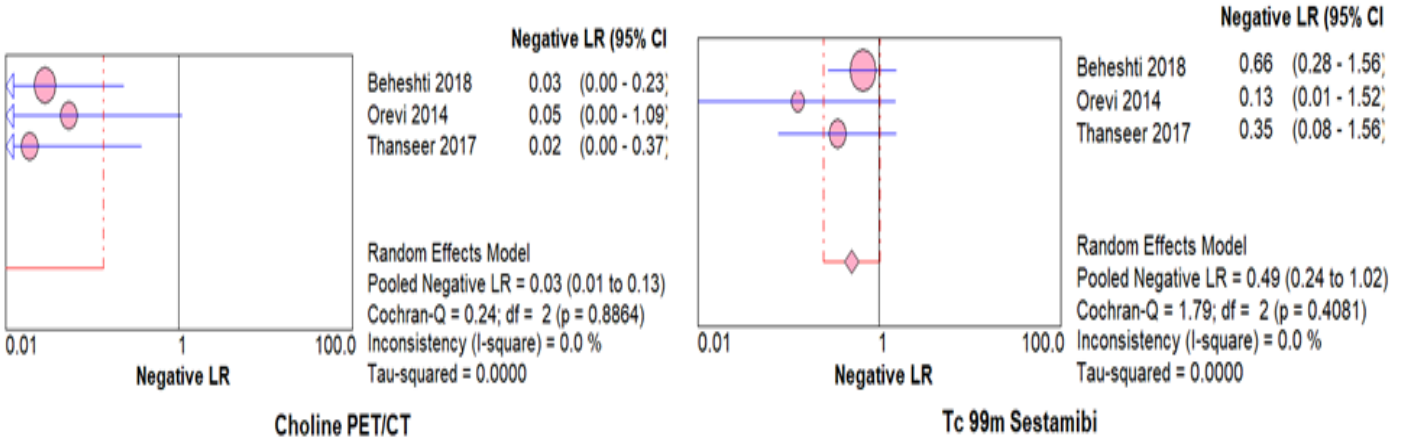

FIGURE 6. Forest plot of Forest plot negative likelihood ratio of Choline PET/CT and Tc 99m Sestamibi Parathyroid imaging with pooled positive likelihood ratio, Q-statistic of the chi-squared, and I-squared results.

In the three studies selected for analysis, a total of 157 patients were included. Mean patient age ranged from 33.7 to 79.9. Mean percentage of male patients ranged from 21% to 35%. Mean serum calcium and PTH levels ranged from 2.44 to 3.27 mmol/L and 115.7 to 432.9 pg/mL, respectively.

In all three studies, the PET/CT machines used were Discovery 710; GE Healthcare, with extended field-of-view full-ring high-resolution LSO PET component with a 128-slice spiral CT component [6, 7, 8] Gamma camera used for Beheshti et. al was Symbia T2 or T6.6 Siemens Healthineers, Dual-headed gamma camera, Symbia T16 was used in the study by Thanseer et al [7]. No specified machine was mentioned in Orevi et al [8].

Diagnostic performance of choline PET/CT and Tc 99m Sestamibi parathyroid imaging was expressed as pooled sensitivity, specificity, pooled positive predictive value and pooled negative predictive value on a per patient basis except for Beheshti et al [6], which only provided lesion-based analysis (Figures 3, 4, 5 and 6).

The pooled sensitivity and specificity of Choline PET/CT in detecting parathyroid adenoma were 0.99 (95% CI, 0.96 - 1.0%; Fig. 3) and 0.45 (95% CI, 0.17 - 0.77%; Fig. 4), respectively. Sensitivity and specificity heterogeneity tests gave I^2 values of 0.0% and 0.0%, respectively, indicating that there was no significant statistical heterogeneity between sensitivity and specificity studies for Choline PET/CT.

The pooled sensitivity and specificity of Tc 99m Sestamibi parathyroid imaging in detecting parathyroid adenoma were 0.77 (95% CI, 0.70 - 0.84%; Fig. 3) and 0.45 (95% CI, 0.17 - 0.77%; Fig. 4), respectively. Sensitivity and specificity heterogeneity tests gave I^2 values of 82.1% and 0.0%, respectively, indicating that there was significant statistical heterogeneity between studies for sensitivity that is evident visually in the forest plot. No significant heterogeneity noted in the specificity study.

The pooled positive and negative likelihood ratios for Choline PET/CT in detecting parathyroid adenoma were 1.79 (95% CI, 1.1 – 2.9%; Fig. 5) and 0.03 (95% CI, 0.0 – 0.1; Fig. 6), respectively. Positive and negative likelihood ratio heterogeneity tests yielded I^2 of 0% and 0%, respectively, indicating no significant heterogeneity between the studies.

The pooled positive and negative likelihood ratios for Tc 99m Sestamibi Parathyroid imaging in detecting parathyroid adenoma were 1.43 (95% CI, 0.8 – 2.4; Fig. 5) and 0.49 (95% CI, 0.2 – 1.4; Fig. 6), respectively. Negative likelihood ratio heterogeneity tests gave, I^2 values of 0% and 0%, respectively, indicating no significant heterogeneity between the studies.

The positive and negative predictive values of Choline PET/CT were 96.0% (95% CI 93.4 - 97.7) and 83.3% (95% CI 39.0 - 97.6), respectively. The positive and negative predictive values of Tc 99m Sestamibi parathyroid imaging were 96.0% (95% CI 93.4 - 97.7) and 83.3% (95% CI 39.0 - 97.6), respectively.

DISCUSSION

Tc 99m Sestamibi parathyroid imaging with SPECT/CT is the most widely used functional imaging modality in localizing parathyroid adenoma locally. Recently, in line with the PET/CT expansion in our country, a fairly new radiolabeled Choline has been used in the detection of parathyroid adenoma and has shown promising results in limited studies abroad. A meta-analysis by Treglia et. al showed high diagnostic accuracy of this new imaging modality with a sensitivity 95% (95% CI: 92 – 97%), PPV 97% (95% CI: 95 – 98%) and DR 91% (95% CI: 87 – 94%) in comparison with multiple other imaging modalities [9].

There are limited existing meta-analyses in investigating the diagnostic accuracy of Choline PET/CT as a diagnostic tool for parathyroid adenoma. The superiority of Choline PET/CT over the more widely used Tc99m Sestamibi parathyroid imaging with SPECT/CT for the detection of parathyroid adenoma using a head-to-head comparison has not been established using histopathology as its reference standard in detecting the said lesions.

Choline PET/CT showed superior sensitivity over Tc 99m Sestamibi parathyroid imaging, with pooled sensitivities of 0.99 (0.96 to 1.00, 95% CI) and 0.77 (0.70 to 0.84, 95% CI), respectively. However, the two modalities showed equal specificity of 0.45 (0.17 - 0.77, 95% CI).

The pooled results derived from the meta-analysis showed that overall, Choline PET/CT had superior diagnostic accuracy compared to Tc 99 Sestamibi parathyroid imaging. These findings are consistent with those published in the studies by Beheshti et al (2018) [6], Thanseer et al (2017) [7] and Orevi et al (2014) [8]. These pooled results are expected, since the individual studies included in the meta-analysis found Choline PET/CT to have superior sensitivity, positive likelihood ratio and negative likelihood ratio in comparison to Tc 99m Sestamibi parathyroid imaging [6, 7, 8].

Aside from the higher diagnostic accuracy of Choline PET/CT over the more widely used Tc 99m Sestamibi parathyroid imaging, it also offers advantages in terms of shorter acquisition time and lower radiation dose. However, the significantly lower cost of Tc 99m Sestamibi SPECT/CT makes it preferrable for some patients.

However, a significant limitation of this study is the very limited total number of patients. Hence, further studies directly comparing the diagnostic accuracy of Choline PET/CT and Tc 99m Sestamibi parathyroid imaging using randomized controlled trials and subsequent meta-analyses are recommended.

CONCLUSION

Choline PET/CT showed superior sensitivity, negative predictive value and negative likelihood ratio over Tc 99m Sestamibi SPECT/CT parathyroid imaging. The measured specificities, positive predictive values and positive likelihood ratios of both modalities were found to be similar. However, heterogeneity among the results of the included studies, as well as the limited number of patients included in the study, limits the conclusions drawn from these measures of diagnostic accuracy. Therefore, further studies comparing Choline PET/CT and Tc 99m Sestamibi SPECT/CT parathyroid imaging are needed for more robust results.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Greenspan B, Dillehay G, Intenzo C, Lavely W, O'Doherty M, Palestro C et al. SNM Practice Guideline for Parathyroid Scintigraphy 4.0. Journal of Nuclear Medicine Technology. 2012;40(2):111-118.
2. De Francisco A. Secondary hyperparathyroidism: Review of the disease and its treatment. Clinical Therapeutics. 2004;26(12):1976-1993.
3. Ziessman H, O'Malley J, Thrall J, Fahey F. Nuclear medicine. Philadelphia, PA: Elsevier/Mosby; 2014.
4. Mettler F, Mettler F, Guiberteau M. Essentials of nuclear medicine and molecular imaging. 7th ed. 2019.
5. Huber G, Hüllner M, Schmid C, Brunner A, Sah B, Vetter D et al. Benefit of 18F-fluorocholine PET imaging in parathyroid surgery. European Radiology. 2018;28 (6):2700-2707.
6. Beheshti M, Hehenwarter L, Paymani Z, Rendl G, Imamovic L, Rettenbacher R et al. 18F-Fluorocholine PET/CT in the assessment of primary hyperparathyroidism compared with 99mTc-MIBI or 99mTc-tetrofosmin SPECT/CT: a prospective dual-centre study in 100 patients. European Journal of Nuclear Medicine and Molecular Imaging. 2018;45(10):1762-1771.
7. Thanseer N, Bhadada S, Sood A, Mittal B, Behera A, Gorla A et al. Comparative Effectiveness of Ultrasonography, 99mTc-Sestamibi, and 18F-Fluorocholine PET/CT in Detecting Parathyroid Adenomas in Patients With Primary Hyperparathyroidism. Clinical Nuclear Medicine. 2017;42 (12):e491-e497.
8. Orevi M, Freedman N, Mishani E, Bocher M, Jacobson O, Krausz Y. Localization of Parathyroid Adenoma by 11C - Choline PET/CT. Clinical Nuclear Medicine. 2014;39 (12):1033-1038.
9. Treglia G, Piccardo A, Imperiale A, Strobel K, Kaufmann P, Prior J et al. Diagnostic performance of choline PET for detection of hyperfunctioning parathyroid glands in hyperparathyroidism: a systematic review and meta-analysis. European Journal of Nuclear Medicine and Molecular Imaging. 2018;46(3):751-765.