Diagnostic performance of dual phase ^{99m}Tc-MIBI planar and SPECT/CT scintigraphy in primary hyperparathyroidism

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Abstract:

Background: Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by excessive parathyroid hormone secretion, resulting in hypercalcemia. For the reason that Para-thyroidectomy (PTx) is the most effective treatment for PHPT, precise preoperative localization of the abnormal parathyroid gland(s) is required.

Aim: The purpose of this study was to assess the diagnostic performance of ^{99m}Tc-MIBI SPECT/CT scintigraphy in the management of patients with suspected parathyroid adenoma/hyperplasia.

Patients and Methods: Thirty patients were prospectively imaged using ^{99m}Tc-MIBI dual phase scan. Early (15 min. after I.V tracer injection) and delayed (120 min. after I.V tracer injection) images were obtained. SPECT/CT images were obtained at both imaging time points. Additionally, ^{99m}Tc-pertechntate was done after delayed imaging. We relied upon the clinical/imaging validation and histopathology whenever available as the gold standard.

Results: Twenty two females and 8 males with a mean age of 29 ± 14.3 years (range; 5-55 years) were enrolled in this study. On a per patient basis, 11 subjects were positive for one or more parathyroid lesions while the remaining 19 proved negative. Out of the 11 positive cases, nine had single adenoma (3 were right inferior, 1 was right superior, 2 were left superior, 2 were left inferior and 1 was ectopic in the mediastinum); one had two adenomas and the other had three adenomas. Early planar imaging detected 8 true positive and 19 true negative cases, giving sensitivity of 72.7% and specificity of 100%. Delayed planar imaging identified 9 and 19 true positive and true negative lesions respectively, giving sensitivity of 81.8% and specificity of 100%. Both early and delayed SPECT/CT imaging revealed 10 true positive and 17 true negative lesions yielding 100 sensitivity and specificity.

Conclusion: Hybrid SPECT/CT improves preoperative localization of parathyroid lesions, provides important additional clinical information especially in the setting of ectopic lesions, and shows slightly superior results compared to dual-phase planar imaging.

Key words: Hyperparathyroidism, Added value, SPECT/CT, MIBI scanning.

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Introduction:

Primary hyperparathyroidism (PHPT) is a common endocrine disorder with an estimated prevalence of about 0.23% among females and 0.085% among males; it is caused by abnormal increased secretion of parathyroid hormone, resulting in hypercalcemia. This disease is attributed in most of the cases (80–85%) to solitary parathyroid adenoma, followed by glandular hyperplasia in 10–15% of the cases, and double adenoma in 4% with malignancy accounts for only 1–3% of the cases[1-3].

Primary hyperparathyroidism is generally asymptomatic but it has the potential to become symptomatic, resulting in bone loss and renal stones[4].

Para-thyroidectomy (PTx) is a highly effective treatment for PHPT, especially in symptomatic patients, since it effectively increases bone mineral density (BMD) and hence reduces the risk of fracture and nephrolithiasis [5]. Although PHPT patients are always asymptomatic, PTx may be done on specific situations, including at least one of the following: firstly serum calcium concentrations > 1 mg/dL above the upper limit of normal, T-score ≤ − 2.5 assessed by dual-energy X-ray absorptiometry (DXA) or history of vertebral fracture, nephrocalcinosis or nephrolithiasis or creatinine clearance of < 60 mL/min/1.73 m2, urinary calcium excretion > 400 mg/24 h with a biochemical profile suggestive for increased nephrolithiasis risk, and lastly age < 50 years old[6,7].

Preoperative localization of abnormal parathyroid gland(s) is mandatory, since primary hyperparathyroidism is increasingly being diagnosed in a subclinical or even asymptomatic stage of the disease [8]. Several imaging modalities have been used in the assessment of parathyroid adenomas, including neck ultrasound, CT, MRI, and hybrid functional imaging methods such as: ^{99m}Tc-MIBI- SPECT/CT parathyroid scintigraphy, with detection rates ranging from 84 to 88% [9-11].

Ultrasonography (US) of the neck is a simple, non-invasive tool with high sensitivity that is routinely done in all patients with clinical or biochemical disease. Although radionuclide parathyroid imaging plays a crucial role, mainly due to its ability to detect multiple abnormal glands and ectopic ones; yet, its validity is questioned by challenges including: the small weight /size of the normal parathyroid glands and the frequently deep-seated location in the thyroid gland, which has a much greater mass and a higher metabolic activity[12].

The rational for MIBI scintigraphy is that this radiotracer is localized in the parathyroid gland as well as in the functioning thyroid tissue but usually washes out from the normal thyroid quicker than from abnormal parathyroid tissue[13].

The use of hybrid SPECT/CT gamma cameras yields functional 3D- data as well as anatomical information by the CT component. The use of positron emission tomography (PET) imaging is more advantageous than SPECT imaging because of its ability to localize mediastinal adenoma(s). Moreover, high-energy gamma (511 keV) rays are less attenuated by the bony thorax than by the 140 keV gamma rays emitted by ^{99m}Tc tracers [14].

The aim of the current study was to evaluate the role of SPECT/CT as a localization tool in the management of patients with suspected parathyroid adenoma/hyperplasia.

Patients and Methodology:

Following approval by the local institutional committee of medical ethics and obtaining informed consent from all patients, thirty patients diagnosed as primary parathyroid hyper-functioning diseases, with elevated parathormone (PTH) and and/or abnormal serum calcium level, were recruited in this prospective study. Patients with normal/ low PTH level and those with definitely secondary or tertiary hyperparathyroidism were excluded.

All patients underwent complete medical history, complete physical examination, neck ultrasonography and nuclear medicine studies in form of isotope thyroid scan and MIBI scanning. Laboratory investigations (including PTH, calcium, phosphorus, alkaline phosphatase (ALP) and thyroid hormones levels) were included in the study analysis whenever available.

A-^{99m}Tc-MIBI:

The range of intravenously administered radioactivity is 555–925 MBq (15–25 mCi); the dose is adjusted for children according to the EANM pediatric guidelines [15].

1- Planar images of the neck and upper chest were obtained approximately at 15 (Early) and 120 min (Delayed) after injection of the tracer, using a large-field-of-view dual head gamma camera with a mounted CT scanner (SymbiaT; Siemens Medical Systems) that is fitted with a high-resolution low-energy parallel-hole collimator. In some cases with history of bony fractures, whole body MIBI planar imaging was done immediately after early static image or delayed static image.

2- SPECT/CT images were obtained at the two imaging time points for all patients except for 3 cases who did not have SPECT/CT (2 were young aged and that was difficult in imaging; and the 3rd was 55 years old who could not lie comfortably for the whole duration of the scanning). SPECT and CT images were obtained over a 360° arc, using 64 frames at 25 s per frame. The images were acquired using 128 x 128 matrix and reconstructed using iterative protocol "4 iterations, 4 subsets, and Gaussian filter 8". The CT part was acquired at a 1 mm slice thickness, a current of 70-80 mA, and a voltage of 130 kV and no contrast media was used. The total SPECT/CT acquisition took about 30 min. After finishing SPECT/CT, both at early and delayed acquisition, static anterior neck and chest images were obtained using a 256 x 256 matrix -10 minutes each. The acquired image sets were optimally displayed as CT, SPECT, and fused images reconstructed in 3 standard projections (axial, coronal, and sagittal).

B- ^{99m}Tc-Pertechnetate:

A dose of 370-640 MBq (10-20 mCi) of Pertechnetate is injected intravenously to delineate the thyroid gland; then, this image is subtracted from the ^{99m}Tcsestamibi image, and what remains is potentially a parathyroid adenoma.

Image analysis:

Visual analysis was done by a 5-point scoring system for analyzing the different thyroid lesions whereby score 0 = definitely negative; score 1 = uptake related to other causes (muscle, fat, thyroid nodule or brown's tumor) clarified by SPECT/CT images; score 2 = equivocal (cannot be recognized by planar and SPECT/CT images); score 3 = probably adenoma; score 4 = definitely adenoma (positive), eventually score more than 1 was considered positive for parathyroid lesion.

Additionally the sites of uptake at thyroid bed region were categorized as right, left, superior and inferior.

Reference standard:

Subsequent Clinical/imaging validation and histopathology - whenever available - were considered as the gold standard. A lesion was considered as true positive, if ^{99m}Tc-MIBI scan was positive; subsequent follow up imaging was positive for parathyroid lesion and accompanied by clinical worsening of the patient's condition or if histopathology revealed hyperplasia/adenoma. A lesion was considered true negative if ^{99m}Tc-MIBI scan was negative; subsequent follow up imaging was negative for parathyroid lesion, and accompanied by improvement of the patient's clinical condition.

Statistical analysis:

SPSS 20.0 software and MedCalc 11 were used in the analysis. Diagnostic performance parameters in the form of sensitivity, specificity, accuracy, positive predictive value and negative predictive value were calculated. True negative, true positive, false negative and false positive results were identified on the basis of subsequent clinical/imaging validation. The nonparametric McNemar test was used to evaluate the statistical significance of the differences in sensitivity and specificity (P <0.05 was considered significant). Quantitative data were expressed as mean+/- SD and median (range), whereas qualitative data were expressed as frequencies and percentages.

Results:

Patients:

Thirty patients were valid for inclusion in our study (Twenty two females and 8 males), with mean age; 29 ± 14.3 years (range; 5-55 years). We had 5 patients less than 18 years old. Only 3 patients had positive family history. Five out of the 30 patients had previous history of fracture.

All patients continued follow up for a mean duration of 12 + 6 months after our study, 12 of them underwent surgery and histo-pathological examination, 8 were re-evaluated by CT six months later and the rest 10 patients re-evaluated clinically and laboratory twice (6 months and 1 year later). According to the final follow-up status, 11 and 19 patients were respectively positive and negative for parathyroid lesion. Out of the 11 positive cases, 9 had single adenoma (3 were right inferior, 1 was right superior, 2 were left superior, 2 were left inferior and 1 was ectopic in the mediastinum), one had two adenomas and the other one had three adenomas.

The mean value of PTH level was significantly higher in positive cases than negative ones (1116.29+707.14 vs. 207.22+155.27 with P-value <0.001).

Relation of PTH level with the final diagnosis:

ROC analysis was done for PTH level according to final status and identified area under the curve (AUC) of 0.893 with the best predictive cut-off value > 552.8 pg/ml. This point demonstrated high accuracy of 93.3% with specificity of 100% and sensitivity of 81.82%. Its PPV was 100% and NPV was 89.5% (P value < 0.001). Figure 1

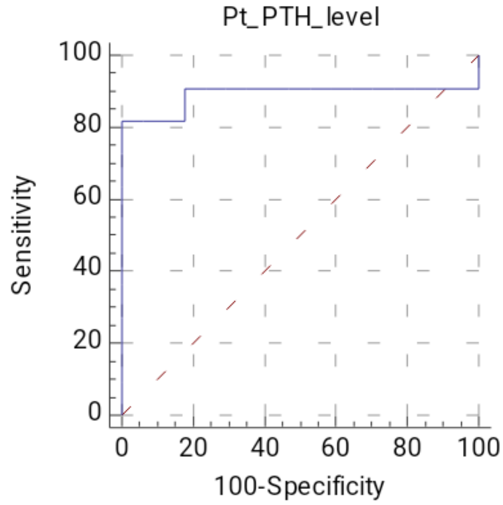


Figure 1: ROC curve of PTH level according to final status

Relation of other investigations (Ca, ALP and phosphorus) with the final diagnosis:

Among positive patients, 3 cases had normal calcium and another 3 cases had low calcium; 4 cases had high ALP and 3 cases had normal phosphorus. On the other hand, in negative patients, most of them (12) had low calcium, 5 cases had high ALP and 3 cases had high phosphorus level. The difference in phosphorus level was marginally significant (P = 0.047). Table 1

Diagnostic performance of planar imaging:

Delayed planar images only, when scored > 1, gave accuracy of 93%, that is only 3% higher than the accuracy obtained from the same score (>1) in the early planar images Figure 2.

Early planar imaging detected 8 true positive and 19 true negative cases, with 3 false negative cases giving sensitivity of 72.7 and specificity of 100%.

Delayed planar imaging identified 9 and 21 true positive and true negative lesions respectively, decreasing the number of false negative to only 2 cases giving sensitivity of 81.8% and specificity of 100%.

Additional thyroid scan, performed after delayed imaging, was deemed useful in (3/30) patients by confirming presence of thyroid lesion as functioning adenoma (n=1), cold nodule (n = 1) and Graves' disease (n = 1).

Diagnostic performance of SPECT/CT imaging:

Both early and delayed SPECT/CT imaging identified 10 true positive and 17 true negative lesions, with no false negative results detected giving sensitivity and specificity of 100%. Table 2 SPECT/CT images confirmed all the lesions seen in the planar images and overcome the false negative cases of planar imaging (3 cases in early planar and 2 cases in delayed planar) by confirming the presence of small adenomas in CT images with faint uptake. Furthermore, SPECT/CT provided significant additional information over planar imaging in 6 patients, either positive or negative results. Also it identifies the actual site as either in the thyroid gland (intra-thyroid nodule or toxic thyroid adenoma or goiter), around the thyroid gland as (ectopic parathyroid gland) or early washout occur in delayed planar image.

ROC analysis was done for early and delayed SPECT scores according to final status identified AUC of 1.00 with overall accuracy, specificity and sensitivity equal 100%. No significant difference was found between early and delayed SPECT. Figure 3

Difference between planar and SPECT/CT findings:

McNemar test was used to evaluate difference between early and delayed planar, early and delayed SPECT/CT, early planar and early SPECT, delayed planar and delayed SPECT according to their true positivity, true negativity, false positivity and false negativity. Early and delayed planar imaging agreed in 8 positive and 21 negative lesions and disagreed in one case. Table 3

Both early and delayed SPECT/CT imaging showed agreement in all positive and negative cases. Table 4

Early planar and SPECT/CT imaging showed agreement in 7 positive lesions and 17 negative lesions and showed disagreement in 3 cases. Table 5

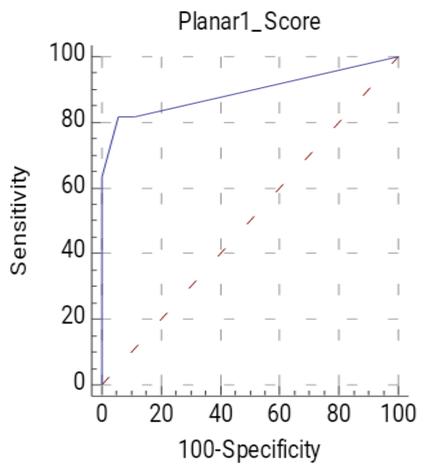
Delayed planar and delayed SPECT/CT imaging showed agreement in 8 positive and 17 negative cases with 2 different readings. Table 6

Table 1: Comparison between positive and negative cases according to calcium, ALP and Phosphorus:

	Final diagnosis		P. value
	Positive (n=11) No. (%)	Negative (n=19) No. (%)	
Calcium result			
Normal	3(42.9%)	4(25%)	0.168
High	1(14.3%)	0	
Low	3(42.9%)	12(75%)	
Total	7(63.6%)	16(84.2%)	
ALP result			
Normal	0	2(28.6%)	0.237
High	4(100%)	5(71.4%)	
Total	4(36.4%)	7(36.8%)	
phosphorus result			
Normal	3(100%)	1(25%)	0.047*
High	0	3(75%)	
Total	3(27.3%)	4(21.1%)	

*Chi-square test.

(A)



(B)

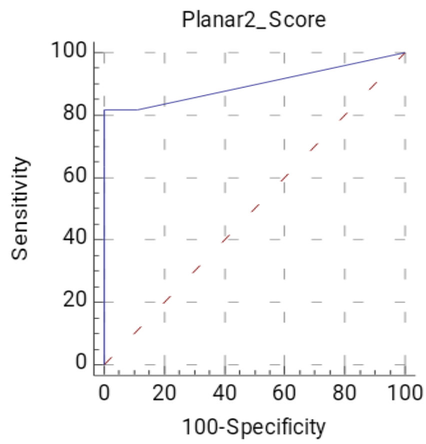


Figure 2: ROC curve for final status according to early planar score (A) and delayed planar score (B)

Table 2: Diagnostic performance of planar and SPECT/CT imaging

	PTH level	Early Planar	Delayed Planar	Early SPECT	Delayed SPECT
AUC	0.893	0.894	0.899	1.00	1.00
Cutoff	>552.8 pg/ml	Score >1	Score >1	Score >1	Score >1
Sensitivity	81.82%	72.7 %	81.82%	100%	100%
Specificity	100%	100%	100%	100%	100%
PPV	100%	100%	100%	100%	100%
NPV	89%	86.4 %	90%	100%	100%
Accuracy	93.3%	90%	93.3%	100%	100%
P. value	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**

AUC: Area under the curve, PPV; positive predictive value, NPV; negative predictive value, ** statistically significant difference.

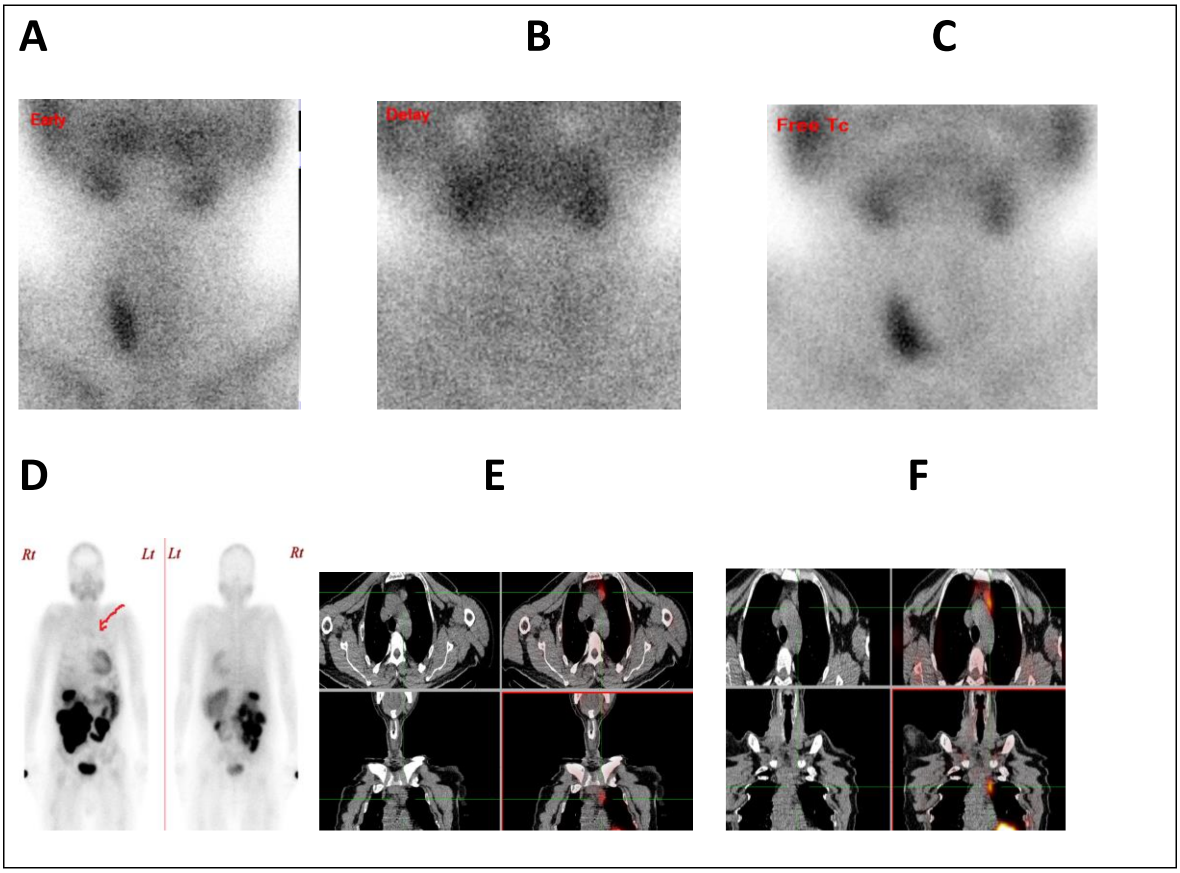


Figure 3: Male patient, 37 years old with hyperparathyroidism, PTH level was 1000 pg/ml, previous history of hemi-thyroidectomy. (A): Planar static view of the neck and upper chest in anterior projection, the early image shows rather uniform tracer uptake in average sized right thyroid lobe. (B): The delayed image shows complete washout of the tracer from the thyroid area with no persistence of MIBI tracer at the expected parathyroid glands sites or other ectopic sites. (C): Technetium scan shows uniform tracer uptake at the right thyroid lobe with no nodules or adenomas detected. (D): Whole body MIBI planar view in anterior and posterior projection shows normal distribution of MIBI tracer in the body with abnormal focal uptake seen in the upper mediastinum. (E): Early SPECT/CT images show faint uptake in the upper mediastinum related to the aortic arch most probably related to ectopic parathyroid adenoma. (F): Delayed SPECT/CT images show persistence of focal intense uptake at the same lesion. The patient underwent surgical excision and histo-pathological examination that revealed parathyroid adenoma.

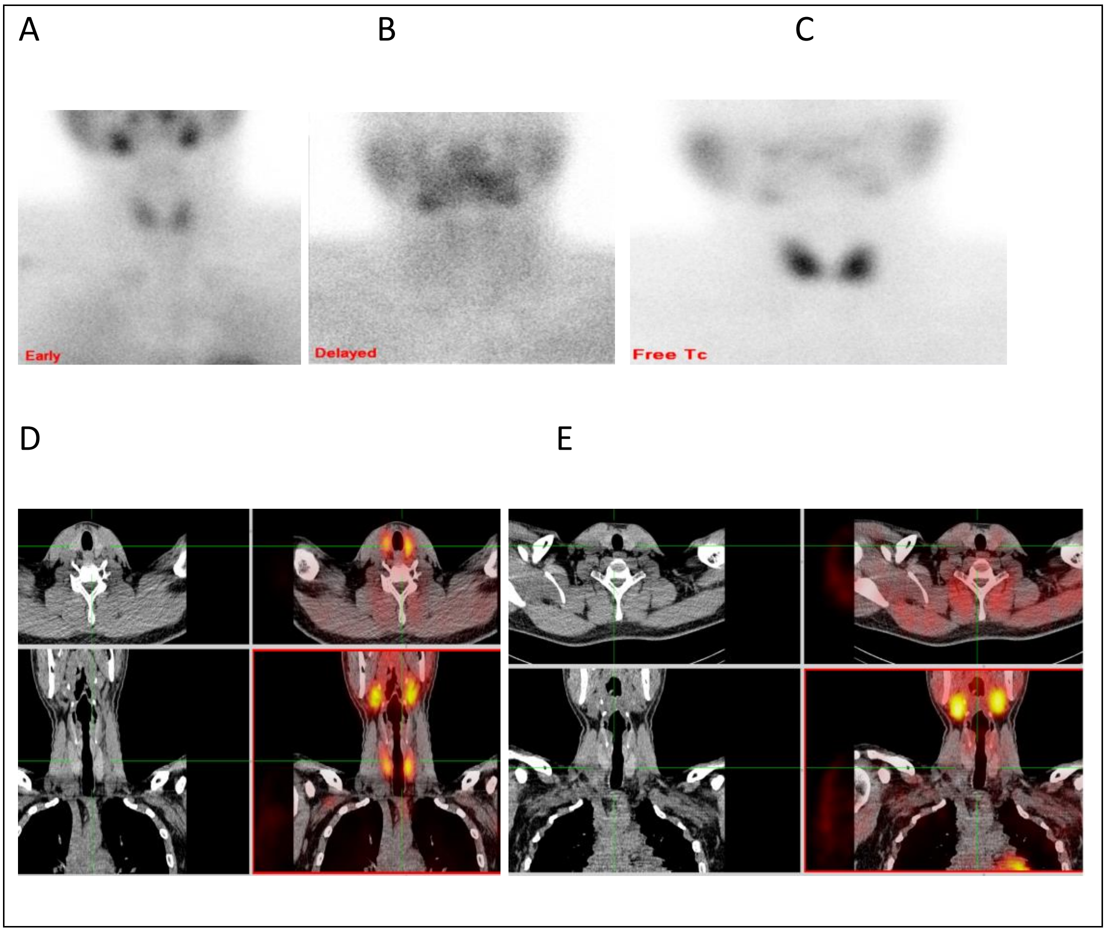


Figure 4: Male patient, 23 years old with hyperparathyroidism. (A): Planar static view of the neck and upper chest in anterior projection, the early image shows uniform tracer uptake at thyroid gland. (B): The delayed image shows complete washout of MIBI tracer from the thyroid gland with no focal retention at the expected parathyroid glands or other ectopic sites. (C): Technetium scan shows uniform tracer uptake at both thyroid lobes with no nodules or adenomas detected. (D): Early SPECT/CT images show uniform tracer uptake at thyroid gland. (E): Delayed SPECT/CT images show complete washout of tracer from thyroid gland with no parathyroid adenomas seen in its normal site or ectopic sites. Clinical and laboratory follow up of the patient 6 and 12 months later revealed improvement of the symptoms and laboratory findings.

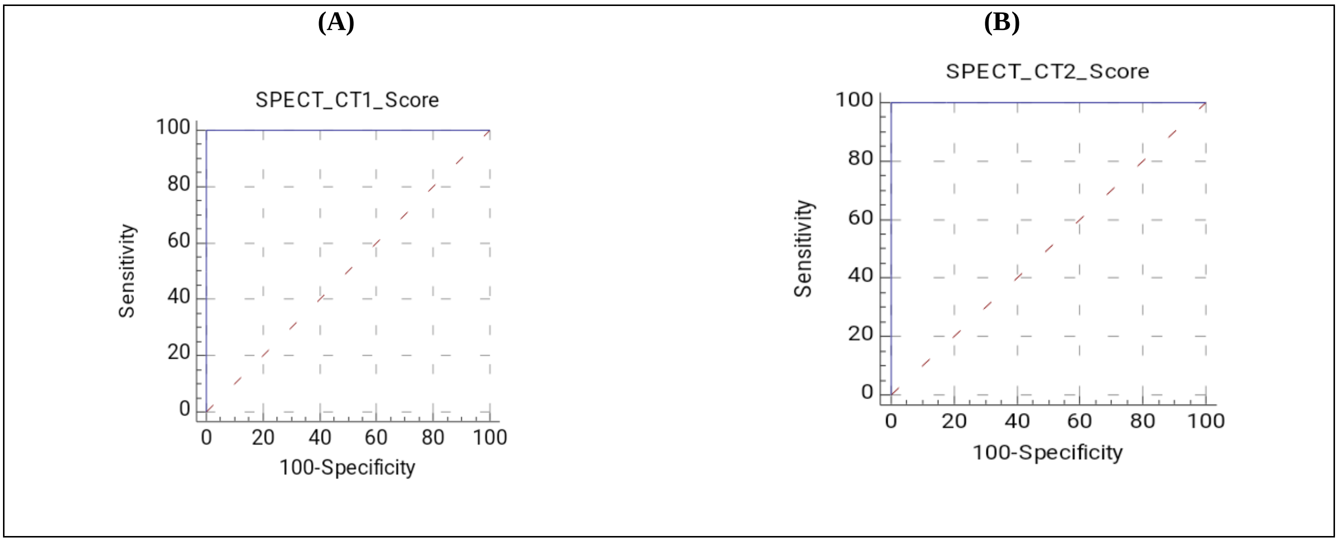


Figure 5: ROC curve for final status according to early SPECT score (A) and delayed SPECT score (B)

Table 3: Difference between early planar and delayed planar

		Early Planar		McNemar		
		Positive	**Negative**	**Difference**	**95% CI**	**P. value**
Delayed Planar	**Positive**	8	1	3.57%	-3.4: 3.6	1.000
	Negative	0	21			

Table 4: Difference between early SPECT and delayed SPECT

		Early SPECT		McNemar		
		Positive	**Negative**	**Difference**	**95% CI**	**P. value**
Delayed SPECT	**Positive**	10	0	-	-	-
	Negative	0	17			

Table 5: Difference between early planar and early SPECT

		Early Planar		McNemar		
		Positive	**Negative**	**Difference**	**95% CI**	**P. value**
Early SPECT	**Positive**	7	3	7.41%	-5.1:7.41	0.500
	Negative	0	17			

Table 6: Difference between delayed planar and delayed SPECT

		Delayed Planar		McNemar		
		Positive	**Negative**	**Difference**	**95% CI**	**P. value**
Delayed SPECT	**Positive**	8	2	11.11%	-4.6:11.1	0.25
	Negative	0	17			

Discussion:

Since the advent of laboratory screening and imaging techniques, hyperparathyroidism is detected with increasing frequency. It is estimated that over 85% of the diagnosed cases are asymptomatic or oligosymptomatic (nonspecific symptoms as depression, fatigue and/or lethargy). The classic description of musculoskeletal pain, fatigue, polyuria, nocturia, polydipsia, constipation, heartburn, memory loss, and depression are now infrequently encountered[4].

It is important to precisely localize the abnormal parathyroid gland(s) in patients with PHPT prior to surgery. In this setting, ^{99m}Tc-MIBI SPECT and particularly ^{99m}Tc-MIBI SPECT/CT may be the optimal choice[16].

Hybrid functional imaging, using ^{99m}Tc-MIBI-SPECT/CT parathyroid, scintigraphy proved useful in preoperative localization of the parathyroid pathology with detection rates ranging from 84 to 88% [9-11]. Christakis et al., concluded that ^{99m}Tc-MIBI was superior to US and CT[17].

In this study, direct comparison of the two scintigraphic techniques, for detection of parathyroid lesions, was performed. SPECT/CT showed a slightly higher sensitivity and accuracy compared to planar imaging, alone; nonetheless, the difference was not statistically significant.

Limitations of planar imaging in this study included early washout of suspicious adenoma, inadequate anatomical localization, presence of thyroid pathology, and presence of ectopic mediastinal parathyroid adenoma; so, we encountered 3 false negative cases. This study also emphasized the added value of ^{99m}Tc-pertechnetate thyroid scan in 3 patients with intra-thyroidal nodules that retain ^{99m}Tc-MIBI causing false positive results.

SPECT/CT overcame the above mentioned limitations of planar imaging by confirming the presence of functioning parathyroid adenoma either at its normal or ectopic sites, and successfully differentiated between parathyroid and thyroid lesions such as functioning adenoma or thyroid nodules, with adequate anatomical localization of its exact site. It worth noting that some of the positive lesions, that seen only on SPECT/CT imaging, were retrospectively seen in planar images.

SPECT/CT also added significant information in (6/30) patients. In the first case, the patient had history of sub-total thyroidectomy, and the early images showed two areas of focal increased MIBI uptake. Washout of these two foci was seen in delayed images with detection of another separate focus in a new site. SPECT/CT confirmed the presence of three adenomas.

In two more cases, early static images showed normal thyroid gland with no abnormal tracer retention in delayed images. Thyroid scan was also unremarkable. SPECT/CT showed left inferior parathyroid adenoma in first case and right inferior parathyroid adenoma in second case. Both demonstrated faint tracer uptake seen in early SPECT images. Retrospective revision of early planar images showed faint uptake related to the lower pole of left and right thyroid lobes, respectively.

The fourth case had history of hemi-thyroidectomy. Early image showed diffuse MIBI uptake at right thyroid lobe with no abnormality in delayed images. Additional thyroid scan also showed diffuse pertechnetate uptake at right thyroid lobe similar to the early MIBI images. SPECT/CT showed upper mediastinal ectopic parathyroid adenoma that was masked by normal cardiac activity of MIBI tracer.

In the fifth and six cases, SPECT/CT excluded the diagnosis of parathyroid lesion by localizing the tracer retention to a functioning thyroid adenoma and intrathyroidal nodule; respectively.

The sensitivity of early and delayed planar imaging were 72.7 % and 81.8% respectively, while those for SPECT/CT was 100% for both early and delayed imaging. These figures are higher than those by Zhang et al, who found 76.67%, sensitivity for dual-phase ^{99m}Tc-MIBI scintigraphy, 98.33% for early and 98.33% for delayed ^{99m}Tc-MIBI SPECT/CT [18].

The studies comparing SPECT versus planar imaging showed variable results. Several studies have reported higher sensitivity for SPECT than for planar imaging, which comes in agreement with our results. Most of the studies reported a statistically significant difference in lesion detection [19-21].

On the other hand, few studies found no added advantage for SPECT over planar imaging, except in patients with ectopic parathyroid glands[22, 23].

SPECT is often acquired at a single time interval, either early or delayed. With early SPECT, several studies had reported a high sensitivity (96%)[19,24] which is parallel to our study that is 100%. Using delayed SPECT/CT, Kim et al. reported 100 % sensitivity and specificity [25] that is in line with ours. Our results did not show a statistically significant difference between early and delayed SPECT/CT due to multiple problems that face us in delayed SPECT - early washout of MIBI tracer or presence of very small adenoma that didn't retain MIBI adequately.

Limitations of this study included the inclusion of small group of patients with no surgical validation of all the results and even no enough surgical notes for the patients who underwent surgery. The follow-up of non-surgery patients was not optimum and their exact clinical management was not clear enough. The point of strength included the direct comparison of the current commonly employed scintigraphic techniques using a hybrid SPECT/CT machine.

Conclusion:

Hybrid SPECT/CT combines the 3-dimensional functional information of SPECT as well as the anatomic information of CT component, thereby improving preoperative localization. SPECT/CT shows slightly superior results compared to dual-phase planar imaging and provided important clinical information in parathyroid lesion detection. Future prospective trials with larger sample size and employing histopathology after surgical excision as the gold standard are warranted to further clarify the exact clinical role and impact on patient management of these results.

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