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Usefulness of PTH measurements in FNAB washouts in the identification of pathological parathyroids — analysis of the factors that influence the effectiveness of this method

Przydatność oznaczania stężenia PTH w popłuczynach z igły do biopsji aspiracyjnej cienkoigłowej w identyfikowaniu patologicznych przytarczyc — analiza czynników wpływających na skuteczność tej metody

Bożena Popowicz*[1], Mariusz Klencki*[1], Stanisław Sporny[2], Joanna Jankiewicz-Wika[3], Jan Komorowski[3], Hanna Pisarek[4], Dorota Słowińska-Klencka[1]

****B. Popowicz and M. Klencki contributed equally to this work***

[1]*Department of Morphometry of Endocrine Glands, Chair of Endocrinology, Medical University of Lodz, Poland*
[2]*Department of Dental Pathology, Chair of Pathology, Medical University of Lodz, Poland*
[3]*Clinic of Endocrinology, Chair of Endocrinology, Medical University of Lodz, Poland*
[4]*Department of Neuroendocrinology, Chair of Laboratory Diagnostics, Medical University of Lodz, Poland*

Abstract

Introduction: The aim of this investigation was to assess the usefulness of the measurement of PTH concentration in the material obtained during FNAB (PTH-FNAB) in the identification of pathological parathyroids in patients with frequently coexisting thyroid abnormalities (nodular goitre, chronic thyroiditis, previous thyroidectomy). Additionally, the influence of the size of goitre, parathyroid localisation and size on the results of PTH-FNAB measurement was examined.

Material and methods: Fifty patients with primary hyperparathyroidism and sonographically detected focal lesion that was suggestive of parathyroid gland were included in this study. PTH-FNAB results were correlated with the outcome of routine cytological examination and biochemical indices of hyperparathyroidism, SPECT-CT (33 patients) and histopathological examination (20 patients).

Results: Positive PTH-FNAB was observed in 80% of patients, and in more than 70% of persons with non-diagnostic smears or smears 'contaminated' with thyroid follicular cells. In the group of operated patients, sensitivity of PTH-FNAB (95.0%) was higher than SPECT-CT (64.3%, $p < 0.05$). Presence of nodular goitre and/or chronic thyroiditis exerts a two times stronger negative effect on percentage of negative results of SPECT-CT than of PTH-FNAB. On the other hand, lower frequency of positive PTH-FNAB but not SPECT-CT was observed when the thickness of the thyroid was ≥ 20 mm (50% *v.* 87.5%, $p < 0.05$) and when the thickness of a lesion suspected of parathyroid pathology was ≤ 5 mm (66.7% *v.* 93.3%, $p < 0.05$).

Conclusions: In patients with thyroid abnormalities, PTH-FNAB measurements show advantages over routine biopsy and SPECT-CT in the identification of typically located pathological parathyroids. **(Endokrynol Pol 2014; 65 (1): 25–32)**

Key words: *PTH; parathyroid; FNAB; thyroid*

Streszczenie

Wstęp: Celem badania była ocena przydatności pomiaru stężenia PTH w materiale uzyskanym podczas biopsji (PTH-BAC) w identyfikacji patologicznych przytarczyc u pacjentów z często współistniejącymi nieprawidłowościami tarczycy (wolem guzkowym, przewlekłym zapaleniem tarczycy i stanem po operacji tarczycy). Dodatkowo analizowano wpływ wielkości tarczycy, lokalizacji przytarczyc i ich rozmiaru na skuteczność powyższej metody.

Materiał i metody: Do badania zakwalifikowano 50 pacjentów z pierwotną nadczynnością przytarczyc i wykrytymi w USG zmianami ogniskowymi mogącymi odpowiadać patologicznym przytarczycom. Wyniki oceny PTH-BAC zostały skorelowane z rezultatami rutynowego badania cytologicznego i biochemicznymi wskaźnikami nadczynności przytarczyc, a także wynikami SPECT-CT (33 pacjentów) oraz pooperacyjnego badania histopatologicznego (20 pacjentów).

Wyniki: Dodatnie wyniki PTH-BAC stwierdzono u 80% chorych, w tym u ponad 70% osób z rozmazami niediagnostycznymi lub z rozmazami zawierającymi komórki pęcherzykowe tarczycy. W grupie operowanych czułość PTH-BAC była wyższa niż SPECT-CT (95% *v.* 64,3%, $p < 0,05$). Stwierdzono, że obecność wola guzkowego i/lub przewlekłego zapalenia tarczycy wywiera 2-krotnie silniejszy negatywny wpływ na odsetek ujemnych wyników SPECT-CT niż wyników PTH-BAC. Z drugiej strony, mniejszą częstość dodatnich wyników PTH-BAC, ale nie SPECT-CT, zaobserwowano, gdy grubość tarczycy była ≥ 20 mm (50% *v.* 87,5%, $p < 0,05$) lub gdy grubość zmiany podejrzanej była ≤ 5 mm (66,7% *v.* 93,3%, $p < 0,05$).

Wnioski: U chorych z nieprawidłowościami morfologicznymi tarczycy ocena PTH-BAC ma przewagę nad rutynową biopsją i SPECT-CT w identyfikacji typowo położonych patologicznych przytarczyc. **(Endokrynol Pol 2014; 65 (1): 25–32)**

Słowa kluczowe: *PTH; przytarczyce; BAC; tarczyca*

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Prof. Dorota Słowińska-Klencka M.D., Ph.D., Department of Morphometry of Endocrine Glands, Chair of Endocrinology, Medical University of Lodz, Poland, Sterlinga St. 5, 91–425 Lodz, Poland, tel./fax: 48 42 632 25 94, e-mail: dsk@tyreo.umed.lodz.pl

Introduction

Selective surgical excision of the hyperfunctioning parathyroid gland is the treatment of choice in patients with clinically significant primary hyperparathyroidism (PHP) [1–2]. Therefore, preoperative localisation of the adenoma is critical in the evaluation of the patient before surgical resection. Unfortunately, there are significant diagnostic problems with identification of the glands that are the source of overproduction of parathormone (PTH). Ultrasound imaging (US) lacks necessary specificity in this respect. Scintigraphy shows some advantages over US, as it not only localises the lesion, but also allows confirmation of its parathyroid origin. However, thyroid nodularity and the presence of chronic thyroiditis lower the efficiency of both those examinations [3–9]. Other imaging examinations (e.g. computed tomography (CT), and magnetic resonance imaging) do not present satisfactory effectiveness either but significantly increase the diagnostic costs [10].

Better prospects are related to a combination of CT and scintigraphy (SPECT-CT system), which - according to some investigators — is particularly useful in the diagnostics of parathyroids in patients with thyroid nodules [11–12]. However, this needs confirmation in further studies.

The routine microscopic evaluation of specimens obtained by fine-needle aspiration biopsy (FNAB) of suspected neck lesions in the majority of cases does not solve diagnostic doubts because of the significant overlap in cytomorphologic features of parathyroid and thyroid follicular cells [13–14]. However, it is possible to determine PTH in the material aspirated by means of FNAB. The published reports on this method are encouraging so far [6, 8, 9, 15–25]. But only in a few studies has the influence of co-existing nodular goitre on the discussed method been analysed [6, 8, 24]. This method has been applied in patients with chronic thyroiditis in a single report only [9]. Both mentioned disorders not only make it more difficult to localise pathological parathyroids in the extrathyroidal space but also present an additional need for differentiation of parathyroids from intrathyroid lesions in imaging studies [9, 27, 28]. The disorders may also influence the effectiveness of FNAB because of the goitre size, presence of calcifications, or fibrosis of the gland in the course of chronic thyroiditis (or as a result of radioiodine therapy).

The aim of this investigation was to assess the usefulness of the measurement of PTH concentration in material obtained during FNAB (PTH-FNAB) in confirmation of the origin (parathyroid/non-parathyroid) of a sonographically detected lesion in patients with frequently coexisting thyroid abnormalities (nodular goitre, chronic thyroiditis, previous thyroidectomy). Additionally, the role was evaluated of the factors which can potentially influence the effectiveness of that method — size of goitre, parathyroid localisation and its size.

Material and methods

This study was performed in 2010–2012 at the Department of Ultrasonography and Thyroid Biopsy, University Hospital No 2 in Lodz, Poland. The analysis included 50 patients with PHP (48 females and two males), with a focal lesion that was suggestive of a parathyroid gland detected in US (i.e. homogenously echogenic structure, usually less echogenic than the thyroid gland, with the presence of feeding polar vessel, located most commonly behind the inferior part of the thyroid lobe) (Fig. 1). The diagnosis of PHP was made on the basis of elevated PTH (with corrected vitamin D supply), accompanied — in the majority of patients — by hypercalcaemia. In nine patients, normocalcaemic PHP was diagnosed after the exclusion of other causes of elevated PTH with normal serum calcium according to the guidelines of the Third International Workshop on Asymptomatic Primary Hyperparathyroidism [29]. The patients were referred to US examination of the thyroid and parathyroid glands from the endocrine outpatient clinic. PTH-FNAB was examined in the material from the lesions suspected of parathyroid origin as well as in the material obtained from accompanying thyroid nodules (internal controls — 36 lesions in 32 patients). In the case of thyroid nodules, FNAB was performed in accordance with the current recommendations on thyroid cytology [30–31].

PTH-FNAB results were correlated with biochemical indices of hyperparathyroidism (PTH and calcium serum concentration, urinary calcium excretion), the outcome of routine cytological examination, results of scintigraphic imaging (33 patients) and histopathological examination (20 patients). Additionally, the occurrence of conditions associated with PHP was analysed (pancreatitis, nephrolithiasis, peptic ulcers, osteoporosis, neuromuscular dysfunction) and the presence of indications for surgery (in asymptomatic patients, as recommended by the Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism) [29].

The influence of various factors on the efficacy of the PTH-FNAB method in confirming parathyroid origin of the suspected lesions was evaluated. That analysis included localisation of the suspected lesion in relation to the thyroid, size of the lesion, type of the coexisting thyroid pathology (nodular goitre, chronic thyroiditis, previous thyroidectomy), and the distance between the lesion and the skin surface. Finally, in the group

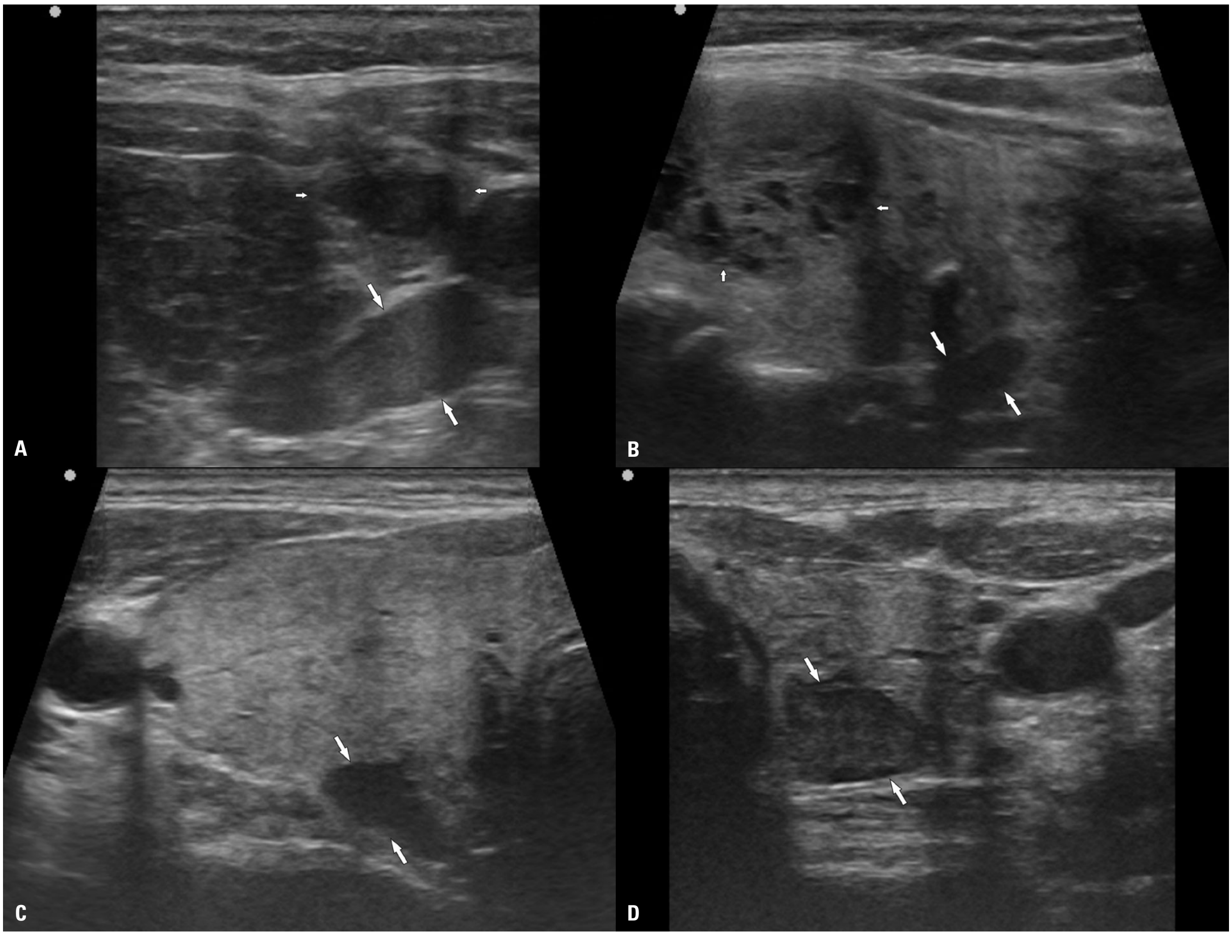

Figure 1A. *Pathological parathyroid (long arrows) in a patient with chronic thyroiditis and a thyroid nodule (short arrows).* **B.** *Pathological parathyroid (long arrows) in a patient with a thyroid nodule (short arrows) and an intrathyroid calcification.* **C.** *Pathological parathyroid (arrows) located in the posterior part of the thyroid right lobe.* **D.** *Pathological parathyroid (arrows) in a patient with chronic thyroiditis*

Rycina 1A. *Patologiczne zmieniona przytarczyca (długie strzałki) u pacjenta z przewlekłym zapaleniem tarczycy i zmianą ogniskową tarczycy (krótkie strzałki).* **B.** *Patologicznie zmieniona przytarczyca (strzałki) u pacjenta ze zmianą ogniskową tarczycy i wewnątrztarczycowym zwapnieniem.* **C.** *Patologicznie zmieniona przytarczyca (strzałki) zlokalizowana w tylnej części prawego płata tarczycy.* **D.** *Patologicznie zmieniona przytarczyca (strzałki) u pacjenta z przewlekłym zapaleniem tarczycy*

of operated patients, the sensitivity of PTH-FNAB was evaluated on the basis of postoperative histopathological examinations.

The study protocol was approved by the local bioethical committee. Written informed consent was obtained from each patient before participation in the study.

US examination

All the US examinations were performed by two experienced sonographers, with the use of two high-resolution sonographs with a 7.5–14 MHz linear transducer and power Doppler capability: before September 2011 — Siemens Elegra Advanced (Siemens Medical Systems Inc., Issaquah, WA, USA), and subsequently Aloka Prosound Alpha 7 (ALOKA Co Ltd, Tokyo, Japan).

FNAB

All the biopsies were US-guided. In order to obtain a sufficient amount of diagnostic material, usually two aspirations of each examined lesion were performed. Ten-millilitre syringes, mounted in aspirating syringe holders with 25 gauge (0.5 or 0.42 mm) needles, were used in the process. Biopsy samples were smeared onto glass slides for cytologic examination. Then the needle was immediately washed out with 1 ml of normal saline solution, and the collected fluid was sent to the laboratory for PTH determination. All the smears were fixed in 95% ethanol and stained with haematoxylin and eosin.

PTH, PTH-FNAB measurements

PTH levels were measured after centrifugation of fluid in supernatant by means of solid phase, two-site chemiluminescent enzyme-labelled immunometric assay (IMMULITE 1000 from Siemens). The sensitivity of the PTH assay was 3 pg/mL (0.6 pmol/L) and the measuring range was 3–5,000 pg/mL. Intra-assay precision varied between 5.5–6.3% and inter-assay precision between 7.9–8.6%; normal range was 10–69 pg/mL. We regarded PTH-FNAB samples with a value above 50 pg/mL and amounting to at least 20% of serum PTH concentration as indicative of sampling parathyroid tissue. One can safely assume that the residual material in a needle while being washed out with 1 ml of 0.9% NaCl is diluted at least 20 times. Thus the threshold of 50 pg/mL in the washout corresponds to at least 1,000 pg/mL of PTH in an undiluted sample. Such a value is usually found in pathological parathyroids, according to the report by Kiblut et al. [32]. An additional condition, for positive PTH-FNAB to be higher than 20% of serum PTH concentration, was set to secure the reliability of the method in patients with very high serum PTH levels.

Other laboratory examinations

Serum total-calcium was determined by fully automatic equipment (Roche Diagnostics Cobas Integra System Calcium, method according to Schwarzenbach with o-cresolphthalein complexone). Normal ranges were 2.2–2.65 mmol/L for serum calcium (analytical sensitivity 0.01 mmol/L) and 2.5–8.0 mmol/d for urine calcium excretion on a 24-h urine collection (analytical sensitivity 0.013 mmol/L).

Scintigraphic imaging

The analysis included the outcomes of routinely performed scintigraphic imaging. The examinations were performed at University Hospital No 2 in Lodz, Poland and Central Teaching Hospital in Lodz, Poland with single photon emission computed tomography (SPECT) with the use of technetium-99m (99mTc) sestamibi as the radiotracer, combined with X-ray based computed tomography (CT) — SPECT-CT. Two distinct types of data acquisition protocols were used. The first was a dual radionuclide approach with subtraction of a 99mTc pertechnetate image from sestamibi image; the second approach was sestamibi alone with early and delayed imaging (double-phase study). The latter imaging protocol is based on the different washout of the sestamibi in the thyroid and parathyroid lesions.

Surgical treatment and histopathological examination

The examined patients were operated in several hospitals. The bilateral exploration was performed in the majority of them. Because of the high incidence of nodular goitre, subtotal thyroidectomy was simultaneously performed in nearly half of the patients. Minimally invasive surgery was performed in some cases. The removed tissues were processed by standard procedures. If necessary, immunohistochemical examinations were applied.

Statistical analysis

Continuous variables were analysed with ANOVA and Newman–Keuls test or if necessary with the non-parametric Kruskal-Wallis and Mann-Whitney U tests. The comparison of frequency distributions was performed with Chi-square test (or with Yates corrected Chi-square test). Correlations were assessed with the Pearson *r* coefficient. A value of 0.05 was assumed as the level of significance.

Results

In all the examined patients, mean serum PTH concentration was 312.6 ± 395.3 pg/mL (mean ± SD), mean serum Ca level was 2.81 ± 0.35 mmol/L, and mean urinary calcium excretion was 8.31 ± 3.54 mmol/d. Moderate positive correlation was found between serum PTH and serum Ca concentrations ($r = 0.475$, $p < 0.05$) as well as between serum Ca level and urinary calcium excretion ($r = 0.341$, $p < 0.05$).

Positive PTH-FNAB was observed in 40 patients. Table I shows data on the patients in relation to the result of PTH-FNAB. The mean positive PTH-FNAB concentration was many times higher than that observed in the case of negative results ($p < 0.0002$), as well as in the case of thyroid nodules – internal controls: 3.42 ± 2.19 pg/mL (< 3 — 5.38 pg/mL) ($p < 0.0001$). A weak negative correlation was noted between the patient's age and PTH-FNAB concentration ($r = –0.331$, $p < 0.05$). Mean serum PTH and Ca concentrations as well as mean urinary Ca excretion did not differ significantly between the patients with positive and negative PTH-FNAB results. It should be noted that the higher values tended to be observed in the PTH-FNAB positive group.

Routine FNAB was positive (parathyroid cells described in cytological outcome) in 15 cases (30.0%) of biopsied lesions suspected of parathyroid origin. In all those cases, PTH-FNAB result was also positive. High PTH-FNAB concentration was also observed in 25 out of 35 (71.4%) other biopsies, including 12 cases out of 17 non-diagnostic FNAB (70.6%) and 13 out of 18 cases with thyroid follicular cells identified in cytological smears (72.2%). The results of FNAB of neighbouring thyroid nodules (internal negative control — 36 nodules in 32 patients) showed benign lesions in 26 (72.2%) cases (including chronic thyroiditis in seven patients), follicular lesions of undetermined significance in two cases (5.6%), and papillary cancer in one patient (2.8%). Diagnostic cellular material was not obtained from

Table I. *Data on age, laboratory findings, outcomes of routine FNAB and scintigraphy of the patients with positive and negative PTH-FNAB results*

Tabela I. *Dane dotyczące wieku, rezultatów badań laboratoryjnych oraz rutynowej BAC i scyntygrafii u pacjentów z dodatnimi i ujemnymi wynikami oceny PTH-BAC*

	PTH-FNAB positive	PTH-FNAB negative
No/% of patients	40/80.0	10/20.0
Age, mean ± SD	59.5 ± 11.5	70.0 ± 8.9[a]
Min–Max	30–88	50–64
PTH-FNAB [pg/mL], mean ± SD	2,822.4 ± 2,061.3	12.3 ± 8.7[b]
Min–max	72.7–> 5,000.0	< 3.00–21.1
Serum PTH [pg/mL], mean ± SD	333.5 ± 428.3	220.4 ± 196.9
Min–max	70.0–1,852.0	92.9–744.8
Serum Ca [mmol/L], mean ± SD	2.8 ± 0.4	2.8 ± 0.2
Min–max	2.5–4.6	2.5–3.0
Urine Ca [mmol/d], mean ± SD	8.4 ± 3.6	8.2 ± 3.4
Min–max	2.5–20.0	3.1–12.0
No/% of patients with diagnostic FNAB	28/70.0	5/50.0
No/% of patients with positive FNAB	15/53.4	0/0.0
No/% of patients with non-diagnostics FNAB	12/30.0	5/50.0
No/% of patients with scintigraphy	24/60.0	9/90.0
No/% of patients with positive scintigraphy	17/70.8	4/44.4
No/% of patients with equivocal scintigraphy	0/0.0	3/33.3
No/% of patients with negative scintigraphy	7/29.2	2/22.2
No/% of patients with surgical treatment	19/47.5	1/10.0

[a]$p < 0.01$; [b]$p < 0.0002$

seven (19.4%) nodules (three of them were partially cystic and mainly blood and macrophages were aspirated) (Table I).

Scintigraphy of the parathyroids was performed in 33 (66.0%) patients. In 21 patients (63.6%), scintigraphy was positive and in 17 of them (81.0%) PTH-FNAB was positive too. Negative PTH-FNAB results in two cases were related to the lesions located behind the thyroid, deeper than 35 mm from the skin surface; in one case the lesion suspected of parathyroid origin was identified by ultrasound imaging in the lateral section of the neck in the neighbourhood of large vessels, and in another case the negative PTH-FNAB result was probably a consequence of the very small size of the lesion (its thickness equalled 4 mm). Of nine patients with a negative result of scintigraphy, positive PTH-FNAB results were observed in seven cases (77.8%). In all three patients with equivocal scintigraphy, PTH-FNAB was negative (in two cases the thickness of the suspected lesion was ≤ 5 mm, in all of them multiple thyroid nodules were present, while chronic thyroiditis was present in two of them) (Table I).

No significant differences were found in the mean thyroid volume or its thickness between the patients with positive and negative PTH-FNAB, although in both cases higher mean values were observed in the PTH-FNAB negative group (Table II). Positive PTH-FNAB results were noted in 25 out of 32 (78.1%) cases of suspected lesions located behind the thyroid gland, in 14 out of 16 (87.5%, NS) cases of lesions located below the lower pole of the thyroid lobe, and in one case of intrathyroidal lesion. In the case of lesions located behind the thyroid, the higher frequency of negative PTH-FNAB was observed when the thyroid thickness was ≥ 20 mm compared to the thyroid thickness < 20 mm 50.0% (4/8 cases) *v.* 12.5% (3/24 cases), ($p < 0.05$). Similar relations were not observed between the patients with positive and negative scintiscans.

No significant differences were found between lesions with positive and negative PTH-FNAB in terms of either their volume or thickness (Table II). However, after the exclusion from the analysis of three cases which — because of goitre and adipose tissue — were located deeper than 35 mm from the skin surface, a marked decrease in the mean volume and thickness of PTH-FNAB negative lesions was noted — to the level observed in the cases with negative scintigraphy. After that exclusion, a moderate positive correlation between

Table II. *Comparison of the thyroid size, the size of focal lesion suggestive of pathological parathyroid, and the presence of thyroid abnormalities in patients with positive and negative results of PTH-FNAB and SPECT-CT*

Tabela II. *Porównanie rozmiarów tarczycy i rozmiarów ognisk mogących odpowiadać przytarczycom oraz obecności nieprawidłowości morfologicznych tarczycy u pacjentów z dodatnimi i ujemnymi wynikami oceny PTH-BAC i SPECT-CT*

	PTH-FNAB		SPECT-CT	
	Positive	Negative	Positive	Negative
Mean thyroid volume ± SD [cm^3]	15.7 ± 12.3	19.6 ± 14.9	17.1 ± 14.7	14.1 ± 4.3
Mean thyroid thickness ± SD [mm]	15.7 ± 5.3	18.3 ± 4.8	15.2 ± 6.2	16.1 ± 3.1
Mean volume of PTH lesion ± SD [mm^3]	0.808 ± 1.450 (0.821 ± 1.473#)	1.115 ± 2.175 (0.314 ± 0.378#)	0.906 ± 1.502	0.292 ± 0.189
Mean thickness of PTH lesion ± SD [mm]	8.05 ± 3.09 (8.13 ± 4.01#)	8.10 ± 6.05 (5.62 ± 3.46#)	8.4 ± 4.5	6.2 ± 2.6
No/% of examined patients	40/80.0	10/20.0	21/63.6.0	12/36.4.0
No/% of patients without thyroid abnormalities	4/100.0	0/0.0	3/75.0	1/25.0
No/% of patients with previous thyroidectomy	3/100.0	0/0.0	1/100.0	0/0.0
No/% of patients with thyroid nodules	26/76.5	8/23.5	13/59.1	9/40.9
No/% of patients with chronic thyroiditis	17/73.9	6/26.1	7/46.7	8/53.3
No/% of patients with thyroid nodules and chronic thyroiditis	10/71.4	4/28.6	3/33.3	6/66.7

#lesions located deeper than 35 mm were excluded

PTH-FNAB concentration and the volume (r = 0.304, p < 0.05) and thickness of the examined lesion was noted (r = 0.359, p < 0.05). It was also found that the frequency of negative PTH-FNAB results was higher in the case of lesions of thickness ≤ 5 mm when compared to the lesions of thickness above 5 mm: 35.3% (6/17) *v.* 6.7% (2/30), p < 0.05. A similar relation was not found in respect to scintigraphic examination - negative results were observed in 46.2% (6/13) of lesions of which thickness was ≤ 5 mm and in 30.0% (6/20) of lesions of which thickness was above 5 mm (NS).

In general, negative PTH-FNAB results and negative SPECT-CT outcomes were observed, with increasing frequency, in patients with nodular goitre, chronic thyroiditis and with both abnormalities coexisting, but this effect was more distinct for scintigraphic examination (Table II).

Indications for surgical treatment were found in 41 patients. Signs or symptoms of PHP occurred in 38 (76.0%) patients (osteoporosis was the most frequent finding — in 30 patients). In two patients, the only indication for surgery was serum Ca, and in another one it was serum Ca and age. However, parathyroid surgery was performed in 20 patients only (including 14 patients with scintigraphy results available). The other patients had contraindications to surgical treatment or did not give their consent. In all the operated patients, the presence of pathological parathyroids was confirmed: parathyroid hyperplasia in five (25.0%) patients, adenoma in 14 (70.0%), and cancer — of intrathyroidal location - in one (5.0%). No false positive (FP) or TN results were observed for any of the analysed methods in relation to histopathological examination and only their sensitivity was determined. It was found that sensitivity of PTH-FNAB amounted to 95.0% (19/20) and was higher than that of scintigraphy — 64.3% (9/14), p < 0.05, and of routine cytological examination — 40.0% (8/20), p < 0.001. There were no significant differences in the mean PTH-FNAB concentration between the patients with parathyroid adenoma and parathyroid hyperplasia (3,428.8 ± 2,285.5 pg/mL *v.* 2,758.4 ± 2,063.6 pg/mL).

Discussion

Our results confirm that examination of PTH concentration in aspirated material is an effective method for establishing the parathyroid origin of cervical lesions detected sonographically. PTH-FNAB measurements showed significant advantage in relation to classical cytological examination. This method allows positive outcomes to be obtained even when aspirated material is scarce or it is contaminated with thyroid follicular cells from the needle tract (in our material, PTH-FNAB was positive in above 70.0% of non-diagnostic or confusing smears). Usually, it is not possible to clearly distinguish these cells from the parathyroid gland cells, which has been indicated by many investigators [13–14]. In the presented study, the routine FNAB allowed us to diagnose parathyroid tissue in 30% of cases. That value is similar to data reported by Bancos et al. [20] — 31% — and is higher than that showed by Giusti et al. [8] — 17%. The relatively high percentage of non-diagnostic

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smears from parathyroid lesions is not surprising either. This could be related to the difficult location of such lesions, especially in patients with goitre. In reports from other centres, the observed percentage of non-diagnostic cytological examinations of parathyroids was also high [14]. Particularly difficult conditions for aspirating the proper material — also for PTH-FNAB determination – occur, according to our observations, when the lesion is very small (thickness < 5 mm), or when it is deeply located (especially above 35 mm from the skin surface) or when it is located in proximity to large neck vessels. Additionally, when parathyroid is located behind thyroid lobe it is significant if the thickness of the thyroid is above 20 mm.

Our data showed that PTH-FNAB measurements have some advantages over the SPECT-CT in the identification of parathyroids in patients with nodular goitre and/or chronic thyroiditis. Sensitivity of PTH-FNAB measurements is higher than that of scintigraphy (95.0% *v.* 64.3%). Moreover, PTH-FNAB allowed us to confirm parathyroid origin of nearly 80% of lesions with negative scintiscans. It is the case, in spite of the fact that SPECT-C is especially useful in patients with nodular goitre.

Our results indicated that both nodular goitre and chronic thyroiditis affect the effectiveness of scintigraphy more than that of the PTH-FNAB method. The negative influence of the presence of thyroid nodules on both methods has already been described [6, 8–9, 24]. An unfavourable effect of coexisting chronic thyroiditis on scintigraphy has been recently reported by Boi et al. [9]. However, the authors noticed the negative effect of chronic thyroiditis on the effectiveness of scintigraphy only, and did not find any negative influence of thyroid abnormalities on parathyroids identification with the use of PTH-FNAB. This difference may be due to the fact that Boi et al. examined parathyroids of markedly larger sizes [9].

It should be stressed that there is no established standard as to what level of PTH-FNAB should be regarded as evidence that the aspirated tissue represents parathyroid tissue. Some investigators assume PTH-FNAB to be positive when the result is higher than the normal range on their assay [25], while others do so when it is higher than serum PTH concentration [26]. Obviously the applied limit depends on whether PTH-FNAB concentration is determined in the diluted material or directly. If the aspirate is rinsed and diluted, the measured PTH-FNAB level probably corresponds to a much higher concentration in the original sample. Usually a needle is flushed with 0.5–1 mL of fluid (0.9% NaCl, serum or other). Thus, in the comparison with determination in the serum, such a sample is diluted at least 10–20 times before assay. Therefore, clearly detectable PTH in the aspirate, even if it does not exceed the corresponding circulating level, can be considered as indicative of the parathyroid nature of the aspirated mass. However, in all the cases, we observed PTH-FNAB concentrations to be either higher than serum PTH concentrations (frequently elevated into the hundreds or thousands of pg/mL) or very low if not undetectable, doubtlessly negative. Similarly, other reports have indicated that PTH level in the aspirate is rarely equivocal [6, 8–9, 24]. Blood contamination in biopsies of non-parathyroid lesions may explain the small amounts of PTH detected in negative aspirates [15]. Our data did not show any differences in PTH-FNAB concentrations between hyperplastic lesions and parathyroid neoplasms. Similar observations have been reported by others [32–33].

We did not observe any complications after FNAB of parathyroid lesions, nor were they mentioned in postoperative histopathological reports. Similar observations were reported by Kendrick et al. [34]. It should be mentioned that during the FNAB procedure we performed at the most two punctures. A relation between the number of punctures and the occurrence of complications has been shown for the FNAB of the thyroid gland [35], and it is also very probable for the FNAB of the parathyroids.

A weakness of our study is the lack of postoperative histopathological verification in all examined patients, which along with biochemical normalisation after surgery is the best confirmation of the proper localisation of pathological parathyroid gland. Some patients did not give their consent to surgical treatment despite the indications to such treatment and positive PTH-FNAB, routine FNAB or scintiscans. In some patients, there were also contraindications to surgery. Others did not satisfy the current criteria for surgical treatment and were treated conservatively. With missing histopathological examination, we were unable to exclude if negative PTH-FNAB result in the case of negative or equivocal scintiscans and routine FNAB was a consequence of wrong interpretation of US images or some mistake during the aspiration. On the other hand, it should be stressed that limitation of the analysed series of patients to the operated ones does not reflect the clinical spectrum of patients diagnosed for PHP. So, such selection of patients could be the source of significant bias.

Summing up, in our series the incidence of thyroid abnormalities was very high — above 90%. In this group of patients, the PTH-FNAB measurements showed advantages in the relation to routine biopsy and SPECT-CT in identification of typically located pathological parathyroids. This method does not rely on any additional puncture and practically brings no risk of false positive results nor risk of complications (provided the number of punctures is low). The main limitation of PTH-FNAB measurements is the need to initially identify a potential parathyroid lesion by US. False negative results of this method may also occur if there are technical difficulties in performing a biopsy — in the cases of very small lesions or when a lesion's location is difficult to access with a biopsy needle.

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