

## Original Article

# Complementary role of parathormone washout test to $^{99m}\text{Tc}$ -MIBI parathyroid scintigraphy and histopathologic analysis of cell types in parathyroid adenomas<sup>☆</sup>

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## ABSTRACT

**Objective:** Parathyroid scintigraphy (PS) can be negative or equivocal (N/E) in a considerable number of cases with highly suspicious clinical findings and biochemical results for parathyroid adenoma (PA). The aims of this study were to investigate the complementary role of parathormone washout test (PWT) to PS in patients with primary hyperparathyroidism (PHPT) and evaluate histopathologic aspects of PAs in comparison with PS results.

**Material and methods:** Thirty-eight patients with PHPT referred for PS were included in the study. Seventeen patients had both scintigraphic and ultrasonographic findings concordant with PA (Group A). Twenty-one patients having N/E PS, but suspected lesions for PA on ultrasonography (US) formed Group B. PWT was performed for all patients and they underwent the surgical intervention. An adenoma was removed in all patients and the histopathologic cell characteristics were established.

**Results:** The tumor size on US was larger in those patients whose adenomas were seen on the PS ( $p < 0.001$ ). The percentages of chief (or principal), oxyphilic and clear cells in PAs were not statistically different between the groups. Serum parathormone level and PWT were not statistically significant between Group A and Group B ( $p = 0.095$  and  $p = 0.04$ , respectively).

**Conclusion:** Although there is not a definitive threshold value, the sensitivity of PS increases with lesion size. While chief cell and oxyphilic cell content of PAs tend to deplete in N/E PS, clear cell rate increases substantially. Combining PS with both US and PWT increases the sensitivity of detection and localization of PAs.

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## Gammagrafía paratiroidea con $^{99m}\text{Tc}$ -MIBI: valor complementario de la paratohormona en el aspirado y análisis histopatológico de los tipos de células en los adenomas paratiroideos

## RESUMEN

**Objetivo:** La gammagrafía paratiroidea (GP) puede ser negativa o equívoca (N/E) en un número considerable de casos con alta sospecha clínica y bioquímica de adenoma de paratiroides (AP). Los objetivos de este estudio fueron investigar el papel complementario de la determinación de paratohormona en punción con aguja fina (PTH en PAAF) con la GP en pacientes con hiperparatiroidismo primario (HPTP) y evaluar los aspectos histopatológicos de los AP en comparación con los resultados de GP.

**Material y métodos:** Fueron incluidos en el estudio 38 pacientes con HPTP remitidos para realizar GP. 17 pacientes tuvieron resultados gammagráficos y ecográficos concordantes con AP (Grupo A). 21 pacientes con GP N/E pero sospecha de AP en la ecografía formaron el Grupo B. Se realizó PTH en PAAF en todos los pacientes y todos fueron operados. Se extirpó un adenoma en cada uno de ellos y en todos los casos se establecieron las características histopatológicas.

## Palabras clave:

Células principales

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**Resultados:** El tamaño del tumor en la ecografía fue mayor en aquellos pacientes cuyos adenomas se vieron en la GP ( $p < 0,001$ ). Los porcentajes de células principales, oxífilas y claras en AP no fueron estadísticamente diferentes entre los grupos. El nivel de paratohormona sérica y PTH en PAAF no fueron estadísticamente significativos entre los grupos A y B ( $p = 0,095$  y  $p = 0,04$ , respectivamente).

**Conclusión:** Aunque no existe un valor umbral definitivo, la sensibilidad de la GP aumenta con el tamaño de la lesión. Mientras que el contenido de células principales y oxífilas tiende a reducirse en los AP con GP N/E EP, la tasa de células claras aumenta sustancialmente. La combinación de GP con la US y la PTH en PAAF aumenta la sensibilidad de detección y localización de los AP.

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## Introduction

Primary hyperparathyroidism (PHPT) is caused by a single parathyroid adenoma (PA) in 85% of the cases, the other 15% being caused by multiple hyperfunctioning PA, hyperplasia or, in rare cases, carcinomas.<sup>1</sup> The standard treatment of hyperparathyroidism is bilateral neck exploration with excision of the hyperfunctioning parathyroid gland (or glands). However, the first surgery does not provide an absolute cure even in the hands of an experienced surgeon and subsequent surgery is mandatory in 2–7% of the patients.<sup>2</sup> Reinterventions have technical difficulties due to intense scarring and distortion of normal cervical anatomy with higher complication rates besides.<sup>2,3</sup> Precise preoperative localization of hyperfunctioning parathyroid glands can decrease both the surgical effort and the complication rates in patients with primary, recurrent or persistent hyperparathyroidism.<sup>3</sup>

Currently, ultrasonography (US) and dual-phase <sup>99m</sup>Tc-MIBI parathyroid scintigraphy (PS) are the choice of conventional imaging modalities to locate the pathologic parathyroid gland in primary surgery and in the reintervention setting.<sup>4</sup> However, the sensitivity (Sv) and specificity (Sp) of PS are 71–93% and 90%, respectively. It has a high rate of false positivity due to concurrent cervical pathologies and previous surgery.<sup>5</sup> Fine-needle aspiration (FNA) with parathormone washout test (PWT) is the latest adjunct to parathyroid surgery.<sup>6,7</sup> Sv, Sp and positive predictive value (PPV) of preoperative PWT to detect PAs and confirm the eligibility of patients for a minimally invasive thyroid surgery are high and reported as 94%, 91–100% and 100%, respectively.<sup>8</sup>

The parathyroid gland is normally formed by 3 types of cell types. These are composed by 50–60% chief cells, 30–40% clear cells and <5% oxyphil cells.<sup>9</sup> The chief cells contain few mitochondria and mainly secrete parathormone (PTH).<sup>9</sup> While clear cells are transformed from chief cells and contain excessive cytoplasmic glycogen, oxyphil cells have an intensely eosinophilic cytoplasm enriched with numerous and tightly packed mitochondria,<sup>10</sup> the function of clear and oxyphil cells is still not clear.<sup>9–12</sup> Although, a chief cell adenoma is the most common cause of PHPT presenting its classical symptoms, the exact percentage of various cell types of PA is not known.<sup>13</sup>

PS can be negative or equivocal (N/E) in a not neglectable patient population despite highly suspicious clinical findings and biochemical results for PHPT.<sup>14</sup> Some of these patients have either small size PA below the spatial resolution of the gamma camera, or concomitant thyroid diseases such as nodular goiter or Hashimoto thyroiditis with perithyroidal lymph nodes (LNs) on US that render the differential diagnosis more difficult and may lead to false positive results on PS for PA.<sup>15</sup> The aims of this study were to investigate the complementary role of PWT to PS in patients with PHPT and to evaluate the histopathologic cell types of PAs in comparison with PS results.

## Materials and methods

### Patients

The study included 38 patients with PHPT who were referred to the Nuclear Medicine Department of a tertiary health care center for PS. Mean age of the patients (15 male, 23 female) was  $46.5 \pm 18.5$  years (26–70). PHPT diagnosis was established according to elevated serum PTH and calcium levels. Eighty-four percent of all patients (32 cases) were newly diagnosed and 16% (6 cases) were relapsed cases of a previously treated disease. Patients with MEN syndromes were not enrolled in the study.

A detailed comprehensive neck US was performed to all patients in order to correlate with PS and to document any intra or extrathyroidal lesion by experienced nuclear medicine specialists. The largest diameter on transverse section was measured as the preferentially accepted lesion size. PWT was performed for all cases under US guidance. All patients were operated for PA and histopathologic slides were analyzed microscopically by a single experienced pathologist. Cell types were recorded as percentage. Minimally invasive parathyroidectomy with the use of radioguided occult lesion localization (ROLL) was used as the surgical method in all patients. Biochemical details (pre and postoperative serum PTH and calcium levels), PWT and histopathology results of the patients were retrieved.

The patients were divided into two groups (Groups A and B) according to PS, US findings and an algorithmic pathway of inclusion criteria for the study is presented in Fig. 1. Serum PTH level, PTH level in PWT, lesion size on US and histopathologic results were compared between Group A and Group B.

### Group A (17 patients): patients with PS (+)/US (+)

PWT was performed in order to exclude any false positive scintigraphic results and confirm the diagnosis of PA in 17 of 38 patients (45%) despite the concordant scintigraphic, ultrasonographic and biochemical results.

### Group B (21 patients): patients with PS (N/E)/US (+)

PWT was done for suspected lesions for PA on US in 21 cases (55%) either for having negative (35%) or equivocal (65%) PS even on single photon emission computed tomography/computed tomography (SPECT/CT).

### Parathyroid scintigraphy

Dual-phase parathyroid scintigraphy was performed 20 min, 1 h and 2 h after intravenous injection of 555–740 MBq (15–20 mCi) <sup>99m</sup>Tc-MIBI following the standard procedure. Anterior planar images of the neck and mediastinum were acquired by a gamma camera with a high-resolution collimator. SPECT/CT was performed for all patients 1 h after <sup>99m</sup>Tc-MIBI injection by a 16-slice multi-detector SPECT/CT hybrid imaging system (GE Discovery NM/CT 670). Focal uptake in the neck on early images (in order not to

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