ORIGINAL ARTICLE

Impact of thyroid nodular disease on ^{99m}Tc-sestamibi scintigraphy in patients with primary hyperparathyroidism

**Joaquin Gómez-Ramírez · Juan Jose Sancho-Insenser ·
Jose Antonio Pereira · Jaime Jimeno ·
Assumpta Munné · Antonio Sitges-Serra**

Abstract

Background Primary hyperparathyroidism with coexisting thyroid nodular disease (TND) has been considered a contraindication for selective parathyroidectomy because the low sensitivity of preoperative localization studies, especially ^{99m}Tc-sestamibi scanning (MIBI) and ultrasound. The aim of this study was to assess the impact of concomitant TND in the preoperative image studies.

Methods A total of 236 consecutive patients who had parathyroidectomy for sporadic hyperparathyroidism and the preoperative localization study that was done with MIBI were reviewed. Patients were divided into three groups: those who did not have any thyroid disease, those who had concomitant TND not necessary to resect, and those in whom thyroid resection due to TND was necessary at the time of parathyroidectomy.

Results MIBI showed a sensitivity of 78.5% in patients without concomitant TND, 73% in patients with TND but not thyroidectomy needed, and 54.5% in the cases that thyroid resection was necessary. When MIBI and ultrasound were both suspicious for an adenoma, the sensitivity was not influenced by the TND.

Conclusion In patients with coexisting thyroid disease but not thyroidectomy needed, MIBI scintigraphy contributes to the detection of a solitary adenoma. When thyroid resection is required, MIBI imaging is often negative.

Keywords Ultrasonography · Sestamibi · Goiter · Parathyroidectomy · Thyroid nodular disease

J. Gómez-Ramírez · J. J. Sancho-Insenser · J. Jimeno ·
A. Sitges-Serra
Endocrine Surgery Unit, Department of Surgery,
Hospital Universitari del Mar,
Barcelona, Spain

J. A. Pereira
Departament de Ciències Eperimentals i de la Salut,
Hospital Universitari del Mar,
Barcelona, Spain

A. Munné
Department of Pathology, Hospital Universitari del Mar,
Barcelona, Spain

J. Gómez-Ramírez (✉)
General Surgery Department, Hospital de La Princesa,
C/Diego de León 62,
28006 Madrid, Spain
e-mail: jgomezramirez@hotmail.com
e-mail: jgomezramirez@aecirujanos.es

Introduction

In recent years, surgical trends for primary hyperparathyroidism (PHPT) are moving toward selective parathyroidectomy (SP). A coexisting thyroid disease has previously been considered a relative contraindication to SP because of the decrease in the sensitivity of localizing techniques [1].

It is well known that in most cases, PHPT is sporadic and caused by a single adenoma in 85%–95% of the instances [2]. The increasing use and accuracy of ^{99m}Tc-sestamibi scanning (MIBI) allow for preoperative localization of solitary adenomas in 75%–90% of the cases; this has led surgeons to progressively implement SP [3, 4]. Sometimes, however, there are some false-positive and false-negative results that may be attributed to coexisting thyroid nodular disease [5].

The prevalence of associated thyroid nodular disease in patients with PHPT has been reported to range from 20% to 60% [6–8], and although the characteristics and outcomes of these "false-images" are not well characterized, it has

been speculated that parathyroid glands not visualized with image diagnostic techniques carry a higher risk of multi-nodular disease, not diagnosed in the preoperative workup. Due to the lower sensitivity of localization techniques, the approach in patients with associated thyroid nodular disease has been a traditional cervicotomy with four gland examination with resection of the abnormally enlarged gland(s), but progressively, the traditional contraindications for SP have been considered relative, except those patients requiring thyroid resections.

The aim of this study was to assess the impact of concomitant thyroid nodular disease on accuracy of ^{99m}Tc-sestamibi used for the preoperative image diagnosis.

Methods

Between January 1992 and May 2009, 236 patients with biochemically proven PHPT and preoperative MIBI were identified by retrospective review of the prospectively maintained endocrine surgery database. Patients with hereditary multiple endocrine neoplasia, parathyroid hyperplasia, or previous neck surgery were excluded.

MIBI technique All patients received an intravenous injection of 450 MBq sestamibi. Planar images were acquired using a low-energy, high-resolution collimator positioned as near as possible to the neck, in a 128×128 matrix with a 2-zoom and an energy window of 140 keV±10% using a single-head General Electric gamma camera. The initial image (early images) was acquired in the anterior, left and right anterior 30º oblique view 15 min after tracer administration. Similar views were obtained starting 90–

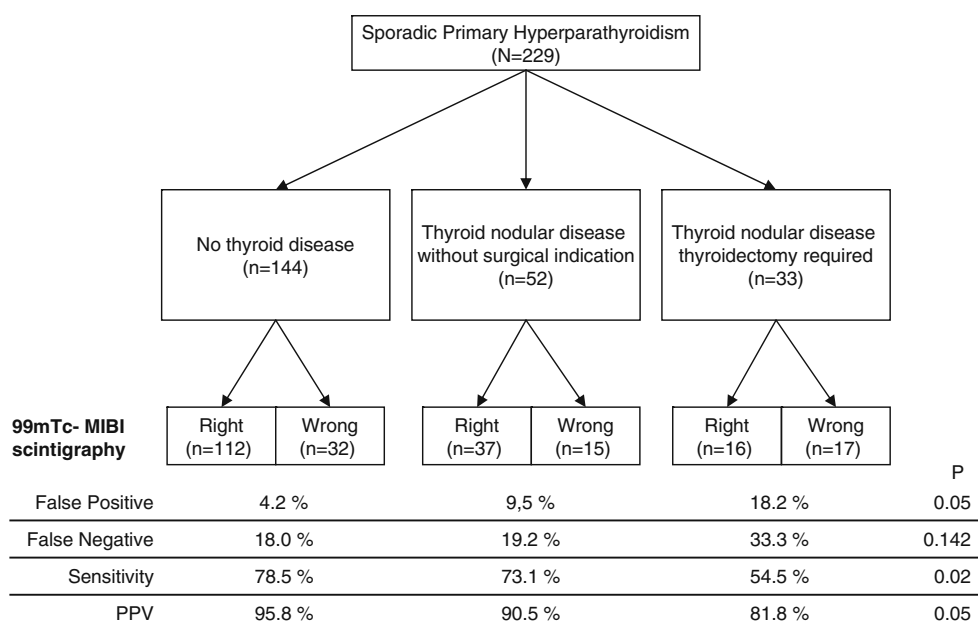120 min after injection (delayed images) and were acquired for identical times.

Ultrasound technique All cervical ultrasound (US) were performed using a 6- to 13-MHz scanner. If thyroid nodules were found, malignancy was determined on the bases of ultrasonographic features (calcification, shape, echo structure, and echogenicity) and cytological findings (US–fine-needle aspiration biopsy).

Patients were divided into three categories: those with no thyroid disease, those with concomitant thyroid nodular disease without indication for thyroidectomy, and those in whom thyroid resection due to concomitant disease was necessary at the time of parathyroidectomy.

Scintigraphic data were correlated with intraoperative findings and site of the thyroid gland nodularity. A false positive was defined when MIBI showed one abnormal focal accumulation that did not correlate with the site of an excised single adenoma. In false-negative cases, MIBI showed no abnormal accumulation/suspected adenoma. True-positive MIBI tests were named "Right" and false-positive plus false-negative MIBI tests were named "Wrong." Sensitivity and positive predictive value (PPV) were calculated. Thyroid estimated volume and weight, parathyroid weight, parathyroid oxyphilic cell content, and biochemical outcomes were also recorded.

Statistical analysis was performed using the SPSS 15.0 for Windows (SPSS Iberica, Madrid, Spain). Contingency tables of qualitative data were assessed using χ^2 or Fisher's exact test when appropriate. In all analyses, $P<0.05$ was accepted as statistically significant. The normality of the distribution of quantitative variables was assessed by Kolmogorov–Smirnov single-sample test. Results were

Fig. 1 Distribution of patients with sporadic PHPT according to coexisting thyroid nodular disease and its effect on the diagnostic accuracy of cervical scintigraphy with ^{99m}Tc-sestamibi. Right: MIBI correctly identified the side and position of a pathologic parathyroid gland. Wrong: MIBI did not identify any gland or identified a false gland in the wrong place

99mTc- MIBI scintigraphy	Right (n=112)	Wrong (n=32)	Right (n=37)	Wrong (n=15)	Right (n=16)	Wrong (n=17)	P
False Positive	4.2 %		9,5 %		18.2 %		0.05
False Negative	18.0 %		19.2 %		33.3 %		0.142
Sensitivity	78.5 %		73.1 %		54.5 %		0.02
PPV	95.8 %		90.5 %		81.8 %		0.05

Table 1 MIBI results in sporadic PHPT patients with or without associated thyroidectomy required

	No thyroid disease or concomitant thyroid nodular disease without indication for thyroidectomy (n=196)	Concomitant thyroid disease and thyroidectomy needed (n=33)	P
False positive	5.6%	18.2%	0.032
False negative	18.4%	33.3%	0.049
Sensitivity	77.0%	54.5%	0.01
PPV	94.4%	81.8%	0.032

expressed as arithmetic mean ± SD, unless specified otherwise. For quantitative variables, two-tailed Student's *t* test for nonpaired data was used to assess the significance of differences in means between two groups and analysis of variance for three or more groups.

Results

There were 199 women and 37 men with a mean age 61± 14 years (range, 19–89 years). Preoperative mean serum calcium level was 2.8±0.2 mmol/L, and mean parathyroid hormone level was 262±435 ng/L.

A distinct solitary focus of increased MIBI uptake relative to the thyroid gland was considered positive for abnormal parathyroid disease in 187 patients, whereas 49 patients did not have any image suggestive of an enlarged parathyroid gland. In 171 patients, a preoperative cervical ultrasound (US) examination was also obtained before surgery; in 58 patients, a CT scan was done; and in 8 patients, we did not have any thyroid gland image.

Regarding the thyroid gland, 144 patients (62.8%) did not exhibit any thyroid alteration, 52 patients (22.7%) had a

Table 2 Combined MIBI and ultrasonography results (if concordant) in sporadic PHPT patients with or without associated thyroidectomy required

	No thyroid disease or concomitant thyroid nodular disease without indication for thyroidectomy (n=81)	Concomitant thyroid disease and thyroidectomy needed (n=7)	P
False positive	1.4%	0/70%%	0.9
False negative	8.6%	0%	0.5
Sensitivity	90.1%	100%	0.1
PPV	98.6%	100%	0.9

Table 3 Effects of patient, thyroid, and parathyroid characteristics on the accuracy of ^{99m}Tc-setamibi in localizing a parathyroid abnormal gland in patients with sporadic PHPT

	MIBI result*	Mean±SD	P
Age (y)	Wrong	61±12.7	0.92
	Right	61.1±13.9	
Serum calcium level (mmol/L)	Wrong	2.8±0.2	0.52
	Right	2.9±0.2	
Parathyroid hormone level (ng/L)	Wrong	191±182.7	0.12
	Right	288.7±495.4	
Creatinine clearance	Wrong	77.7±26.9	0.86
	Right	78.2±28.2	
TSH (mIU/L)	Wrong	2.4±2.1	0.82
	Right	2.3±2.1	
Number of nodules	Wrong	2.2±1.5	0.6
	Right	1.9±1	
Size of biggest nodule (mm)	Wrong	13±11	0.73
	Right	13.6±13.2	
Mean gland weight (mg)	Wrong	1,068.3±1874.7	0.0005
	Right	1,655.7±2243.5	
Mean thyroid weight (g)	Wrong	45.85±27.4	1
	Right	49.47±26.4	
Mean thyroid volume (mL)	Wrong	28.77±18.2	0.39
	Right	32.10±17.9	
Parathyroid oxyphil cell content	Wrong	0.4	
	Right		

*Right: MIBI correctly identified the side and position of a pathologic parathyroid gland. Wrong: MIBI did not identify any gland or identified a false gland in the wrong place

TSH thyroid-stimulating hormone

concomitant nodular thyroid disease without indication for thyroidectomy, and finally, 33 patients (14.4%) had a uninodular or multinodular goiter that made an associated thyroidectomy necessary at the time of parathyroidectomy. Thyroid nodular disease requiring surgery was defined as suspicion of thyroid cancer by fine-needle aspiration cytology, size of the nodules bigger than 4 cm, and/or presence of compressive symptoms.

In 84 patients (35.6%), the initial approach was an SP, of which in 3 cases (3.6%), the procedure was converted to bilateral neck exploration. In 152 patients (64.4%), the

Table 4 MIBI results and affected gland

		Affected gland		P
		Inferior parathyroid	Superior parathyroid	
MIBI result	Wrong	3 (2.7%)	12 (15.8%)	0.002
	Right	107 (97.3%)	64 (84.2%)	
	Total	110	76	

initial procedure was a conventional cervicotomy with four gland exploration.

Sensitivity, PPV, false-positive, and negative of the MIBI scan are shown in Fig. 1. Preoperative MIBI was positive in 182 patients. In patients without thyroid disease, the sensitivity was 78.5% and the PPV was 95.8%. Differences of sensitivity and PPV were higher if patients are divided by the need for thyroid surgery (Table 1). When both MIBI and US identified a parathyroid adenoma, the results were not influenced by the thyroid nodular disease, and the sensitivity and PPV were 90.1% and 98.6% in the group without thyroid surgery, and 100% in the patients who needed thyroid resection (Table 2).

In the analysis of the adenoma characteristics, only the adenoma weight was significantly associated to the MIBI performance ($P=0.005$). Other features as thyroid gland characteristics or parathyroid gland oxyphilic cell content were not significantly associated with MIBI results (Table 3).

The anatomic position of the adenoma (superior vs. inferior parathyroid glands) was associated with the MIBI accuracy, with MIBI sensitivity being higher in detecting adenomas of inferior parathyroid glands (Table 4).

Discussion

The surgical management of PHPT has evolved over the last two decades toward a more selective approach since first suggested by Tibblin et al [9]. With the advent of more refined preoperative localizing studies and intraoperative tools, focused parathyroidectomy can be performed in 60%–75% of all patients with sporadic PHTP, even under local anesthesia [10]. The accuracy of the preoperative localizing techniques is essential to ensure a successful selective parathyroid approach.

Many clinical researchers have assessed the decrease of the sensitivity and PPV of both MIBI and US as localization preoperative studies when a nodular thyroid disease coexists with PHPT. The hypothesis is that false-positive MIBI results could be originated by MIBI accumulation in thyroid nodules [1, 5, 8, 11–13].

In this clinical study, nodular thyroid disease requiring thyroidectomy had more impact on the MIBI results than the mere presence of thyroid nodular disease. In case of no concomitant thyroid disease, the MIBI had a sensitivity of 77%, and if thyroidectomy was required, the sensitivity fell to 54.5%. This difference was not observed in cases where both MIBI and US coincided in the localization of the parathyroid adenoma, with the sensitivity being higher than 90% in both groups. This distinction is of importance because it shows that MIBI is affected more easily by the nodular thyroid disease requiring thyroidectomy than by the mere presence of benign nodules without surgical indication that coexists in approximately 20%–60% of cases. Patients with PHTP and nodular disease in whose thyroid surgery is not needed, MIBI shows a false-positive result lower than 6% and a sensitivity of 77%.

Also, in accordance with some recently published studies, in our analysis, the adenoma weight in true-positive scans was significantly larger than those in false-negative scans, and those in the upper position are less likely to be localized. In our series, however, we have not identified a relationship of the MIBI accuracy with the oxyphilic cell content of the parathyroid adenoma [14, 15].

We have observed that in patients with coexisting thyroid disease but not thyroidectomy needed, MIBI scintigraphy contributes to the detection of a solitary adenoma and allows unilateral exploration, but when thyroid resection is planned, parathyroid scintigraphy is much less accurate.

Conflict of interests None.

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