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Institutional experience of PTH evaluation on fine-needle washing after aspiration biopsy to locate hyperfunctioning parathyroid tissue[#]

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Abstract: Assaying parathyroid hormone (PTH) in the washing liquid after fine-needle aspiration biopsy (FNAB) seems to be a valid approach to locate parathyroid tissue. PTH-FNAB was evaluated in 47 patients with a clinical picture of primary hyperparathyroidism (PHP) and ultrasonography (US) suggestive of parathyroid lesion. The patients were subdivided into two groups on the basis of the absence or presence of US thyroid alterations. The result of PTH-FNAB was compared with those of cytology, scintigraphy and, in 24 patients, surgical outcome. PTH-FNAB samples with a value higher than that recorded in the serum and higher than our institutional cut-off were deemed to be probable samples of parathyroid tissue. Cytology proved diagnostic for benign thyroid lesions, non-diagnostic for thyroid lesions, hyperplastic parathyroid tissue, undetermined or malignant thyroid lesions and other lesions in 45%, 30%, 17%, 4%, and 4% of cases, respectively. In 47% of cases, PTH-FNAB indicated that the sample had been taken in parathyroid tissue. In patients without US alterations, the diagnostic accuracy of PTH-FNAB was greater than that of scintigraphy. After surgery, comparison between the results of PTH-FNAB and scintigraphy, in terms of positive predictive value (PPV), revealed the superiority of PTH-FNAB; PPV was 94% for FNAB and 71% for scintigraphy, while sensitivity was 83% and 69%, respectively. PTH-FNAB evaluation after FNAB appears to be more diagnostic than cytology and scintigraphy. Of all the procedures used, PTH-FNAB appears to be the method of choice when the target is US suggestive and reachable. PTH-FNAB appears to be a useful method of guiding surgical intervention.

Key words: Primary hyperparathyroidism, Nodular goitre, Scintigraphy, Ultrasonography, Fine-needle aspiration biopsy (FNAB), Parathyroid hormone (PTH)-FNAB
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INTRODUCTION

Primary hyperparathyroidism (PHP) is a common cause of hypercalcemia; in the majority of patients, it is due to a parathyroid adenoma. The standard therapeutic approach entails surgical removal of all enlarged parathyroid tissue and bilateral exploration of the neck. Surgery has a high rate of success and a low rate of adverse events when performed by an expert surgeon. More recently, minimally invasive parathyroidectomy (MIP) has been considered the surgical procedure of choice when the location of the hyperfunctioning parathyroid tissue is undoubted and intra-operative parathyroid hormone (PTH) assay is available (Rodgers *et al*., 2008). Ultrasonography (US) and ^{99m}Tc-methoxyisobutylisonitrile (MIBI) scintigraphy are currently the most widely used methods of locating hyperfunctioning parathyroid tissue. US can be considered the first-line technique; if this proves inconclusive, MIBI is required (Bhansali *et al*., 2006; Grosso *et al*., 2007). However, one of the main obstacles to imaging studies is the high incidence of false positive results due to other cervical abnormalities, such as non-nodular or nodular goitre, or false negative results due to the size and

[#] This paper was presented orally at the XXVII Giornate Endocrinologiche Pisane, June 26~28, 2008, Pisa, Italy location of hyperfunctioning parathyroid tissue (Masatsugu *et al*., 2005). Fine-needle aspiration biopsy (FNAB) of suspected parathyroid tissue and PTH assay on the needle wash-out after preparation of cytological specimens are further methods of localizing parathyroid adenomas. In 1983 this procedure was described by Doppman *et al*.(1983); since then, several reports on US-guided PTH-FNAB have been published (Abraham *et al*., 2007; Barczynski *et al*., 2006; Erbil *et al*., 2006; 2007; Kiblut *et al*., 2004; Marcocci *et al*., 1998; Maser *et al*., 2006). This approach enables sonographic, cytological and biochemical results to be combined in order to localize parathyroid tissue with greater certainty. The contribution of PTH-FNAB to localizing parathyroid adenomas in patients with PHP and concomitant thyroid nodules has not yet been fully evaluated (Marcocci *et al*., 1998; Erbil *et al*., 2007). The aim of the present prospective study was to evaluate the diagnostic role of PTH-FNAB in our series of patients with PHP. In our hands, PTH-FNAB seems more diagnostic than cytology and scintigraphy in patients without echographic thyroid alterations. Of all the procedures used, PTH-FNAB appears to be the method of choice when the target is echographically suggestive and reachable.

MATERIALS AND METHODS

Patients and protocol

We studied 47 consecutive outpatients (38 females, 9 males) aged 38~89 years (mean age (63.6±11.8) years; mean±*SD*) undergoing endocrine evaluation for PHP. The biochemical diagnosis of PHP was performed by standard criteria. At the time of FNAB evaluation, PTH, total calcium, free-thyroxine (f-T4), thyroid stimulating hormone (TSH), and thyroglobulin (Tg) were further evaluated in all patients (Table 1). Patients were divided into two groups on the basis of absence (Group 1) or presence (Group 2) of concomitant thyroid abnormalities on US. Written informed consent was obtained from all patients. FNAB was performed under US guidance on each nodular lesion suspected of being enlarged parathyroid tissue. One pass was generally made. Data from cytology evaluation and from biochemical evaluation of PTH on needle washing (PTH-FNAB) were recorded. As a negative control value for sampling in parathyroid tissue, Tg was also evaluated in needle washing (Tg-FNAB). When necessary, FNAB was also performed on thyroid nodules, and the data were regarded as an internal negative control. Cytological and biochemical results and those of US-guided FNAB were compared with the results yielded by parathyroid MIBI scintigraphy. After diagnostic evaluation, parathyroid surgery was performed in several patients and the histological result was further evaluated.

Instrumental evaluation

Neck US examination was carried out by means of an Esaote AU5 Idea equipped with a 7.5 MHz linear transducer of 60 mm length (Esaote, Genoa, Italy). The usual location of parathyroid glands was scanned to detect any lesion suggestive of parathyroid pathology. Any hypoechogenic lesion that was retrothyroid or polar in relation to the thyroid lobe, which had one or more vascular stalks, was suspected of being parathyroid tissue. In addition, solid hypoechogenic intra-thyroid lesions were also regarded as suspect when no other extra-thyroid lesions were seen in overt clinical PHP. If suspected parathyroid tissue was located, US-guided FNAB was performed by using a 21-gauge needle attached to a 10-ml syringe. The needle was inserted into the suspicious parathyroid tissue and negative pressure was applied. A smear from the needle used for aspiration was collected on a glass slide and the needle was then washed with 1 ml of normal saline solution. Cell debris were removed by centrifugation and the supernatant was collected for biochemical evaluations. ^{99m}Tc-MIBI was administered intravenously and images were acquired 10 min and 2~3 h post-injection. Early and late anterior planar images of the neck and mediastinum were compared for focal abnormalities and for areas of increased retention of MIBI. Parathyroid scintigraphy was interpreted by an experienced nuclear physicist, who was unaware of the results of the PTH-FNAB.

Biochemical and cytological analyses

PTH was analyzed by chemiluminescence immunoassay (Immulite 2000, Diagnostic Products, San Juan Capistrano, CA, USA). Intra- and inter-assay variations, expressed as coefficients of variation (CVs), were 4% and 6%, and assay sensitivity was 2 ng/L. In our laboratory, the normal PTH range in sera is <65 ng/L. Tg was assayed by chemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). The functional sensitivity is ≤0.5 μg/L. In our laboratory, the intra- and inter-assay CVs were 5% and 8%, respectively. In patients without goitre, normal Tg values are 1.5~78.0 μg/L. PTH-FNAB and Tg-FNAB levels were also assayed by means of the same methods on needle wash-out (1 ml of saline solution) after preparation of cytological specimens. PTH-FNAB and Tg-FNAB levels are expressed respectively in ng/L and μg/L regardless of dilution. F-T4 and TSH levels were measured by means of chemiluminescence immunoassay (Roche Diagnostics). Normal ranges are 12.0~22.0 pmol/L and 0.3~4.2 mU/L for f-T4 and TSH, respectively. Serum total-calcium was determined by fully automatic equipment (Modular P800, Roche Diagnostics). In our laboratory, normal calcium levels are 2.12~2.70 mmol/L.

The sample material obtained from FNAB was smeared between 2 slides, fixed by means of Cytofix, and stained with Papanicolau or dried and stained with May Grunwald-Giemsa. When cellularity was adequate (>50 cells), the parathyroid origin of the specimens was determined according to cell distribution and characteristics and background. FNAB results are frequently classified as Thy 1 to Thy 5 according to the diagnostic categories of the British Thyroid Association (BTA).

Statistical analysis

In any given patient, we regarded a PTH-FNAB value greater than that found in sera, and in any case greater than 132 ng/L, as indicative of sampling in parathyroid tissue. This value is the mean±2.5*SD* of PTH-FNAB performed in thyroid nodules in a group of 24 patients without PHP. The Tg-FNAB value was considered a further parameter of judgment. In 64 evaluations of thyroid nodules, we found a Tg-FNAB value ranging from 2 to over 2500 μg/L (median 804 μg/L; mean±*SEM* (1354±146) μg/L). The sensitivity and positive predictive value (PPV) of cytology and PTH-FNAB versus MIBI alone were evaluated.

Data were analyzed by means of the Prism 4.0 software (GraphPad Software, San Diego, CA, USA). All values quoted are mean±*SEM*. Significance was taken as $P<0.05$. To compare continuous or percentage data, the Mann-Whitney test and Fisher's exact test were used.

RESULTS

Only 10 patients showed a normal thyroid pattern on US (Group 1), while thyroid abnormalities were observed in the remaining 37 patients (Group 2). Single or multiple thyroid nodules, a diffuse goitre or hypoechogenic pattern, and a non-nodular thyroid remnant of previous thyroid surgery were found in 30, 4, and 3 patients, respectively (Table 1). A significant difference in age was noted between Group 1 and Group 2 ($P=0.03$). On average, f-T4 and TSH levels were similar in both groups (Table 1). At the time of FNAB, the average value of serum calcium was (2.75±0.05) mmol/L. No difference in average calcemia was noted between Group 1 and Group 2 (Table 1). PTH levels varied widely, ranging from 65 to 1674 ng/L, with a mean value of (275.3±45.7) ng/L (median 169 ng/L). No difference was noted in PTH levels between Group 1 (median 250 ng/L; range 69~624 ng/L) and Group 2 (median 160.5 ng/L; range 65~1674 ng/L) (Table 1).

Table 1 Some clinical data of patients in Group 1 and Group 2

	Value		Significance
	Group 1	Group 2	
Age (year)	69.3±10.7	61.7±11.7	$P=0.03$
PTH (ng/L)	232.8±56.5	285.6±55.0	ns
Calcium (mmol/L)	2.77±0.10	2.75±0.05	ns
F-T4 (pmol/L)	13.5±1.7	14.8±0.5	ns
TSH (mU/L)	1.5±0.2	1.4±0.3	ns
Patient number			
Sex, M/F	2/8	7/30	−
US finding			−
Normal	10	−	
Multi-nodular goitre	−	18	
Uni-nodular goitre	−	12	
Thyroid remnant	−	3	
Goitre	−	2	
Diffuse hypoechogenic	−	2	

Data are expressed as mean±*SEM*, except those for age as mean±*SD*

On US, the average size of lesions suspected of being enlarged parathyroid glands was (18.0±1.2) mm, with no significant difference between Group 1 ((15.0±1.5) mm) and Group 2 ((18.7±1.5) mm). Post-FNAB cytology was indicative of sampling in thyroid tissue in the majority of patients (79%, 37/47), but a precise Thy score (from 2 to 5 according to the BTA) was obtained in only 38% cases (14/37). In 2 patients of Group 2 (cases 5 and 18) cytology prompted surgical evaluation. In 8 patients, cytological results were indicative of sampling in hyperplastic parathyroid tissue (Group 1: 30%, 3/10; Group 2: 13.5%, 5/37; ns) (Table 2). Table 2 reports individual PTH-FNAB and Tg-FNAB values. In 47% (22/47) of patients PTH-FNAB values were indicative of sampling in parathyroid tissue, while Tg-FNAB values were elevated in 51% (22/43) of patients, as a result of thyroid contamination (Group 1: 67%, 6/9; Group 2: 47%, 16/34). No correlation was found between PTH-FNAB and Tg-FNAB.

Cytology plus US-guided PTH-FNAB indicated that the sample had been taken in parathyroid tissue in 47% (22/47) of patients, positivity being higher (P=0.08, ns) in Group 1 (70%, 7/10) than in Group 2 (38%, 14/37) patients. MIBI proved positive for parathyroid localization in 64% (21/33) (Group 1: 57%, 4/7; Group 2: 65%, 17/26) of assessable patients. A concordance between FNAB and MIBI was observed in 66% (22/33) of patients (positive concordance n=12; negative concordance n=10). Surgery

Table 2 Individual size and location of target, and cytological and biochemical results of FNAB

Case	Ø target size (mm)	FNAB cytology[1]	Location[2]	PTH-FNAB (ng/L)	Tg-FNAB (μg/L)	Case	Ø target size (mm)	FNAB cytology[1]	Location[2]	PTH-FNAB (ng/L)	Tg-FNAB (μg/L)
Group 1						Group 2					
1	22	Thy 1	L, I	260	>2500	14	24	Thy 2	L, I	>2000	466
2	18	Thy 1	L	5	747	15[9]	16	Thy 2	L, I	734	1
3	12	Thy 1	L	>2000	>2500	16	11	Thy 2	L	12	1000
4	8	Thy 1	R, I	>2000	>2500	17	26	Thy 2	L	2	>2500
5	19	Thy 1	L	>2000	>2500	18	20	Thy 3	R, I	33	274
6	21	HP	R, I	1854		19	22	HP	R, I	>2000	54
7	12	HP	L, S	>2000	>2500	20	8	Thy 1	R, I	11	4
8[3]	15	Thy 1	R, S	2	3	21	17	HP	R, I	1715	674
9	18	HP	R, I	>2000	>2500	22	20	Thy 2	L, I	5	
10	10	Thy 1	L, I	23	36	23[10]	10	Thy 2	R, I	2	799
Group 2						24	11	Thy 2	L, I	3	30
1	31	Thy 2	R, I, C	>2000	>2500	25	11	Thy 2	R, S	14	>2500
2	10	Thy 2	R, S	<2		26	31	Thy 2	L	7	>2500
3	18	Thy 2	L, I	4	>2500	27	14	Thy 1	R, I	>2000	
4	24	HP	R	>2000	>2500	28	30	Thy 2	R	3	1839
5	10	Thy 5	R	6	>2500	29[11]	12	Thy 1	L, I	2	>2500
6	46	FC	R, I	>2000	>2500	30[12]	21	Thy 2	L	111	76
7[4]	16	HP	L, I	820	820	31[13]	9	Thy 2	L	2	>2500
8[5]	22	Thy 1	R, I, C	156	3	32	45	Thy 2	R	2	370
9	17	LN	L	2	1097	33	16	Thy 2	R, I	2	771
10	12	Thy 1	L, I	>2000	199	34	15	Thy 1	R, I	1249	8
11[6]	15	Thy 2	L, I	>2000	274	35[14]	13	Thy 2	R	3	431
12[7]	11	Thy 2	R	20	>2500	36	22	Thy 1	R	>2000	652
13[8]	9	Thy 2	R	5	>2500	37	28	HP	R, C	>2000	2

[1]Cytological diagnoses are reported according to the BTA when follicular cells were seen; the other cytological diagnoses were: HP: hyperplastic parathyroid cells; FC: fat cells; LN: lymph node cells. [2]Location (R: right side; L: left side; I: inferior; S: superior; C: cystic) of target is reported. [3]FNAB was not repeated owing to a concomitant disease diagnosed (prostatic cancer); hyperparathyroidism was considered to be secondary (creatinine 141.4 μmol/L). [4]FNAB was also performed on isthmic thyroid nodule (size 5 mm): PTH-FNAB 15 ng/L; Tg-FNAB >2500 μg/L; Thy 2. [5]FNAB was also performed on R cystic thyroid nodule (size 12 mm): PTH-FNAB 27 ng/L; Tg-FNAB 1245 μg/L; Thy 1. [6]FNAB was also performed on R cystic thyroid nodule (size 13 mm): PTH-FNAB 2 ng/L; Tg-FNAB >2500 μg/L; Thy 1. [7]FNAB was also performed on isthmic thyroid nodule (size 22 mm): PTH-FNAB 27 ng/L; Tg-FNAB >2500 μg/L; Thy 2. [8]FNAB was also performed on L thyroid nodule (size 22 mm): PTH-FNAB 3 ng/L; Tg-FNAB >2500 μg/L; Thy 2. [9]FNAB was also performed on L thyroid nodule (size 5 mm): PTH-FNAB 2 ng/L; Tg-FNAB >2500 μg/L; Thy 2. [10]FNAB was also performed on L nodule (size 36 mm): PTH-FNAB 2 ng/L; Tg-FNAB 84 μg/L; Thy 2. [11]Patient lost to follow-up. [12]FNAB was also performed on R thyroid nodule (size 23 mm): PTH-FNAB 114 ng/L; Tg-FNAB >2500 μg/L; Thy 2. [13]FNAB was also performed on L thyroid nodule (size 14 mm): PTH-FNAB 2 ng/L; Tg-FNAB 2460 μg/L; Thy 1. [14]FNAB was also performed on L thyroid nodule (size 15 mm): PTH-FNAB 3 ng/L; Tg-FNAB 1475 μg/L; Thy 2

was not undertaken on account of mild PHP (*n*=9) and/or high surgical risk (*n*=7), multiple type-1 endocrine neoplasia diagnosed (*n*=1), and death of patient from gastric carcinoma and cardiovascular events (*n*=2). Surgery was our choice in 28 cases and was accepted by 86% (24/28) of patients. The surgical outcome is reported in Table 3. A parathyroid adenoma was located and removed in 21 out of 24 patients (87%; Group 1: 100%, 7/7; Group 2: 82%, 14/17; ns) (Table 3). Table 4 reports the sensitivity and PPV of FNAB and MIBI. FNAB evaluation yielded a higher number of true positive cases than MIBI (*P*=0.04), while no difference was observed in false positive or false negative cases. PPV was 94% and 71% for FNAB and MIBI, while sensitivity was 83% and 69%, respectively (Table 4).

Table 3 FNAB and MIBI results in locating parathyroid adenoma (PA) were compared with the surgical outcome

	FNAB result	MIBI result	Surgical outcome		FNAB result	MIBI result	Surgical outcome
Group 1				Group 2			
1[1]	P (L, I)	P (R)	PA (L, I)	10	P (L, I)	P (L, I)	PA (L, I)
2[1]	N	N	PA (L)	11[3]	P (L, I)	P (L)	PA (L, I)
3[2]	P (L)		PA (L)	12	N	N	PA (ectopic)
4	P (R, I)	P (R, I)	P (L)	13	N	P (L)	PA (R, I)
5	P (L)	N	PA (L, I)	15	P (L, I)	P (L, I)	PA (L, I)
7	P (L, S)		PA (L, S)	19	P (R, I)	P (R, I)	PA (R, I)
9	P (R, I)		PA (R, I)	21	P (R, I)	P (R)	PA (R, I)
Group 2				23	N	P (R, I)	PA not located
1	P (R, I)	N	PA (R, I)	27	P (R, I)		PA (R)
4	P (R)	P (R)	PA (R)	28	N	P (R, I)	PA not located
5[1]	N		PA not located	34	P (R, I)		PA (R, I)
6	P (R, I)	P (R, I)	PA (R, S)	36	P (R)	P (R, I)	PA (R, I)
7	P (L, I)	P (L, I)	PA (L, I)				

FNAB and MIBI results: P: positive; N: negative. The location (R: right side; L: left side; I: inferior; S: superior) of PA is reported in brackets. [1]Other diagnosis after histological evaluation or clinical follow-up: DTC (differentiated thyroid carcinoma); [2]Other diagnosis after histological evaluation or clinical follow-up: ATD (autoimmune thyroid disease); [3]A hyperplastic R I parathyroid gland also surgically removed

Table 4 Number and percentage of patients considered true positive (TP), false positive (FP) and false negative (FN) after FNAB and MIBI. The sensitivity and positive predictive value (PPV) are also reported for both FNAB and MIBI

	TP	FP	FN	PPV	sensitivity
FNAB	20/24 (84%)	1/24 (4%)	3/24 (12%)	94%	83%
MIBI	9/18 (50%)	5/18 (28%)	4/18 (22%)	71%	69%
Significance	*P*=0.04	ns	ns		

Sensitivity=$TP/(TP+FN)$; PPV=$n_1/(n_1+n_2)$, where n_1 is the number of patients with correspondence between pre-operative result and post-surgical histology in locating parathyroid adenoma (PA); n_2 is the number of patients with positive pre-surgical localization but PA in a different location on surgery. ns: not significantly

DISCUSSION

MIP is now the most attractive surgical choice, as it requires less surgery time, shorter hospitalization, and lower overall costs (Miccoli and Berti, 2001). The outcome of MIP is linked to accurate localization of the hyperfunctioning gland. As demonstrated by our study, when PHP is suspected, a US search for parathyroid tissue, together with cytological examination and PTH-FNAB whenever possible, is always justified, irrespective of PTH and calcium levels. MIBI is widely used in the preoperative localization of parathyroid adenoma (Allendorf *et al*., 2003; Bhansali *et al*., 2006; Calva-Cerqueira *et al*., 2007; Grosso *et al*., 2007); its sensitivity is greater in isolated adenomas than in multiple adenomatosis (Allendorf *et al*., 2003). False negative results are unavoidable, owing to the size, site and histological characteristics of such lesions. The most frequent cause of false positive results is the concomitant presence of thyroid nodules (Allendorf *et al*., 2003; Mihai *et al*., 2006). Normal parathyroid glands are not visible on US and false positive results are due to thyroid nodules, blood vessels, oesophagus, long collum muscle, and lateral cervical lymph nodes, while false negative results are due to atypical parathyroid location (Solbiati *et al*., 2001). Thyroid nodules were reported during neck US in 20%~80% of PHP cases (Abraham *et al*., 2007; Erbil *et al*., 2007; Lumachi *et al*., 2003; Marcocci *et al*., 1998; Mihai *et al*., 2006). Moreover, sensitivity and PPV were heavily influenced by concomitant uni- or multi-nodular thyroid goitre (Erbil *et al*., 2007; Mihai *et al*., 2006). However, it is well known that the majority of parathyroid adenomas have an inferior extrathyroid localization (Abraham *et al*., 2007); this finding was confirmed in 58% of our patients who underwent surgery.

The use of PTH-FNAB in PHP has recently been reassessed. A value of PTH in the needle-washing fluid, which is even slightly higher than that in blood, should be considered diagnostic for parathyroid localization, on account of the hormone dilution in PTH-FNAB (Marcocci *et al*., 1998). An institutional cut-off is needed. In the present study, a PTH-FNAB value higher than that of the peripheral sample and/or greater than 132 ng/L was considered to indicate that the sample was of parathyroid tissue. Our cut-off is similar to that reported by Kiblut *et al*.(2004). During intra-operative FNAB before thyroid and/or parathyroid removal, they found a PTH-FNAB value <100 ng/L in the thyroid; when sampling takes place in normal or adenomatosous parathyroid tissue, this value is widely variable and higher than 100 ng/L. An intra-operative PTH-FNAB value >1000 ng/L has been reported in 88% of patients with parathyroid adenoma. Maser *et al*.(2006) reported that a PTH-FNAB value >1000 ng/L unequivocally indicates sampling in parathyroid tissue. In our series, only 38% of patients showed PTH-FNAB values >1000 ng/L. However, our data demonstrate that even a PTH-FNAB value above our institutional cut-off is still a valid indication that hyperfunctioning parathyroid tissue has been sampled. Finally, Marcocci *et al*.(1998) regarded a PTH-FNAB >50 ng/L as positive for sampling in parathyroid tissue; considering dilution, this value could correspond to a PTH-FNAB value >1000 ng/L. Moreover, Maser *et al*.(2006) considered only PTH-FNAB <45 mg/L to be inadequate in localizing PHP. In addition, our study shows that contamination of the needle with thyroid material is rather frequent when the target of FNAB is within or adjacent to the thyroid or posterior to the thyroid lobe. A high Tg-FNAB value does not exclude a possible parathyroid nature of the lesion sampled, even though a high Tg-FNAB value associated to a low PTH-FNAB value increases the probability that the lesion pertains to the thyroid.

In our experience, only in 17% (8/47) of patients was parathyroid tissue suspected on the basis of cytology. However, cytological evaluation is an integral part of localizing techniques in PHP, even though it is less sensitive than PTH-FNAB owing to inadequate (Marcocci *et al*., 1998; Solbiati *et al*., 1983) or insufficient (Bergenfelz *et al*., 1991) smeared material or confusing results when thyroid nodules are concomitant (Marcocci *et al*., 1998; Solbiati *et al*., 1983).

In the present study, 79% (37/47) of PHP patients had thyroid alterations, generally nodules, while this finding was reported only in 30%, 45%, and 50% of patients in the studies by Abraham *et al*.(2007), Marcocci *et al*.(1998), and Erbil *et al*.(2007), respectively. In addition, the present study seems to indicate that US, FNAB, and PTH-FNAB together are more diagnostic when a thyroid disease is absent. By contrast, concomitant thyroid pathology raises the age at which diagnostic evaluation is undertaken and consequently delays the diagnosis of PHP. Recently, Erbil *et al*.(2007) reported that thyroid nodules reduce the diagnostic power of imaging studies by 20%~30% in PHP, but not the sensitivity of PTH-FNAB evaluation, in which thyroid nodules can be used as an internal control for suspected parathyroid lesions.

The size of the target can influence FNAB results. In the present experience, the mean diameter of suspected parathyroid lesions was 18 mm. Abraham *et al*.(2007) reported a positive correlation in parathyroid lesions (n=34; average size 8 mm) between the patient's age and the size of the target, and between PTH-FNAB and peripheral PTH values. These authors obtained a direct diagnosis of hyperplastic parathyroid cells in 58% of samples adequate for cytology. The discrepancies between our results and those of Abraham *et al*.(2007) could be due to the smaller number of patients with thyroid abnormalities and to differences in biopsy needles and the number of passes performed. On the other hand, it has been suggested that performing several passes could cause parathyromatosis, hematomas and adhesions around the gland, thus rendering subsequent surgery more difficult (Kendrick *et al*., 2001). No adverse events were reported in our study or in that of Erbil *et al*.(2006; 2007). Maser *et al*.(2006), who made 2~9 passes, reported 1 in situ infection, while Abraham *et al*.(2007) reported 1 syncope and Marcocci *et al*.(1998) 1 local haemorrhage. So far, more than 12 months after successful surgery, no recurrence of hyperparathyroidism as an expression of FNAB parathyromatosis has been noted in our series of patients; similar results were reported by Marcocci *et al*.(1998). However, the number of passes should strike a balance between diagnostic power and the risk of parathyromatosis; more than 2 passes are justified only in patients with a clear target and in whom previous surgery has failed.

In our hands, MIBI often proved non-diagnostic, except in patients with thyroid abnormalities. In the study by Erbil *et al*.(2007), the sensitivity of MIBI was 80% in patients with thyroid nodules and 96% in those without, and PPV was 85% and 100%, respectively. By contrast, we recorded a sensitivity of 69% and a PPV of 71% on comparing MIBI results with those of post-surgical histological analyses. Our data show a greater localizing power of PTH-FNAB than that of MIBI; PTH-FNAB and MIBI yielded true positive results in 83% and 50% of cases, respectively, while false positives plus false negatives were 17% and 50%. Several variables (operator and equipment, sample size, percentage of thyroid abnormalities, and percentage of patients with ectopic parathyroid glands) could explain the differences in the data reported. In the study by Abraham *et al*.(2007), cytological results and PTH-FNAB values were compared with MIBI results in a small number (n=18) of patients; concordance between evaluations and the results of post-surgical histological analysis was observed in 44% of patients, while MIBI alone yielded incorrect or no localization in 17% and 38% of patients, respectively. It is important to note that, in the study by Abraham *et al*.(2007), only 2 out of 7 MIBI-negative patients were also PTH-FNAB negative. Therefore, in our opinion, when MIBI is associated to US evaluation, its diagnostic power increases; however, it is strongly operator- and machine-dependent and is further influenced by abnormal thyroid morphology. PTH-FNAB sensitivity (91%) and specificity (100%) are very high (Barczynski *et al*., 2006). Erbil *et al*. (2007) reported 100% sensitivity and 100% PPV for PTH-FNAB; these percentages are higher than those reported for US (96% and 91%) and MIBI (92% and 87%) or for both investigations combined (95% and 91%).

In conclusion, our study confirms the importance of US-guided PTH-FNAB in locating hyperfunctioning parathyroid tissue. PTH-FNAB data were confirmed by post-surgical histology in 100% of patients without thyroid abnormalities; this success rate fell to 82% when thyroid abnormalities were present. In comparison with MIBI, PTH-FNAB showed greater sensitivity and PPV. In PHP patients, FNAB for cytological purposes alone should not be performed in the light of its low diagnostic sensitivity. Balancing the number of passes can improve PTH-FNAB results without increasing adverse events. The main diagnostic limitation of PTH-FNAB sampling is posed by a small and/or unclear target. All available techniques are sequentially justified in order to improve surgical outcome when thyroid abnormalities are concomitant (Zheng *et al*., 2007).

References

Abraham, D., Sharma, P.K., Bentz, J., Gault, P.M., Neumayer, L., McClain, D.A., 2007. Utility of ultrasound-guided fine-needle aspiration of parathyroid adenomas for localization before minimally invasive parathyroidectomy. *Endocr. Pract.*, **13**(4):333-337.

Allendorf, J., Kim, L., Chabot, J., DiGiorgi, M., Spanknebel, K., LoGerfo, P., 2003. The impact of sestamibi scanning on the outcome of parathyroid surgery. *J. Clin. Endocrinol. Metab.*, **88**(7):3015-3018. [doi:10.1210/jc.2002-021095]

Barczynski, M., Golkowski, F., Konturek, A., Buziak-Bereza, M., Cichon, S., Hubalewska-Dydejczyk, A., Huszno, B., Szybinski, Z., 2006. Technetium-99m-sestamibi subtraction scintigraphy vs ultrasonography combined with a rapid parathyroid hormone assay in parathyroid aspirates in preoperative localization of adenomas and in directing surgical approach. *Clin. Endocrinol. (Oxf)*, **65**(1): 106-113. [doi:10.1111/j.1365-2265.2006.02556.x]

Bergenfelz, A., Forsberg, L., Hederstrom, E., Ahren, B., 1991. Preoperative localization of enlarged parathyroid glands with ultrasonically guided fine needle aspiration for parathyroid hormone assay. *Acta Radiol.*, **32**(5):403-405.

Bhansali, A., Masoodi, S.R., Bhadada, S., Mittal, B.R., Behra, A., Singh, P., 2006. Ultrasonogrphy in detection of single and multiple abnormal parathyroid glands in primary hyperparathyroidism: comparison with radionuclide scintigraphy and surgery. *Clin. Endocrinol. (Oxf)*, **65**(3): 340-345. [doi:10.1111/j.1365-2265.2006.02601.x]

Calva-Cerqueira, D., Smith, B.J., Hostetler, M.L., Lai, G., Menda, Y., O'Dorisio, T.M., Howe, Y.R., 2007. Minimally invasive parathyroidectomy and preoperative MIBI scan: correlation of gland weight and preoperative PTH. *J. Am. Coll. Surg.*, **205**(4 Suppl.):S38-S44. [doi:10.1016/j.jamcollsurg.2007.06.322]

Doppman, J.L., Krudy, A.G., Marx, S.J., Saxe, A., Schneider, P., Norton, Y.A., Spiegel, A.M., Downs, R.W., Schaaf, M., Brennan, M.E., Schneider, A.B., Aurbach, G.D., 1983. Aspiration of enlarged parathyroid glands for parathyroid hormone assay. *Radiology*, **148**(1):31-35.

Erbil, Y., Barbaros, U., Salmaslioglu, A., Tunaci, M., Ozbey, N., Bozbora, A., Ozmarmagan, S., 2006. Values of parathyroid assay for preoperative sonographically guided parathyroid aspirates for minimally invasive parathyroidectomy. *J. Clin. Ultrasound.*, **34**(9):425-429. [doi:10.1002/jcu.20275]

Erbil, Y., Salmaslioglu, A., Kabul, E., Issever, H., Tunaci, M., Adalet, I., Bozbora, A., Ozmarmagan, S., 2007. Use of preoperative parathyroid fine-needle asipiration and parathormone assay in primary hyperparathyroidism with concomitant thyroid nodules. *Am. J. Surg.*, **193**(6): 665-671. [doi:10.1016/j.amjsurg.2006.09.038]

Grosso, I., Sargiotto, A., D'Amelio, P., Tamone, C., Gasparri, G., de Filippi, P.G., Picciotto, G., Isaia, G., 2007. Preoperative localization of parathyroid adenoma with sonography and 99mTc-sestamibi scintigraphy in primary hyperparathyroidism. *J. Clin. Ultrasound.*, **35**(4):186-190. [doi:10.1002/jcu.20319]

Kendrick, M.L., Charboneau, J.W., Curlee, K.J., van Heerden, J.A., Farley, D.R., 2001. Risk of parathyromatosis after fine-needle aspiration. *Am. Surg.*, **67**(3):290-293.

Kiblut, N.K., Cussac, J.F., Soudan, B., Farrell, S.G., Armstrong, J.A., Arnalsteen, L., Biechlin, A., Delattre, A.A., Proye, C.A., 2004. Fine needle aspiration and intraparathyroid intact parathyroid hormone measurement for reoperative parathyroid surgery. *World J. Surg.*, **28**(11): 1143-1147. [doi:10.1007/s00268-004-7563-5]

Lumachi, F., Marzola, M.C., Zucchetta, P., Tregnaghi, A., Cecchin, D., Bui, F., 2003. Hyperfunctioning parathyroid tumours in patients with thyroid nodules. Sensitivity and positive predictive value of high-resolution ultrasonography and ^{99m}Tc-sestamibi scintigraphy. *Endocr. Relat. Cancer*, **10**(3):419-423. [doi:10.1677/erc.0.0100419]

Marcocci, C., Mazzeo, S., Bruno-Bossio, G., Picone, A., Vignali, E., Ciampi, M., Vacava, P., Naccarato, A.G., Miccoli, P., Iacconi, P., Pinchera, A., 1998. Preoperative localization of suspicious parathyroid adenomas by assay of parathyroid hormone in needle aspirates. *Eur. J. Endocrinol.*, **139**(1):72-77. [doi:10.1530/eje.0.1390072]

Masatsugu, T., Yamashita, H., Noguchi, S., Nishii, R., Watanabe, S., Uchino, S., Kuroki, S., Tanaka, M., 2005. Significant differences in primary hyperparathyroidism between patients with and those without concomitant thyroid disease. *Surg. Today*, **35**(5):351-356. [doi:10.1007/s00595-004-2952-9]

Maser, C., Donovan, P., Santos, F., Donabedian, R., Rinder, C., Scoutt, L., Udelman, R., 2006. Sonographically guided fine needle aspiration with rapid parathyroid hormone assay. *Ann. Surg. Oncol.*, **13**(12):1690-1695. [doi:10.1245/s10434-006-9180-z]

Miccoli, P., Berti, P., 2001. Minimally invasive parathyroid surgery. *Best Pract. Res. Clin. Endocrinol. Metab.*, **15**(2):139-147. [doi:10.1053/beem.2001.0131]

Mihai, R., Gleeson, F., Buley, I.D., Roskell, D.E., Sadler, G.P., 2006. Negative imaging studies for primary hyperparathyroidism and unavoidable: correlation of sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. *World J. Surg.*, **30**(5):697-704. [doi:10.1007/s00268-005-0338-9]

Rodgers, S.E., Lew, J.I., Salorzano, C.C., 2008. Primary hyperparathyroidism. *Curr. Opin. Oncol.*, **20**(1):52-58. [doi:10.1097/CCO.0b013e3282f2838f]

Solbiati, L., Montali, G., Croce, F., Bellotti, E., Giangrande, A., Ravetto, C., 1983. Parathyroid tumors detected by fine-needle aspiration biopsy under ultrasonic guidance. *Radiology*, **148**(3):793-797.

Solbiati, L., Osti, V., Cova, L., Tonolini, M., 2001. Ultrasound of thyroid, parathyroid glands and neck lymph nodes. *Eur. Radiol.*, **11**(12):2411-2424. [doi:10.1007/s00330-001-1163-7]

Zheng, Y.X., Xu, S.M., Wang, P., Chen, L., 2007. Preoperative localization and minimally invasive management of primary hyperparathyroidism concomitant with thyroid disease. *J. Zhejiang Univ. Sci. B*, **8**(9):626-631. [doi:10.1631/jzus.2007.B0626]