The Accuracy of 99m Tc-MIBI Scintigraphy for Preoperative Parathyroid Localization in Primary and Secondary-Tertiary Hyperparathyroidism

Yuthana Saengsuda MD*

** Division of Nuclear Medicine, Department of Radiology, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand*

Objective: *The aim of the present study was to assess the accuracy of preoperative parathyroid localization using double phase planar 99mTc-methoxyisobutylisonitrile parathyroid scintigraphy (MIBI scintigraphy) in patients with primary hyperparathyroidism (pHPT) and secondary-tertiary hyperparathyroidism (stHPT) due to chronic renal failure.*

Material and Method: *A retrospective study was conducted. Between 1995 and 2010, seventy-one patients with hyperparathyroidism (mean age 47 $\pm$ 15 years; range 14-84 years) underwent neck surgery; 18 with pHPT and 53 with stHPT. None of these patients had undergone previous neck surgery. Preoperative demographics, clinical and laboratory values, MIBI scintigraphy, operative findings, location, size and histopathological results of all abnormal parathyroid glands were recorded.*

Results: *The abnormal parathyroid gland excised from 18 pHPT patients included 11 solitary adenoma (61%), 5 carcinoma (28%), 1 patient with single gland hyperplasia (6%) and 1 patient with two gland hyperplasia (6%). MIBI scintigraphy correctly laterized and localized 17 of 19 abnormal parathyroid glands with sensitivity 90%, specificity 100%, positive predictive value (PPV) 100% and accuracy 97.2%. The abnormal parathyroid glands excised from 53 stHPT patients included 48 patients with multiple hyperplasia (91%), 1 patient with single hyperplasia (2%), 1 patient with solitary adenoma (2%) and 3 patients with multiple adenomas (6%). MIBI scintigraphy correctly lateralized 116 of 173 abnormal parathyroid glands with sensitivity 67.1%, specificity 92.3%, positive predictive value (PPV) 97.5% and accuracy 71.7%. Precise localization occurred in 63.6% of the abnormal parathyroid glands. Significant differences were found with respect to age, intact parathyroid hormone, serum calcium, phosphorus, BUN levels between the pHPT and stHPT ($p < 0.001$). The average size of abnormal parathyroid glands in pHPT (2.28 $\pm$ 1.05 cm) was greater than that of stHPT (1.56 $\pm$ 0.58 cm) with significant difference ($p < 0.001$). Surgical parathyroid size were significantly greater in MIBI true-positive glands (1.79 $\pm$ 0.68 cm) compared to MIBI-false negative glands (1.29 $\pm$ 0.52 cm) with significant difference ($p < 0.001$).*

Conclusion: *MIBI scintigraphy is very sensitive and highly accurate for pre-operative localization of parathyroid lesion in patients with pHPT. So, it was useful for surgeons as a guide in the preoperative localization for performing unilateral surgery to reduce operating time and morbidity. In stHPT, MIBI scintigraphy appears fair sensitive and is not yet accurate to detect all abnormal parathyroid glands in multiple hyperplasia. So, it is not an essential prerequisite before surgery.*

Keywords: *Parathyroid, Hyperparathyroidism, Primary hyperparathyroidism, Secondary hyperparathyroidism, Tertiary hyperparathyroidism, Adenoma, Hyperplasia, Tc-99m-MIBI scintigraphy, Localization, Neck exploration, Parathyroidectomy, Renal failure*

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Primary hyperparathyroidism (pHPT) is a relatively common disorder affecting one of every 1,000 adults. It is caused by increased secretion of parathyroid hormone (PTH), which results in hypercalcemia. Solitary adenoma is the leading cause in 85% followed by multiple adenomas, hyperplastic glands and very rarely carcinoma[1]. Secondary hyperparathyroidism (sHPT) usually seen in chronic renal failure is the result of a pathophysiologic response of the parathyroid glands to hypocalcemia to maintain calcium homeostasis. Tertiary hyperparathyroidism (tHPT) occurs when one or more hyperplastic glands in secondary hyperparathyroidism begin functioning autonomously,

Correspondence to:
Saengsuda Y, Division of Nuclear Medicine, Department of Radiology, Rajavithi Hospital, College of Medicine, Rangsit University, 2 Phyathai Road, Ratchathewi, Bangkok 10400, Thailand.
Phone: 08-9171-1209
E-mail: yuthanasae@yahoo.com

resulting in hypercalcemia[2]. So, sHPT and tHPT are included in uremic or renal hyperparathyroidism (stHPT). The only effective treatment for hyperparathyroidism is surgery. Preoperative imaging studies are frequently performed to identify and localize abnormal parathyroid glands for reduction in operative times, morbidity rates and increased surgical success rate[3]. Many imaging techniques have been used for the detection of abnormal parathyroid glands, including high resolution sonography, CT, arteriography, venous sampling and MRI[4]. Nuclear medicine imaging which relies on the difference of the cell's metabolic activity, can provide more useful information than other imaging techniques that depict the anatomic location. Previously the most commonly used scintigraphic approach has been a dual isotope procedure combining 201 Thallium with either 99mTc-pertechnetate or 123I sodium iodide. More recently, 99mTc-methoxyisobutylisonitrile (MIBI) has become a popular substitute for 201 Thallium in scintigraphic parathyroid localization studies and was first described for this use by Coakley et al[5]. Later Taillefer R et al[6] reported that double-phase technique using 99mTc-MIBI scintigraphy was very simple and sensitive in the detection of abnormal parathyroids with sensitivity 90%. Numerous imaging protocols were used with some controversy regarding the optimal techniques[7,8]. However, there is increasing acceptance among surgeons of the use of 99mTc-MIBI scintigraphy in the planning of first-time parathyroid exploration[1]. It has also been suggested that this procedure may reduce operating time and the frequency of reoperation, thereby reducing surgical morbidity[9]. Previous reports and meta-analysis studies of the literature mainly done in double phase technique 99mTc-MIBI scintigraphy for preoperative localization of hyperfunctioning parathyroid glands in primary hyperparathyroidism show sensitivities 68-95% and specificities 75-100% with positive predictive values of up to 100%, being further increased by using single-photon emission tomography (SPECT) especially for mediastinum, small tumors and ectopic lesions[10-13].

In secondary hyperparathyroidism, sensitivities seems to be lower ranging 50-80%[14-17]. In Rajavithi Hospital, double-phase 99mTc-MIBI planar parathyroid scintigraphy (MIBI scintigraphy) has been employed for the identification of functional parathyroid tissue in hyperparathyroidism since 1995. The aim of the present study was to assess the accuracy of MIBI scintigraphy as diagnostic imaging modalities for preoperative localization of hyperfunctioning parathyroid glands in pHPT and stHPT.

Material and Method

From January 1995 to November 2010, 165 consecutive patients with a diagnosis of hyperparathyroidism were referred for parathyroid scintigraphy. The present study focused on 71 patients (35 women and 36 men, mean age 47.01 $\pm$ 14.75 years; age range 14-84 years) with hyperparathyroidism underwent preoperative MIBI scintigraphy and surgical exploration at Rajavithi Hospital. Of these patients, 18 were pHPT (5 male 13 female, mean age 56.89 $\pm$ 17.75 years) and 53 with stHPT(31male 22 female,mean age 43.66 $\pm$ 12.03 years). Patients with hyperparathyroidism had been scheduled for surgery because of clinical indication and abnormal biochemical findings. All patients underwent bilateral surgical neck exploration at their first parathyroid surgical operation by experienced parathyroid surgeons. An attempt was made to find out all parathyroid glands. The appearance, size and location of each parathyroid gland was documented and histopathological examination was obtained. Preoperative and postoperative intact parathyroid hormone (PTH), serum calcium and phosphorus levels, BUN and creatinine were evaluated in each patient as normal ranges as 15-65 pg/mL, 8.4-10.2 mg/dL, 2.7-4.5 mg/dL, 5-20 mg/dL and 0.5-1.2 mg/dL respectively. Surgical success in each patient was defined by the identification of the hyperfunctioning parathyroid glands with significant reduction in PTH postoperatively. The present study was approved by Rajavithi Hospital Review Board.

Parathyroid scintigraphy

After 740 MBq 99mTc-MIBI intravenous injection, planar static images of the anterior view of the neck and upper chest were acquired in the supine position with a 256 x 256 matrix size at 20 min of early phase and 120-180 min of delayed phases. A gamma camera (Toshiba GCA-901A or GE Millennium) equipped with a low energy high resolution (LEHR) parallel hole collimators was used for image acquisition. In addition, all patients were submitted for clinical or ultrasound examination to verify the presence of thyroid nodules. Additional 99mTc-pertechnetate scan was performed in some cases of patients suspected of thyroid nodules.

Data analysis

MIBI scintigraphy was considered positive for adenoma, hyperplasia or carcinoma if one or more areas of tracer uptake were visualized either 20 min early images even if not evident on delayed images (hyperfunctioning parathyroid glands with early washout) or on 120-180 min late images due to progressive uptake increased over time as well as prolonged retention (delayed washout vs. thyroid MIBI uptake).

Statistical analysis

MIBI scintigraphy was considered for true positive, false negative, true negative and false positive using histology as the gold standard. When the histology confirmed to the region of abnormality from the images, the results were regarded as true positive. When the histologically confirmed lesion could not be detected on the imaging, false negative was indicated. When the histological results demonstrated normal parathyroid, thyroid lesion or lymph nodes, then it was regarded as false positive. Sensitivity and specificity were calculated on a per parathyroid gland basis. Normal parathyroid glands were considered as true negative for the calculation of specificity. Preoperative and postoperative intact PTH, serum calcium, phosphorus, BUN and creatinine levels and the difference between the longest diameter of the size of the true-positive and false-negative abnormal parathyroid glands, were compared by means of Student t test and Mann-Whitney U test. Data are also expressed as mean $\pm$ SD. Chi-square test was used for categorical data analysis and p-values of less than 0.05 were considered significant.

Results

Surgery

Seventy-one patients with sporadic pHPT or stHPT with parathyroid pathologies confirmed by biochemical measurements and imaging methods were referred for surgery. Bilateral surgical neck exploration was performed on each patient within 1 month of MIBI scintigraphy by experienced surgeons and abnormal parathyroid glands were found in all cases at surgery. In pHPT, only one gland parathyroidectomy was performed in 13 patients (72.3%), two-gland parathyroidectomy 4 patients (22.2%) and three-gland parathyroidectomy in 1 patient (5.6%). In stHPT, total parathyroidectomy with autotransplantation was performed in 33 patients (62.3%), three glands parathyroidectomy and 1/2 gland transplant in 12 patients (22.6%), two glands parathyroidectomy in 5 patients (9.4%) and one gland parathyroidectomy in 3 patients (5.7%). In addition, thyroid lobectomy was performed simultaneously if the patient had concomitant thyroid nodules. Concomitant thyroid diseases were found in 4/18 patients in pHPT (22.2%) and 13/53 patients in stHPT (24.5%), totally 17/71 patients in hyperparathyroidism (23.94%). Surgical success in each patient was defined by their significant reduction PTH postoperatively.

Histologic findings

Pathological results did not show significant correlation with sexes. Adenoma was more commonly seen in women (53%) and hyperplasia more commonly in men (54.9%). Carcinoma was more commonly seen in women (80%).

The histologic findings obtained in 18 patients with pHPT and 53 patients with stHPT are reported in Table 1.

In 18 patients of pHPT, diagnosis were single adenoma 11 patients (61.1%), carcinoma 5 patients (27.8%), single hyperplasia 1 patient (5.6%) and two gland hyperplasia 1 patient (5.6%). In 53 patients of sHPT, diagnosis were multiple hyperplasia 48 patients (90.6%), multiple adenoma 3 patients (5.7%) single hyperplasia 1 patient (1.9%) and single adenoma 1 patient (1.9%).

In pHPT, none of the 11 parathyroid adenoma was < 1 cm in maximum diameter, one was 1 cm and the remaining 10 were > 1 cm. The average size of parathyroid adenoma was 2.55 $\pm$ 1.1 cm (1-4.2 cm). For 5 carcinoma, all carcinoma were larger than 2 cm in

Table 1. Histologic Findings in 18 Patients with pHPT (19 lesions) and in 53 Patients with stHPT (173 lesions)

Histology	No. of lesions (%)	Maximum diameter range	Mean $\pm$ SD
pHPT			
Solidatary adenoma	11 (61.1)	1.0-4.2 cm	2.55 $\pm$ 1.10
Carcinoma	5 (27.8)	2.3-2.7 cm	2.54 $\pm$ 0.17
Hyperplastic glands	3 (11.1)	0.6-1.2 cm	0.80 $\pm$ 0.32
stHPT			
Adenomas	11 (5.8)	1.0-3.0 cm	1.80 $\pm$ 0.56
Hyperplastic glands	162 (94.2)	0.5-3.2 cm	1.55 $\pm$ 0.59

diameter. The average size was 2.54 ± 0.17 cm (2.3-2.7 cm). Three carcinoma were seen at right lower poles (RLP) 2.5, 2.5 and 2.7 cm. One gland was at left upper pole (LUP) 2.7 cm and another at left lower pole (LLP) 2.3 cm. Three hyperplastic glands in two patients were at LUP 0.6 cm + LLP 0.7 cm in the patient with two gland hyperplasia and 1.2 cm LUP for the patient with single hyperplasia. The average size of hyperplastic glands was 0.8 ± 0.32 cm (0.6-1.2). The most common site of the 19 abnormal parathyroid gland was at RLP 10 glands (52.6%), followed by LLP 5 glands (26.3%), LUP 3 glands (15.8%) and right upper pole (RUP) 1 gland (5.3%).

In stHPT, one of the 53 patients had a solitary adenoma 1.5 cm (1.9%) and three patients with multiple adenoma (5.7%) had 4,3,3 adenomas each. The average size of the adenomas were 1.80 ± 0.56 cm (1-3 cm). Twenty eight patients had 4 hyperplastic glands (52.8%). Eleven patients had 3 hyperplastic glands (20.8%), 7 patients had 2 (13.2%) and the remaining 3 patients had a single hyperplastic gland each (5.7%). Total hyperplastic glands were 162 glands (112 + 33 + 14 + 3 = 162 glands). Fifteen lesions (9.3%) of the hyperplastic glands were < 1 cm, 34 lesions (21.0%) were 1 cm and 113 lesions (69.8%) were > 1 cm. The average size of hyperplastic gland was 1.55 ± 0.59 cm (0.5-3.2 cm). The distribution site of 173 abnormal parathyroid glands were at RLP 47 glands (27.2%), LLP 45 glands (26 %), LUP 41 glands (23.7%) and RUP 40 glands (23.1%).

The size of the enlarged glands between pHPT (0.6-4.2 cm) and stHPT (0.5-3.2 cm) did reveal a significant difference (p < 0.001). The mean ± SD values were 2.28 ± 1.05 and 1.56 ± 0.58 cm for pHPT and stHPT, respectively.

In hyperparathyroidism, the size of the adenoma (1-4.2 cm) and hyperplasia (0.5-3.2 cm) did show a significant difference (p < 0.001). The mean ± SD values were 2.18 ± 0.93 and 1.53 ± 0.59 cm for adenoma and hyperplasia, respectively. The mean ± SD values for parathyroid carcinoma was 2.54 ± 0.17 cm (range 2.3-2.7 cm).

Biochemical Data

In pHPT, patients preoperative intact PTH concentration was 814.06 ± 756.46 pg/mL (124 to 3,212 pg/ml). The postoperative intact PTH concentration decreased significantly to 28.59 ± 20.14 pg/mL (p < 0.001). The preoperative serum calcium, phosphorus, BUN and creatinine levels were 14.45 ± 2.51 mg/dL, 2.49 ± 0.59 mg/dL, 24.71 ± 19.06 mg/dL and 1.44 ± 0.65 mg/dL respectively. Serum calcium postoperatively decreased significantly to 9.73 ± 1.12 mg/dL (p < 0.001). There was significant difference of intact PTH level (p < 0.05) between adenoma (622.91 ± 446.33 pg/mL) and carcinoma (1,615.75 ± 1,092.44 pg/mL) (data not shown).

In stHPT, patients intact PTH concentration were 1,653.68 ± 757.61 pg/mL (549.5-3842 pg/mL). Postoperative intact PTH concentration decreased significantly to 169.9 ± 235.06 pg/mL (p < 0.001). Preoperative serum calcium, phosphorus, BUN and creatinine levels were 10.66 ± 1.22 mg/dL, 5.97 ± 2.21 mg/dL, 54.28 ± 24.25 and 10.57 ± 14.22 mg/dL respectivitly. Postoperative serum calcium decreased significantly to 8.63 ± 1.81 mg/dL (p < 0.001) (data not shown). Additionally, significant differences were revealed with respect to age, intact PTH concentration, serum calcium phosphorus, BUN (Table 2) between pHPT and stHPT (p < 0.001) and for creatinine (p < 0.05).

Scintigraphic findings

The results of MIBI scintigraphy in pHPT patients are reported in Table 4.

In pHPT, MIBI scintigraphy were positive in

Table 2. Correlation of biochemical parameters , age and size by pathology

	pHPT n = 18	stHPT n = 53	p-value*
PTH (pg/ml)	814.06 ± 756.46	1,653.68 ± 757.61	< 0.001
Calcium (mg/dl)	14.45 ± 2.51	10.66 ± 1.22	< 0.001
Phosphorus (mg/dl)	2.49 ± 0.59	5.97 ± 2.21	< 0.001
BUN (mg/dl)	24.71 ± 19.06	54.28 ± 24.25	< 0.001
Creatinine (mg/dl)	1.44 ± 0.65	10.57 ± 14.22	< 0.011
Age (years)	56.89 ± 17.75	43.66 ± 12.03	< 0.001
Size (cm)	2.28 ± 1.05	1.56 ± 0.58	< 0.001

Values are represented as means ± SD
* Significant at p < 0.05

17 of 19 lesions: in all 5 carcinomas, in 10/11 adenomas (Fig. 1), in 2/3 hyperplastic glands. There was only 1 patient (5.9%) due to carcinoma with rapid washout of tracer from the abnormal gland detected by the early scan. The smallest true positive lesion size was 0.7 cm LLP in the patient with two gland hyperplasia. False negative results were found in 2 patients with one patient adenoma (RUP 1 cm) and one gland in two gland hyperplasia patient (LUP 0.6 cm). None of two patients had concomitant thyroid nodule. There were no false-positive lesions revealed. The sensitivity of parathyroid scintigraphy in pHPT was 89.5%, specificity 100%, PPV 100% and accuracy 97.2%.

The results of parathyroid scintigraphy in 53 stHPT patients are reported in Table 5.

In 53 stHPT patients, there were a total of 173 lesions identified (Fig. 2). One hundred and sixteen of the 173 surgically resected abnormal parathyroid lesions were correctly lateralized on the MIBI scintigraphy. The overall sensitivity was 67.1%. There were 6 abnormal parathyroid lesions that were correctly lateralized but their positions were not precisely localized to the correct quadrant compared with the surgically confirmed locations. Of those 6,3 superior hyperplastic glands were scintigraphicallly reported as inferior pole lesions. The remaining 3 were reported as upper pole lesions, although they proved to be lower pole lesions. Consequently, MIBI scintigraphy correctly identified and precisely localized 63.6%.

MIBI scintigraphy missed 57 lesions: 2 adenomas (3cmLUP, 2cmLUP) and 55 hyperplastic glands. The missed adenoma (3cmLUP) had concomitant thyroid nodules. The sensitivity for detection adenoma and hyperplasia were 81.8% and 66% respectively. The sensitivity of parathyroid scintigraphy in stHPT was 67.1%, specificity 92.3%,

Table 3. The correlation of calcium and size with PTH in pHPT and stHPT

	PTH	
	pHPT	stHPT
Calcium		
correlation coefficient (r)	0.259	-0.016
p-value	0.315	0.243
Size		
correlation coefficient (r)	0.391	0.119
p-value	0.109	0.128

PTH = parathyroid hormone

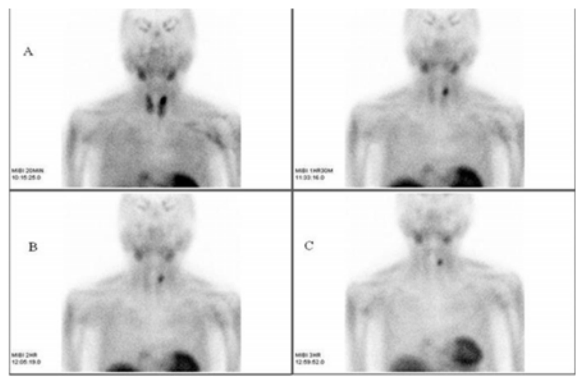

Fig. 1 70-y-old woman affected by pHPT (A) Early 99mTc-MIBI planar image shows uptake in the thyroid gland (B and C) Delayed images clearly reveal MIBI washout from the thyroid gland but delayed MIBI washout in a small 1.2 cm left superior parathyroid adenoma

Table 4. The sensitivity, specificity, accuracy and PPV of MIBI scintigraphy in pHPT

Parameter	MIBI scintigraphy		
	Overall (n = 19)	adenoma/carcinoma (n = 16)	Hyperplasia (n = 3)
True positive(TP)	17	15	2
False negative(FN)	2	1	1
Sensitivity(%)	89.5	93.8	66.7
False positive	0	0	0
PPV(%)	100	100	100
True negative (TN)	53	48	5
Specificity(%)	100	100	100
Accuracy (%)	97.2	98.4	87.5

MIBI = 99mTc-methoxyisobutylisonitrile

Table 5. The sensitivity, specificity, accuracy and PPV of MIBI scintigraphy in stHPT

Parameter	MIBI scintigraphy		
	Overall (n = 173)	adenoma (n = 11)	hyperplasia (n = 162)
True positive(TP)	116	9	107
False negative(FN)	57	2	55
Sensitivity(%)	67.1	81.8	66
True negative (TN)	36	5	31
False positive	3	0	3
PPV(%)	97.5	100	97.3
Specificity(%)	92.3	100	91.2
Accuracy (%)	71.7	87.5	70.4

MIBI = 99mTc- methoxyisobutylisonitrile

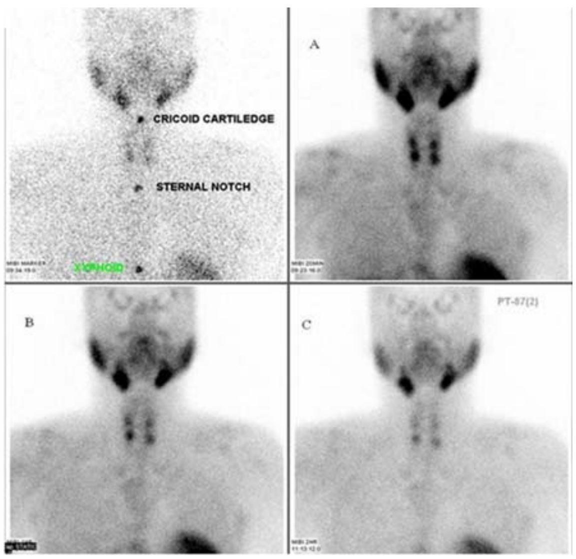

Fig. 2 60-y-old man with stHPT and without concomitant thyroid disease. (A) Early 99mTc-MIBI planar image shows 4 focal areas of MIBI uptake in the thyroid gland. (B and C) Delayed images still show delayed uptake of 4 hyperplastic parathyroid glands in multiple hyperplasia, 1.3, 1.3, 1.8, 2.6 cm

PPV 97.5% , accuracy 71.7%.

Three MIBI false-positive scintigraphy were identified. The 3 false positive scintigraphic lesions could be explained by high tracer accumulation in benign thyroid nodules and nodular goiter. No false positive due to lymph node, thyroid carcinoma, ectopic thyroid or thymus tissue is revealed. Eleven of the missed hyperplastic glands (55 glands) were < 10 mm in size (20%) and the remaining 44 glands (80%) were equal or > 10 mm in size. Seventy percent of the missed hyperplastic glands were sited behind the upper two thirds of thyroid. Of the 116 abnormal glands detected, only 3 lesions (2.6%) were seen from early images indicating rapid washout. For all 133 MIBI true positive scintigraphy in hyperparathyroidism, there were only 4 lesions (3%) seen in early images with rapid washout. Of the 22 adenomas in hyperparathyroidism, MIBI scintigraphhy detected 19 lesions with sensitivity 86.4%. The average size of the adenomas with positive MIBI were 2.21 $\pm$ 0.95 cm (1-4.2 cm) and false-negative MIBI 2.0 $\pm$ 1 cm (1-3cm). There was no significant difference of the size between the two groups (p = 0.733) (data not shown).

Of the 165 hyperplastic glands in hyperparathyroidism, MIBI scintigraphy detected 109 lesions. The sensitivity of MIBI scintigraphy was 66.1%. The average size of the 109 MIBI positive glands were 1.68 $\pm$ 0.59 cm (0.5-3.2 cm). The average size of the 56 MIBI false negative lesions were 1.25 $\pm$ 0.47 cm (0.6-2.5 cm) with significantly different between the two groups (p < 0.001) (data not shown).

Discussion

The author's findings revealed that adenoma was more common in women and hyperplasia more common in men even if no significant difference between sexes but in accordance with another report[14]. It is probably due to the relatively small size of the presented patients in pHPT.

High unusal prevalence of parathyroid carcinoma (27.7%) in pHPT of the present study was due to referral cases to our tertiary care hospital for surgical removal by parathyroid surgeon specialist as compared with less than 1% of cases in pHPT in another report[18].

In stHPT, there were 1 patient with single adenoma and 3 patients with multiple adenomas. These patients had high PTH (> 1,500 pg/mL) and high serum calcium level indicating the condition of tHPT.

In the present study, the authors did not collect the weight of the abnormal parathyroid gland but measured the longest diameter size. There were a wide variation of size which influenced the standard deviation in the present study. The size of the gland did not show a significant correlation with intact PTH in pHPT or stHPT (Table 3). The relation between the preoperative intact PTH levels and the size of the gland is variable and too inconsistent for clinical use[14,19]. In addition, serum calcium level did not reveal a significant correlation with intact PTH in pHPT or stHPT (Table 3).

It is already known that 99mTc-MIBI parathyroid scintigraphy, with its higher target to background ratio[20] is more effective for the localization of adenomas than thallium 201/99mTc subtraction scintigraphy in enlarged glands (> 1g) MIBI scintigraphy provides greater sensitivity than other imaging techniques, such as CT, MRI and US[21]. 99mTc-MIBI, first described for parathyroid scintigraphy by Coakley et al[5], is a sensitive agent in the preoperative identification of the functionally abnormal parathyroid gland. The exact mechanism for MIBI uptake in parathyroid glands is still unclear, but the oxyphil cell contents that are rich in mitochondria have been shown to correlate with MIBI uptake in parathyroid adenomas[22]. Taillefer R et al[6] proposed the double-phase technique of slower washout of 99mTc-MIBI from parathyroid adenomas relative to thyroid tissue and reported 19 of 21 parathyroid adenomas successfully detected with 90% sensitivity. However, early washout is defined as minimal or no retention of the radiotracer in the parathyroid gland on delayed images[9]. In addition, early washout from parathyroid adenomas and hyperplastic parathyroid glands has been reported by others[23,24]. In a series of 52 consecutive patients with primary hyperparathyroidism by Lorberboym M et al[8], delayed washout was noted in only 60% of the parathyroid adenoma. In the present study, the authors stated 3.0% MIBI positive scintigraphy with early washout in hyperparathyroidism with much less than the report by Lorberboym M et al[8]. Many investigators have shown the efficiency of MIBI scintigraphy in detection of abnormal parathyroid glands. In the present study, the sensitivity of MIBI scintigraphy in preoperative localization of hyperfunctioning parathyroid glands in pHPT was 89.5%, specificity 100%, PPV 100% and accuracy 97.2% consistent with previous reports and meta-analysis of the literatures of sensitivity 68-95%, specificity 100% and PPV 100%[10-13]. In sHPT, the sensitivity of MIBI scintigraphy was 67.1%, specificity 92.3%, PPV 97.5% and accuracy 71.7% which are comparable to other reports of sensitivity 50-80%[14-17]. The wide range of sensitivities for the MIBI scintigraphy in patients with hyperparathyroidism may be due to variation in technique, institution experience, patient population, proportion of ectopic glands, concomitant thyroid diseases and whether all patients underwent bilateral neck exploration to confirm imaging results.

Additionally, there are a wide range in reported sensitivities of MIBI scintigraphy for adenoma (58-100%) and hyperplasia (33-78%) in the literatures[25-28]. The present study showed consistent results of sensitivity 86.4% for adenoma and 66.1% for hyperplasia.

For adenoma, in pHPT, the sensitivity of MIBI scintigraphy in detection adenoma (10/11) was 91.7% with average size of the positive gland 2.71 $\pm$ 1.02 cm (1-4.2 cm). The smallest true positive gland size was 1.3 cm. The false negative gland size was 1 cm in diameter and without concomitant thyroid disease. So, size was one of the important factors in detection adenoma in pHPT in the present study. In stHPT, the sensitivity of MIBI scintigraphy in detection adenoma (9/11) was 81.8% with average size of the positive gland 1.8$\pm$0.56 cm (1-3 cm). The smallest true positive gland size was 1 cm in diameter but the 2 false negative gland size were 2 and 3 cm. The 3 cm false negative adenoma also had concomitant thyroid disease. So size is not the only factor in detection of adenoma in stHPT in the present study. Multifactors are involved in detecting adenoma in hyperparathyroidism such as size, the degree of cellularity, mitochondrial density, perfusion, function of glycoprotein, biochemical factor particularly in stHPT[27,28].

For hyperplasia, MIBI scintigraphy detected 109/165 lesions with sensitivity 66.1%. There were 56 false negative lesions. MIBI false-negative findings referred to glands with hyperplasia that are generally more difficult to identify than adenomas, as demonstrated by several authors using conventional planar imaging or SPECT procedures, irrespective of the radiotracer and the acquisition protocol used[29,30], with small size generally considered the most important limiting factor[31]. In pHPT, MIBI scintigraphy detected 2 of 3 lesions with sensitivity 66.7%. There were two patients with hyperplasia, one was single gland hyperplasia (true positive gland 2 cm) and the other two gland hyperplasia (one positive gland 0.7 cm and one false negative gland 0.6 cm). Only one patient (5.26%) of pHPT was demonstrated to have multiglandular disease (two gland hyperplasia) during bilateral neck exploration, which is consistent with reports of 4 to 20 percent[11,32]. The sensitivity of MIBI scintigraphy in detection abnormal parathyroid glands in multiglandular disease was 50% but it should be noticed that there were a small number of cases in pHPT in the present study. Katz SC et al[33] reported that none of the 13 patients with bilateral multiglandular disease were all abnormal glands localized preoperatively with MIBI scintigraphy and a minimally invasive approach such as unilateral exploration based on preoperative imaging studies may result in treatment failure in patients with multiglandular involvement. In stHPT, MIBI scan detected 107/162 lesions (sensitivity 66%) with 55 false negative lesions. It has been speculated that besides size, certain of the limiting factors could cause interference, since some hyperplastic glands smaller than those missed were detected on imaging. Consequently, biological factors[31], such as low proliferative cell activity and a low quantity of mitochondria, the over expression of P-glycoprotein or other multidrug-resistance proteins[34] could also be probable causes of false-negative findings in sHPT hyperplasia.

A metanalysis reveals that an average of only 29 percent of patients with multiglandular disease have all abnormal parathyroid tissue localized preoperative and that 53-67% of abnormal glands were detected[20,23,34]. In the present study, 32.6% of patients with multiglandular disease had all abnormal glands detected and that 66% of abnormal glands detected, which is consistent with the earlier reports[20,23]. Since size is one of the factors involving the detection of abnormal parathyroid glands in both pHPT and stHPT, the present study revealed that in hyperparathyroidism, size of the abnormal parathyroid glands showed significant differences between MIBI positive and false negative glands ($p < 0.001$). The mean $\pm$ SD values were 1.79 $\pm$ 0.68 cm (0.5-4.2 cm) for MIBI positive glands and 1.29 $\pm$ 0.52 cm (0.6-3.0 cm) for MIBI false negative glands. The present study is consistent with other authors who have suggested that a significant correlation exists between scintigraphic findings and the size/weight of the glands[35,36].

The reported prevalence of concomitant thyroid disease with hyperparathyroidism ranged between 22% to 70%[37,38] and it was 23.9% in the present study. The concomitant thyroid pathology significantly decreased detection rate of parathyroid lesions as described by other authors[39,40]. Thyroid nodular goiter can cause MIBI accumulation and obscure the parathyroid lesion leading to false-negative scintigraphy. It has lowered the sensitivity of planar MIBI images, but SPECT improved the results as reported by other studies[8]. In addition, the localization of abnormal parathyroid lesion with MIBI scintigraphy is based on the different clearance rates of the thyroid tissue and the abnormal parathyroid glands. So, limitation of the effectiveness of study will be caused by any condition that interferes the MIBI clearance rate[6]. Thyroid nodules may have a similar clearance rate to that of abnormal parathyroid glands and lead to false-positive scintigraphy[28]. In the present study,there were 3 false-positive lesions (in 3 patients) in stHPT because of benign thyroid nodules and nodular goiter. Although these three lesions were correctly localized on scintigrpahy, they were interpreted as false-positive for the detection of abnormal parathyroid glands. Other earlier reported conditions were papillary cancer, Hurthle cell cancer, enlarged paratracheal lymph nodes, ectopic thyroid and thymic tissues, technical factors in performing SPECT study such as patient motion and reconstruction artifacts[32].

Conclusion

MIBI scintigraphy is highly sensitive in the detection of abnormal parathyroid glands in pHPT. So, it is useful for surgeons as a guide in the preoperative localization for performing unilateral surgery. However, the sensitivity of MIBI scintigraphy for detection of multiglandular disease remains limited. So, surgical experience will never be replaced by imaging alone. However, MIBI scintigraphy enhances the the ability to perform rapid and safe surgery with good success and low morbidity rates.

In stHPT, MIBI scintigraphy is not yet accurate to detect all abnormal parathyroid glands. So, it is not an essential prerequisite before surgery but it can detect ectopic site of abnormal parathyroid glands. However, the combination of MIBI scintigraphy and expert surgeons will lead to a significant increase in the number of hyperplastic glands found at surgery and thus to the reduction of recurrences due to incomplete surgical treatment.

Study limitations

SPECT acquisition has not been obtained in the earlier cases of MIBI scintigraphy due to limitation of gamma camera. So, the authors considered only planar imaging for the whole group of patients although many reports had shown better advantages of SPECT over planar imaging(9,32,36).

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Potential conflicts of interest

None.

References

1. Nguyen BD. Parathyroid imaging with Tc-99m sestamibi planar and SPECT scintigraphy. Radiographics 1999; 19: 601-14.
2. Ben Hamida F, Ghazali A, Boudzernidj M, Amar M, Moriniere P, Westeel P, et al. [Hyperparathyroidism secondary to renal insufficiency. Physiopathology, clinicoradiological aspects and treatment]. Ann Endocrinol (Paris) 1994; 55: 147-58.
3. Chen H, Sokoll LJ, Udelsman R. Outpatient minimally invasive parathyroidectomy: a combination of sestamibi-SPECT localization, cervical block anesthesia, and intraoperative parathyroid hormone assay. Surgery 1999; 126: 1016-21.
4. Sharma J, Mazzaglia P, Milas M, Berber E, Schuster DM, Halkar R, et al. Radionuclide imaging for hyperparathyroidism (HPT): which is the best technetium-99m sestamibi modality? Surgery 2006; 140: 856-63.
5. Coakley AJ, Kettle AG, Wells CP, O'Doherty MJ, Collins RE. 99Tcm sestamibi—a new agent for parathyroid imaging. Nucl Med Commun 1989; 10: 791-4.
6. Taillefer R, Boucher Y, Potvin C, Lambert R. Detection and localization of parathyroid adenomas in patients with hyperparathyroidism using a single radionuclide imaging procedure with technetium-99m-sestamibi (double-phase study). J Nucl Med 1992; 33: 1801-7.
7. Gallowitsch HJ, Mikosch P, Kresnik E, Unterweger O, Lind P. Comparison between 99mTc-tetrofosmin/pertechnetate subtraction scintigraphy and 99mTc-tetrofosmin SPECT for preoperative localization of parathyroid adenoma in an endemic goiter area. Invest Radiol 2000; 35: 453-9.
8. Lorberboym M, Minski I, Macadziob S, Nikolov G, Schachter P. Incremental diagnostic value of preoperative 99mTc-MIBI SPECT in patients with a parathyroid adenoma. J Nucl Med 2003; 44: 904-8.
9. Casas AT, Burke GJ, Mansberger AR Jr, Wei JP. Impact of technetium-99m-sestamibi localization on operative time and success of operations for primary hyperparathyroidism. Am Surg 1994; 60: 12-6.
10. Moka D, Voth E, Dietlein M, Larena-Avellaneda A, Schicha H. Preoperative localization of parathyroid adenomas using 99mTc-MIBI scintigraphy. Am J Med 2000; 108: 733-6.
11. Kaczirek K, Prager G, Kienast O, Dobrozemsky G, Dudczak R, Niederle B, et al. Combined transmission and (99m)Tc-sestamibi emission tomography for localization of mediastinal parathyroid glands. Nuklearmedizin 2003; 42: 220-3.
12. Ishibashi M, Uchida M, Nishida H, Hiromatsu Y, Kohno K, Okuda S, et al. Pre-surgical localization of ectopic parathyroid glands using three-dimensional CT imaging, 99Tcm sestamibi, and 99Tcm tetrofosmin imaging. Br J Radiol 1999; 72: 296-300.
13. Ishibashi M, Nishida H, Hiromatsu Y, Kojima K, Tabuchi E, Hayabuchi N. Comparison of technetium-99m-MIBI, technetium-99m-tetrofosmin, ultrasound and MRI for localization of abnormal parathyroid glands. J Nucl Med 1998; 39: 320-4.
14. Sukan A, Reyhan M, Aydin M, Yapar AF, Sert Y, Canpolat T, et al. Preoperative evaluation of hyperparathyroidism: the role of dual-phase parathyroid scintigraphy and ultrasound imaging. Ann Nucl Med 2008; 22: 123-31.
15. Piga M, Bolasco P, Satta L, Altieri P, Loi G, Nicolosi A, et al. Double phase parathyroid technetium-99m-MIBI scintigraphy to identify functional autonomy in secondary hyperparathyroidism. J Nucl Med 1996; 37: 565-9.
16. Spanu A, Falchi A, Manca A, Marongiu P, Cossu A, Pisu N, et al. The usefulness of neck pinhole SPECT as a complementary tool to planar scintigraphy in primary and secondary hyperparathyroidism. J Nucl Med 2004; 45: 40-8.
17. Palestro CJ, Tomas MB, Tronco GG. Radionuclide imaging of the parathyroid glands. Semin Nucl Med 2005; 35: 266-76.
18. Kaplan EL, Yashiro T, Salti G. Primary hyperparathyroidism in the 1990s. Choice of surgical procedures for this disease. Ann Surg 1992; 215: 300-17.
19. Rutledge R, Stiegel M, Thomas CG Jr, Wild RE. The relation of serum calcium and

immunoparathormone levels to parathyroid size and weight in primary hyperparathyroidism. Surgery 1985; 98: 1107-12.
20. O'Doherty MJ, Kettle AG, Wells P, Collins RE, Coakley AJ. Parathyroid imaging with technetium-99m-sestamibi: preoperative localization and tissue uptake studies. J Nucl Med 1992; 33: 313-8.
21. Wakamatsu H, Noguchi S, Yamashita H, Yamashita H, Tamura S, Jinnouchi S, et al. Technetium-99m tetrofosmin for parathyroid scintigraphy: a direct comparison with (99m)Tc-MIBI, (201)Tl, MRI and US. Eur J Nucl Med 2001; 28: 1817-27.
22. Melloul M, Paz A, Koren R, Cytron S, Feinmesser R, Gal R. 99mTc-MIBI scintigraphy of parathyroid adenomas and its relation to tumour size and oxyphil cell abundance. Eur J Nucl Med 2001; 28: 209-13.
23. Chen CC, Skarulis MC, Fraker DL, Alexander R, Marx SJ, Spiegel AM. Technetium-99m-sestamibi imaging before reoperation for primary hyperparathyroidism. J Nucl Med 1995; 36: 2186-91.
24. Benard F, Lefebvre B, Beuvon F, Langlois MF, Bisson G. Rapid washout of technetium-99m-MIBI from a large parathyroid adenoma. J Nucl Med 1995; 36: 241-3.
25. Gotthardt M, Lohmann B, Behr TM, Bauhofer A, Franzius C, Schipper ML, et al. Clinical value of parathyroid scintigraphy with technetium-99m methoxyisobutylisonitrile: discrepancies in clinical data and a systematic metaanalysis of the literature. World J Surg 2004; 28: 100-7.
26. Moka D, Eschner W, Voth E, Dietlein M, Larena-Avellaneda A, Schicha H. Iterative reconstruction: an improvement of technetium-99m MIBI SPET for the detection of parathyroid adenomas? Eur J Nucl Med 2000; 27: 485-9.
27. Pattou F, Huglo D, Proye C. Radionuclide scanning in parathyroid diseases. Br J Surg 1998; 85: 1605-16.
28. McBiles M, Lambert AT, Cote MG, Kim SY. Sestamibi parathyroid imaging. Semin Nucl Med 1995; 25: 221-34.
29. Gallowitsch HJ, Mikosch P, Kresnik E, Gomez I, Lind P. Technetium 99m tetrofosmin parathyroid imaging. Results with double-phase study and SPECT in primary and secondary hyperparathyroidism. Invest Radiol 1997; 32: 459-65.
30. Pons F, Torregrosa JV, Vidal-Sicart S, Sabater L, Fuster D, Fernandez-Cruz L, et al. Preoperative parathyroid gland localization with technetium-99m sestamibi in secondary hyperparathyroidism. Eur J Nucl Med 1997; 24: 1494-8.
31. Pons F, Torregrosa JV, Fuster D. Biological factors influencing parathyroid localization. Nucl Med Commun 2003; 24: 121-4.
32. Civelek AC, Ozalp E, Donovan P, Udelsman R. Prospective evaluation of delayed technetium-99m sestamibi SPECT scintigraphy for preoperative localization of primary hyperparathyroidism. Surgery 2002; 131: 149-57.
33. Katz SC, Wang GJ, Kramer EL, Roses DF. Limitations of technetium 99m sestamibi scintigraphic localization for primary hyperparathyroidism associated with multiglandular disease. Am Surg 2003; 69: 170-5.
34. Yamaguchi S, Yachiku S, Hashimoto H, Kaneko S, Nishihara M, Niibori D, et al. Relation between technetium 99m-methoxyisobutylisonitrile accumulation and multidrug resistance protein in the parathyroid glands. World J Surg 2002; 26: 29-34.
35. Biertho LD, Kim C, Wu HS, Unger P, Inabnet WB. Relationship between sestamibi uptake, parathyroid hormone assay, and nuclear morphology in primary hyperparathyroidism. J Am Coll Surg 2004; 199: 229-33.
36. Taira N, Doihara H, Hara F, Shien T, Takabatake D, Takahashi H, et al. Less invasive surgery for primary hyperparathyroidism based on preoperative 99mTc-hexakis-2-methoxyisobutylisonitrile imaging findings. Surg Today 2004; 34: 197-203.
37. Regal M, Paramo C, Luna CR, Perez Mendez LF, Sierra JM, Rodriguez I, et al. Coexistence of primary hyperparathyroidism and thyroid disease. J Endocrinol Invest 1999; 22: 191-7.
38. dell'Erba L, Baldari S, Borsato N, Bruno G, Calo-Gabrieli G, Carletto M, et al. Retrospective analysis of the association of nodular goiter with primary and secondary hyperparathyroidism. Eur J Endocrinol 2001; 145: 429-34.
39. Staudenherz A, Abela C, Niederle B, Steiner E, Helbich T, Puig S, et al. Comparison and histopathological correlation of three parathyroid imaging methods in a population with a high prevalence of concomitant thyroid diseases. Eur J Nucl Med 1997; 24: 143-9.
40. Masatsugu T, Yamashita H, Noguchi S, Nishii R, Watanabe S, Uchino S, et al. Significant clinical differences in primary hyperparathyroidism between patients with and those without concomitant thyroid disease. Surg Today 2005; 35: 351-6.

ความถูกต้องของการถ่ายภาพสแกนด้วยสารเภสัชรังสี 99mTc-MIBI เพื่อหาตำแหน่งความผิดปกติของต่อมพาราไทรอยด์ก่อนผ่าตัดในสภาวะพาราไทรอยด์ฮอร์โมนสูงแบบปฐมภูมิ และ แบบทุติย-ตติยภูมิ

ยุทธนา แสงสุดา

***วัตถุประสงค์**: เพื่อศึกษาความถูกต้องของการตรวจหาตำแหน่งของต่อมพาราไทรอยด์ที่ผิดปกติก่อนผ่าตัดด้วยการใช้สารเภสัชรังสี 99mTc-methoxyisobutylisonitrile (MIBI) ถ่ายภาพสแกนต่อมพาราไทรอยด์ 2 ระยะเวลาในผู้ป่วยที่มีสภาวะพาราไทรอยด์ฮอร์โมนสูงแบบปฐมภูมิ (pHPT) และผู้ป่วยที่มีสภาวะพาราไทรอยด์ฮอร์โมนสูงแบบทุติย-ตติยภูมิ (stHPT) จากโรคไตวายเรื้อรัง*

***วัสดุและวิธีการ**: ศึกษาแบบย้อนหลังในช่วงเวลาตั้งแต่ พ.ศ. 2538 ถึง พ.ศ. 2553 ของผู้ป่วย 71 ราย ที่มีสภาวะพาราไทรอยด์ฮอร์โมนสูงอายุเฉลี่ย 47±15 ปี (พิสัย 14-84 ปี) ที่ได้รับการผ่าตัดต่อมพาราไทรอยด์โดยผู้ป่วย 18 รายเป็น pHPT และ ผู้ป่วย 53 รายเป็น stHPT ซึ่งผู้ป่วยทั้งหมดไม่เคยผ่าตัดบริเวณคอมาก่อน รวบรวมข้อมูลก่อนผ่าตัดของผู้ป่วย เกี่ยวกับข้อมูลพื้นฐานของโรคอาการแสดงของโรค ผลการตรวจทางห้องปฏิบัติการ การตรวจสแกนด้วย MIBI ผลการผ่าตัด ตำแหน่ง ขนาด และผลการตรวจลักษณะชิ้นเนื้อทางพยาธิ ของต่อมพาราไทรอยด์ ที่ผิดปกติทั้งหมด*

***ผลการศึกษา**: ผลการผ่าตัด ต่อมพาราไทรอยด์ที่ผิดปกติ ในผู้ป่วย18 ราย ที่มีสภาวะ pHPT เป็น solitary adenoma 1 ต่อม 11 ราย (61%) มะเร็งต่อมพาราไทรอยด์ 5 ราย (28%) hyperplasia 1 ต่อม 1 ราย (6%) และ hyperplasia 2 ต่อม 1 ราย (6%) MIBI สแกนตรวจต่อมพาราไทรอยด์ที่ผิดปกติ ได้ถูกตำแหน่ง 17 ใน 19 รายโดยมีความไว 90% ความจำเพาะ 100% ความคาดหมายที่จะได้ผลบวกถูกต้อง 100% และถูกต้องแม่นยำ 97.2% ในผู้ป่วย 53 รายที่มีสภาวะ stHPT ผลการผ่าตัดต่อมพาราไทรอยด์ที่ผิดปกติเป็น hyperplasia หลายต่อม 48 ราย (91%) hyperplasia 1 ต่อม 1 ราย (2%) adenoma 1 ต่อม 1 ราย (2%) adenomas หลายต่อม 3 ราย (6%) MIBI สแกนตรวจต่อมพาราไทรอยด์ที่ผิดปกติ ได้ถูกข้าง 116 ใน 173 ราย โดยมีความไว 67.1% ความจำเพาะ 92.3% ความคาดหมายที่จะได้ผลบวกถูกต้อง 97.5% และถูกต้องแม่นยำ 71.7% MIBI สแกนตรวจต่อมพาราไทรอยด์ที่ผิดปกติ ได้ถูกตำแหน่ง 63.6% ผลการเปรียบเทียบ อายุ ระดับฮอร์โมนพาราไทรอยด์ ระดับแคลเซียม ฟอสฟอรัส ยูเรียในเลือดในสภาวะ pHPT และ stHPT พบว่ามีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) ค่าเฉลี่ยของขนาดต่อมพาราไทรอยด์ที่ผิดปกติในสภาวะ pHPT (2.28 ± 1.05 เซนติเมตร) มีขนาดใหญ่กว่าค่าเฉลี่ยของขนาดต่อมพาราไทรอยด์ที่ผิดปกติในสภาวะ stHPT (1.56 ± 0.58 เซนติเมตร) อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) ค่าเฉลี่ยขนาดต่อมพาราไทรอยด์ที่ผิดปกติในผลตรวจ MIBI สแกนเป็นบวก (1.79 ± 0.68 เซนติเมตร) มีขนาดใหญ่กว่าค่าเฉลี่ยขนาดต่อมพาราไทรอยด์ที่ผิดปกติในผลตรวจ MIBI สแกนที่เป็นลบเท็จ (1.29 ± 0.52 เซนติเมตร) อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$)*

***สรุป**: การตรวจ MIBI สแกนก่อนผ่าตัดเพื่อหาตำแหน่งต่อมพาราไทรอยด์ที่ผิดปกติในสภาวะ pHPT มีค่าความไวและถูกต้องแม่นยำสูงมาก จึงเป็นประโยชน์ช่วยชี้นำสำหรับศัลยแพทย์ในการผ่าตัดเฉพาะข้างของต่อมพาราไทรอยด์ที่ผิดปกติในสภาวะ stHPT การตรวจ MIBI สแกนมีค่าความไวปานกลาง แต่ไม่ถูกต้องเพียงพอในการหาตำแหน่งต่อมพาราไทรอยด์ที่ผิดปกติได้ทั้งหมด การตรวจ MIBI สแกนจึงอาจไม่ใช่สิ่งจำเป็นที่ศัลยแพทย์ต้องส่งตรวจก่อนผ่าตัดทุกราย*