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The accuracy of ultrasonography for detection of enlarged parathyroid glands in patients with different forms of hyperparathyroidism

Tačnost ultrasonografije u detekciji uvećanih paratireoidnih žlezda kod bolesnika sa različitim oblicima hiperparatireoidizma

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Abstract

Background/Aim. Ultrasonography is a cheap, easily available and convenient method for diagnosis. The aims of this study were: to determine the utility of ultrasonography for preoperative identification and localization of enlarged parathyroid glands (PTG) in patients with different forms of hyperparathyroidism (HPT); to examine the frequency of PTG detection in patients previously non-suspected for HPT but having symptoms relevant to the disease; to determine sensitivity and positive predictive value (PPV) of ultrasonography for identification of PTG in HPT and to compare obtained results with those obtained by scintigraphy. **Methods.** This investigation was designed as a retrospective–prospective study. The total number of patients undergoing ultrasonography prior to surgery was 179 and the number of those subjected to scintigraphy, mostly by the ^{201}Tl/^{99m}Tc method, was 112. The patients (52 male, 128 female) were divided into the following four groups: group A – patients with primary (p)HPT (n = 78); group B – patients with secondary (s)HPT (n = 47); group C – patients with tertiary (t)HPT (n = 13); group D – patients with unrecognized (u)HPT, but with anamnestic data implying the disease (n = 42). High resolution ultrasonography was performed by a single experienced observer. Diagnosis of HPT was based on characteristic clinical and biochemical parameters. Final proof of HPT diagnosis was surgery followed by histopathological examination. **Results.** Ultrasonography detected enlarged PTG in 93.85% of total patients, whereas scintigraphy uncovered 75.89% of positive cases ($p < 0.05$). The total number of positive PTG detected by ultrasonography was 211 *vs* 225 detected by surgery (sensitivity – 95.9%; PPV – 99.4%). Histopathology confirmed the predominance of adenoma in the A and D groups in comparison with the B group of patients having PTG hyperplasia. The group C was characterized by the presence of adenomas in hyperplastic PTG. The mean size of PTG measured by ultrasonography was 17.59 ± 8.0 mm (n = 164) *vs* 18.36 ± 8.54 mm (n = 179) measured after surgery. Ultrasonography proved itself as an accurate technique in all HPT groups, regarding its high sensitivity (range 93.6–100%) and PPV (95.6–100%). In contrast, scintigraphy was shown to be less reliable, especially in the sPTH group (sensitivity: 51.7%; PPV: 78.4%). **Conclusion.** Ultrasonography is more sensitive and accurate method for pre-operative localization of PTG in comparison with ^{201}Tl/^{99m}Tc scintigraphy. It can be also efficiently used for detection of PTG and diagnosis of HPT in patients previously not suspected for this disease.

Key words:
parathyroid glands; hyperparathyroidism; ultrasonography; diagnosis, differential; radionuclide imaging; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Ultrasonografija je jeftina, lako dostupna i pogodna dijagnostička metoda. Ciljevi ove studije su bili: odrediti korisnost ultrasonografije kod preoperativne detekcije i lokalizacije uvećanih paratireoidnih žlezda (PTŽ) kod bolesnika sa različitim oblicima hiperparatireoidizma (HPT); odrediti učestalost detekcije uvećanih PTŽ kod bolesnika kod kojih se prethodno nije sumnjalo na ovo oboljenje, ali koji su imali simptome HPT; odrediti senzitivnost i pozitivnu prediktivnu vrednost (PPV) ultrasonografije u identifikaciji PTŽ kod HPT i uporediti ih sa rezultatima dobijenim scintigrafijom. **Metode.** Istraživanje je dizajnirano kao retrospektivno-prospektivna

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studija. Ukupan broj bolesnika kod kojih je urađena ultrasonografija pre hirurškog zahvata je iznosio 179, a broj bolesnika kod kojih je urađena scintigrafija, pretežno $^{201}Tl/^{99m}Tc$ metodom, iznosio je 112. Bolesnici (52 muškarca i 128 žena) bili su podeljeni u sledeće četiri grupe: grupa A – bolesnici sa primarnim (p)HPT (n = 78); grupa B – bolesnici sa sekundarnim (s)HPT (n = 47); grupa C – bolesnici sa tercijarnim (t)HPT (n = 13); grupa D – bolesnici sa neprepoznatim HPT, ali čija anamneza ukazuje na ovo oboljenje (n = 42). Visoko-rezoluciona ultrasonografija korišćena je za dijagnostiku od strane samo jednog iskusnog radiologa. Dijagnoza HPT postavljena je na osnovu karakterističnih kliničkih i biohemijskih parametara. Konačna potvrda bila je na hirurškom i patohistološkom nalazu. Uvećane PTŽ bile su detektovane kod 93,85% bolesnika pomoću ultrasonografije, a kod 85,89% bolesnika pomoću scintigrafije ($p < 0,05$). Ukupan broj pozitivnih PTŽ detektovanih ultrasonografijom iznosio je 211 u odnosu na 225 PTŽ detektovanih na osnovu hirurškog nalaza (senzitivnost – 95,9%; PPV – 99,4%). Histopatološkom analizom potvrđena je najveća zastupljenost adenoma u grupama A i D, dok je u grupi B bila dokazana hiperplazija. Grupu C je karakterisalo prisustvo adenoma u hiperplastičnim PTŽ. Prosečna veličina PTŽ izmerena ultrasonografijom je iznosila 17,59 ± 8,0 mm (n = 164), a veličina žlezda izmerenih nakon hirurškog zahvata je bila 18,36 ± 8,54 mm (n = 179). Ultrasonografija se pokazala kao tačna metoda kod svih formi HPT u pogledu senzitivnosti (93,6–100%) i PPV (95,6–100%). Nasuprot ovoj metodi, scintigrafija se pokazala manje pouzdanom i tačnom metodom kod preoperativne lokalizacije PTŽ, posebno kod sHPT (senzitivnost: 51,7%; PPV: 78,4%). **Zaključak.** Ultrasonografija je senzitivnija i tačnija metoda za preoperativnu detekciju PTŽ u poređenju sa $^{201}Tl/^{99m}Tc$ scintigrafijom. Ova metoda se, takođe, može uspešno koristiti za detekciju uvećanih PTŽ, a time i dijagnoze HPT kod bolesnika kod kojih se na ovo oboljenje prethodno nije sumnjalo.

Ključne reči:
paratireoidne žlezde; hiperparatireoidizam; ultrasonografija; dijagnoza, diferencijalna; scintigrafija; osetljivost i specifičnost.

Introduction

Normal sized parathyroid glands (PTGs) are very small [approximately 6 mm (craniocaudal) and 3–4 mm (transverse) dimensions], and could not be usually identified by most imaging methods. Therefore, a parathyroid gland that is imaging-visible is very suspicious for the presence of a pathological lesion which is a cause of primary hyperparathyroidism (pHPT) [1, 2]. The pathologic entities of PTGs include solitary adenoma (80%–85%), multiglandular disease (15%–20%), and rarely carcinoma (< 1%). Multiglandular PTG diseases include hyperplasia of all of the parathyroid glands or, occasionally, double/triple adenomas [2, 3].

Primary HPT is the third most frequently diagnosed endocrine disorder [4] with serious complications on the skeletal system due to bone demineralization, recurrent peptic ulcers, renal stones and many neurological, psychiatric and vascular disturbances. Secondary (s) HPT is caused by hyperplasia of PTGs due to renal insufficiency. A decrease of calcium (Ca) levels in plasma, as a result of renal failure, results in an increase of parathyroid hormone (PTH) secretion. In addition, sHPT can be caused by malnutrition, vitamin D deficiency, increased Ca^{2+} excretion and by an influence of certain drugs [4, 5]. Tertiary (t) HPT is developed as an autonomous PTG hyperfunction in patients on renal dialysis and the pathological lesions include diffuse or nodular PTG hyperplasia [4, 6, 7].

The treatment of HPT involves primarily surgical approach which is the most successful therapy of HPT. The traditional technique has been a bilateral neck exploration under general anaesthesia, involving the evaluation of all four glands. Subsequent removal of pathological PTGs by skilled surgeons provides a high rate of cure exceeding 95% [8]. Parathyroid surgery is also indicated for patients with hipercalcemia, high PTH levels and/or renal osteodystrophy in sHPT which cannot be successfully medicated. However, there is still no consensus whether any asymptomatic HPT patient needs [5, 9]. Nowadays, due to the availability of preoperative PTG imaging techniques, less invasive surgical alternatives are used such as minimally invasive parathyroidectomy and endoscopic parathyroidectomy [9, 10]. These techniques demand an accurate preoperative localization of enlarged PTGs; this is especially important for patients with solitary PTG adenomas. The main reason for insufficiently successful surgical intervention is failure to localize the ectopic PTG and undiagnosed multiple PTGs in pHPT [9–11].

Localization of an abnormal PTG preoperatively can reduce operative time, postoperative morbidity, costs and the requirement for repeated surgery. The other reasons for preoperative localization include ectopic PTG adenoma and familiar HPT with multiglandular disease [10, 12].

Different methods for localization of PTGs have been used in the last three decades, such as high-resolution ultrasonography, scintigraphy imaging, computerized tomography (CT) (conventional and new 4D), and magnetic resonance imaging (MRI) [11]. All these methods have varying rates of success, so it is difficult to suggest any single imaging modality to be routinely used before surgical neck exploration [13–15].

High-resolution ultrasonography was first described as a method for detection of PTG tumours in 1979 by Edis and Evans [16]. Subsequently, many studies have confirmed its efficacy for preoperative localization of abnormal PTGs. However, the results of these studies have been quite varying with sensitivities of PTG detection ranging from 34% to 82% and an unacceptably high false-positive rates of 4–25% [17]. Among PTG imaging techniques, ultrasonography has the advantage of convenience, easy availability and low cost,

and is preferred by some authors [18–20]. Ultrasonography shows an abnormal PTG as an oval, bean-shaped, or infrequently, multilobulated hypoechoic mass with a well-defined margin, located posteriorly or inferiorly to the thyroid gland [2, 19–21]. PTGs are usually very vascular, typically showing a peripheral vascular arc and a prominent polar feeding artery that arises from the branches of the inferior thyroidal artery. Its identification can distinguish PTGs from lymph nodes, which usually have a hilar blood supply. Other features include asymmetrically increased vascularity in the thyroid gland on the side of identified PTGs and in the hyperechoic capsule [21].

In 1989, a new approach using the radiopharmaceutical 99m Tc-MIBI (sesta methoxyisobutylisonitrile) was reported for identification and localization of PTGs and this imaging method gradually replaced the previous subtraction method based on $^{201}Tl/^{99}Tc$ [22]. Several investigators confirmed the use of this technique for the identification of abnormal PTGs using either MIBI alone or with subtraction imaging. The sensitivity was in range of 71–93% [23–25]. Numerous studies comparing scintigraphy and ultrasonography suggest that both methods have similar sensitivities and specificities in the detection of solitary adenomas with a range of 68%–95% for scintigraphy and a range of 72%–89% for ultrasonography [25–27]. Both methods have significantly lower sensitivities in the detection of the multiglandular disease [27]. However, very often, these methods are not comparable as suggested by meta-analyses based on a large number of publications [26, 27]. It is generally suggested that a preoperative approach that combines both ultrasonography and scintigraphy is more accurate than technique alone [11, 28, 29].

There are many factors influencing the accuracy of ultrasonography for detection of pathological PTGs, but it seems that the careful examination by a very experienced observer is of crucial importance [19]. This was the reason why we wanted to present our own results, which show very high sensitivity of this imaging method in identification and localization of pathological PTG. The concrete aims of the study were: to determine the utility of ultrasonography in preoperative identification and localization of enlarged PTGs in patients with different forms of HPT; to examine the frequency of PTGs detection in patients previously non-suspected for HPT, but having symptoms relevant to the disease; to determine sensitivity and positive predictive value (PPV) of ultrasonography for identification of PTGs in HPT and to compare them with results obtained by scintigraphy.

Methods

This was a retrospective–prospective study on patients with HPT, conducted at the Military Medical Academy (MMA) in Belgrade, Serbia during the period between 1989 and 2014. The study was approved by the Ethics Committee of the MMA. The number of patients was 180 and all of them were subjected to surgery in order to remove pathological PTGs. There were 52 males and 128 females. Their main age was 51.78 years (range: 18–79 years). Only one patient was false positive on surgery and thus excluded from the study. The patients were divided into four groups. The group A (n = 78) was consisted of patients with primary HPT (pHPT); the group B (n = 47) and group C (n = 13) included patients with secondary HPT (sHPT) and tertiary (tHPT), respectively. The group D consisted of patients with previously unrecognized HPT (uHPT) both by clinical and biochemical means. They were directed for the ultrasonographic examination of abdomen and pelvis. After a carefully conducted anamnesis related to kidney stones, peptic ulcers, skeletal and joint problems, neuromuscular and psychiatric disturbances, the patients gave their consent for ultrasonographic examination of PTGs. This group consisted of 523 patients of which 124 had enlarged PTGs. Of them, only 42 were fully processed and included in the study. The main demographic characteristics of these patients were given in Table 1.

Table 1

Demographic characteristics of patients with hyperparathyroidism (HPT)

Group	Total number	Male	Female	Age (years), mean ± SD
A (pHPT)	78	22	56	50.95 ± 12.39
B (sHPT)	47	17	30	51.09 ± 8.40
C (tHPT)	13	8	5	48.92 ± 9.78
D (uHPT)	42	5	37	55.00 ± 10.52

***p* – primary; s – secondary; t – tertiary; u – unrecognized; SD – standard deviation.**

Ultrasonography

The ultrasonography of the neck was performed at the Institute for Radiology, MMA, by a single experienced radiologist (D.S.), by using a high resolution transducer (Diasonics type CV 400 aparatus equipped with 10 MHz array transducer or SPECTRA, 7.5 MHz transducer). In some patients, Doppler and Color Doppler examination was performed by using SPECTRA probe 7.5 MHz and Acuson128 xp multifrequent probe of 7.5 MHz. The ultrasonography examiner was aware about clinical and laboratory parameters characteristic for the HPT groups A, B and C, while being unaware of any prior scintigraphy imaging results. The ultrasonographic examination was performed with the patient supine and the neck extended. The central neck was examined from the subclavian vein to the submandibulary glands using the thyroid gland as a reference point. PTGs were recognized as hypoechoic, oval/round encapsulated structures laying posterior and adjacent to the upper one third of the thyroid lobes, adjacent to the lower pole of the thyroid lobes, or variably inferior to the thyroid lobe in the case of ectopic localization. Both cross-sectional and longitudinal images were obtained. In some cases, the examined area was extended to the superior part of mediastinum. The Color Doppler was used to detect

the feeding artery entering one pole of PTGs. The size of abnormal PTGs was measured by taking the largest dimension.

Scintigraphy

In most patients, subtraction scintigraphy by using ^{201}Tl/^{99m}Tc was performed as described [30]. In brief, scintigraphy of the neck region was done in dinamic mode during 25 min, after iv. injection of 2 mCi (74 MBq) 201Tl. After Tl scintigraphy, dynamic scintigraphy during 25 min in the same position was done after *iv* injection 5 mCi (185 MBq) 99mTc. A direct subtraction view was obtained by subtracting the ^{99}Tc image from the ^{201}Tl image. Only some images were obtained with a new scintigraphy method by using 740MBq of ^{99m}Tc-MIBI followed by ^{99m}Tc-pertechnetate, exactly as was described [31]. Scintigraphy was carried out at the Institute for Nuclear Medicine, MMA.

Biochemical parameters, surgery and statistical analysis

Biochemical parameters, such as plasma concentration of Ca and phosphorus (P), serum activity of alkaline phosphatase (ALP) and serum concentrations of PTH were taken from medical history of patients.

All patients were operated on by using classical bilateral neck exploration in the Clinic for Surgery, MMA. After removal, the size of PTGs was measured and then the glands were processed for histopathology and examined by light microscopy (Institute for Pathology, MMA). The histopathological reports were taken from medical history of patients and used for definitive diagnosis. Histopathological diagnosis was classified as: adenoma, atypical adenoma, hyperplasia, combination of adenoma and hyperplasia, and carcinoma.

Data were expressed as mean ± standard deviation (SD) or mean ± standard error (SE). Comparisons between groups were analyzed by the Student *t*-test, Mann-Whitney *U* test or Kruskal-Wallis test (multiple groups). Categorical data were compared by the Chi-square (χ^2) test. Correlations were analyzed by the Spearman rank test. Sensitivity was defined as the ratio of true positive (TP) tests to the sum of TP and false negative (FN) tests. PPV was defined as the ratio of TP tests to the sum of TP and false positive (FP) tests. Statistical significance was accepted at $p < 0.05$. For statistical analysis, SPSS computer program was used.

Results

Characteristics of PTGs detected by ultrasonography

Ultrasonography was performed in 179 patients in which the diagnosis of HPT was confirmed by surgery and subsequent histopathological evaluation. The enlarged PTGs were detected in 169 (93.9%) patients with HPT.

The total number of ultrasonographically detected PTGs was 211, out of 225 detected during surgery. Of them, 199 were TP, 6 were TN, and 20 were FN. Ultrasonography did not detect 12.9% of PTGs. There was a statistically significant correlation between ultrasonography and surgery in the number of PTGs (Spearman range correlation, r = 0.79; $p < 0.001$). Histopathology confirmed 67.6% of adenomas, 24.0% of hyperplasia, 7.3% of adenomas combined with hyperlasia and 1.1% of carcinoma. Adenomas had typical ultrasonographic characteristics: ovoid/round shape with homogenic echogenicity lower in comparison to that of the thyroid gland. Their size was higher than 5 mm × 3 mm × 1 mm. Those PTGs were located in the close proximity to the posterior capsule of the thyroid gland. The fibro-fatty capsule of PT adenomas was usually presented as hyperechoic line separating them from the thyroid gland (Figure 1). When combined with Power Doppler or Color Doppler, extrathyroidal feeding artery entering one pole of PT adenomas (Figures 2a and 2b, Figure 3) or diffuse blood flow within them were visible.

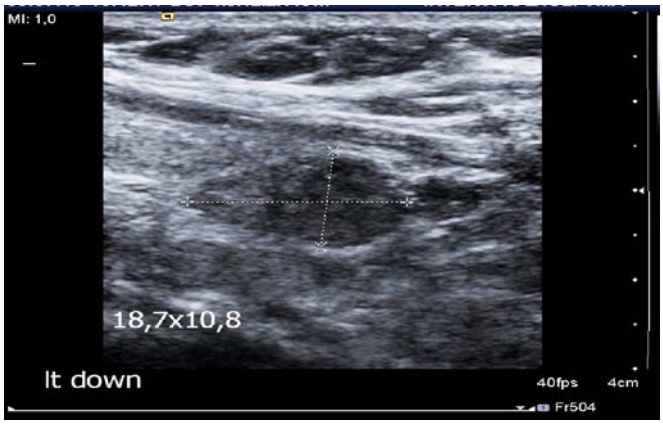
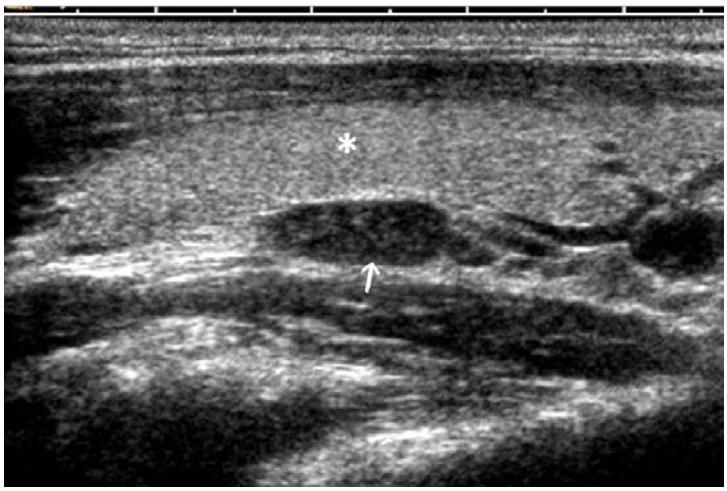
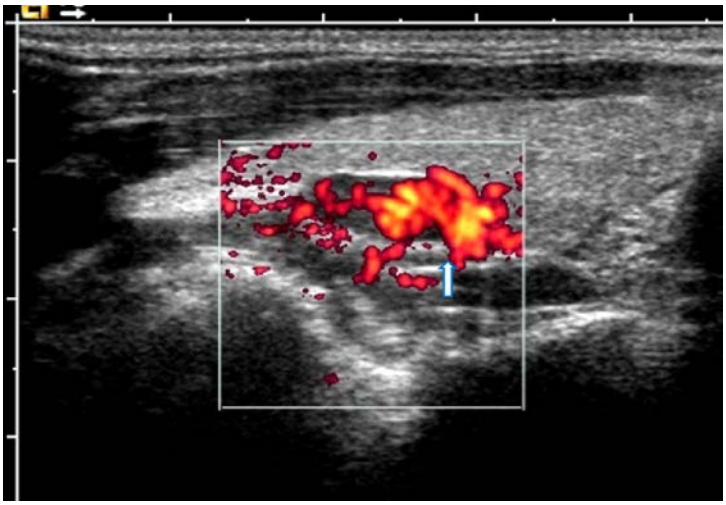


Fig. 1 – Adenoma (primary hyperparathyroidism – pHPT): ultrasonographic appearance of a parathyroid adenoma (gray scale) appearing as a solid, encapsulated, hypoechogenic lesion with a well-defined margin, located adjacent to the lower pole of the left thyroid lobe.



a)



b)

Fig. 2 – Adenoma (primary hyperparathyroidism – pHPT): a) ultrasonographic appearance of a parathyroid adenoma (gray scale) appearing as a solid, oval, hypoechogenic lesion with a well-defined margin, located under the upper pole of the right thyroid lobe (marked by an asterix); b) the same adenoma visualized by Power Doppler. Note extrathyroidal feeding blood vessels entering at the parathyroid gland (white arrow).

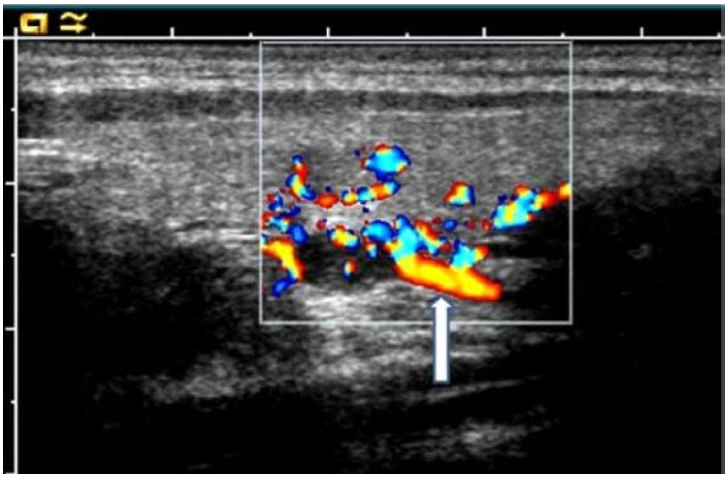


Fig. 3 – Adenoma (primary hyperparathyroidism – pHPT): Color Doppler of the right inferior parathyroid gland. Note an artery entering at the one pole of the gland. A thyroid parenchymal node with a typical intrathyroid vascularization is visible above the parathyroid adenoma.

The PTG had various side and site localizations. Most of them had lower side position. (left lower: 38.2%; right lower: 22.7%; left upper: 6.6%; right upper: 5.7%). Of the total PTG number, 18.2% were multiple; 6.2% had atypical topic localization, and 2.4% were localized ectopically in the upper mediastinum (Table 2). The collision between ultrasonography and surgery regarding localization was observed in 27 (13.5%) of PTGs.

Table 2

Distribution of parathyroid glands (PTGs) detected by ultrasonography

Localization	PTGs (%)
Right upper	5.7
Left upper	6.6
Right lower	22.7
Left lower	38.2
Multiple	18.2
Topic atypic	6.2
Ectopic	2.4

The mean size of PTGs measured by ultrasonography was 17.59 ± 8.0 mm (n = 164) *vs* 18.36 ± 8.54 mm (n = 179) after the surgery.

Biochemical, anamnestic and clinical parameters in patients with different forms of HPT

Biochemical, anamnestic and clinical parameters in HPT patients divided into different groups were studied. Biochemical parameters included serums levels of PTH, Ca, P and ALP activity.

As shown in Figure 4, mean values of serum ALP activity were above normal values (120–180 IU/L) and those in the group C were statistically significantly higher ($p < 0.05$) compared to other groups.

The concentrations of PTH were in the range between 25.2–2,300 pMol/L (normal range, 60–120 pMol/L). The levels of this hormone in patients with secondary and tertiary HPT (the groups B and C, respectively) were higher than in the groups with primary HPT (the groups A and D), ($p < 0.05$).

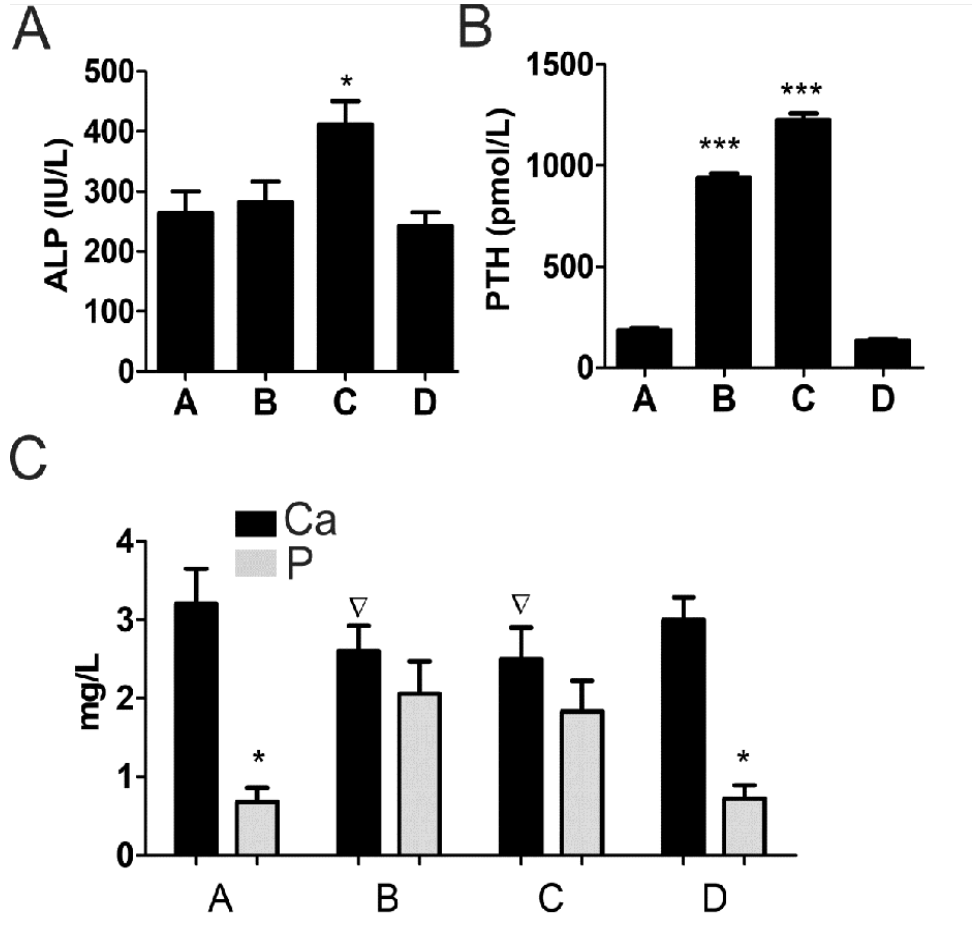


Fig. 4 – Biochemical parameters in patients with different forms of hyperparathyroidism (HPT): ALP – alkaline phosphatase; Ca – calcium; P – phosphorus. Values are given as mean ± SE for n = 78 (group A), n = 47 (group B), n = 13 (group C) and n = 42 (group D). (A) * $p < 0.05$ compared to A, B and D groups; (B) *** $p < 0.001$ compared to group A and D; (C) *$p < 0.05$ compared to B and C groups, ▽$p < 0.05$ compared to A and D groups.

Table 3

Dominant anamnestic and clinical parameters in patients with different forms of hyperparathyreoidism (HPT)

Parameters	Group A (n = 78)	Group B (n = 47)	Group C (n = 13)	Group D (n = 42)
Symptoms				
renal colica	$72^{B,C}$	11	8	$76^{B,C}$
kidney stone	$71^{B,C}$	14	8	$69^{B,C}$
peptic ulcus	30	51^{D}	46	21
bladder stone	12	15	8	8
bone pain	63	$96^{A,D}$	$100^{A,D}$	45
joint stiffness	34	$60^{A,D}$	$92^{A,D}$	22
bone fracture	11	23	31	3
psych. symptoms	49	64^{D}	$92^{A,D}$	34
neurol. symptoms	32	$94^{A,D}$	$100^{A,D}$	24
Clinical signs				
osteoporosis	75	100	100	76
positive EMNG	58	$14^{A,C}$	61	ND
positive findings of urinary system	73	100	100	76
positive findings of GD system.	45	40	38	16

Group A – primary HPT; Group B – secondary HPT; Group C – tertiary HPT; Group D – unrecognized HTP. EMNG – electromyoneurography; GD – gastroduodenal; ND – not done.
Superscript letters point out statistically significant differences (χ^2 test; $p < 0.05$): ^{A} in relation to the group A; ^{B} in relation to the group B; ^{C} in relation to the group C, and ^{D} in relation to the group D

Table 4

Comparison of positive parathyroid glands (PTGs) findings between ultrasonography and scintigraphy in patients with different forms of hyperparathyroidism (HPT)

Group*	Imaging method	Total number of patients**	Number of patients with positive PTGs	χ^2 value	*p*
Total	Ultrasonoraphy	179	169	21.29	< 0.0001
	Scintigraphy	112	85		
A (pPTH)	Ultrasonography	78	71	4.28	< 0.039
	Scintigraphy	50	39		
B (sPTH)	Ultrasonography	47	44	13.82	< 0.0002
	Scintigraphy	32	19		
C (tPTH)	Ultrasonography	13	13	1.36	0.244
	Scintigraphy	10	9		
D (uPTH)	Ultrasonography	42	41	1.71	0.191
	Scintigraphy	20	18		

***For explanation see under Table 1; **Total number of patients with positive PTGs detected by surgery/pathology.**

The concentrations of Ca in plasma in the groups A and B were higher than physiological ones, and the differences in relation to values in the groups C and D, were statistically significant ($p < 0.05$). In contrast, the concentrations of P in the groups B and C were statistically significantly higher ($p < 0.05$) than those in the groups A and D. Certain patients in the group D were normocalcemic. In most patients, total Ca levels correlated with the concentrations of ionized Ca and their levels were normalized after one year following surgery (data not show).

Dominant anamnestic and clinical data relevant to HPT are presented in Table 3. Patients from the groups A and D had dominant anamnestic and clinical signs of urinary system pathology, which were more frequent than in the groups B and C ($p < 0.05$). In contrast, the symptoms/signs associated with the skeletal system, psychiatric disturbances and neurological disorders were higher in the groups B and C in comparison to the other two ($p < 0.05$). It is interesting that the percentage of patients with positive electromyoneurography (EMNG) results in the groups A and C was higher in comparison to the group B ($p < 0.05$). The percentage of patients with the amanestic data of peptic ulcer was higher in the group B than in the group D ($p < 0.05$). However, these differences were not confirmed by gastroscopy (Table 3).

Comparison of positive PTG findings between ultrasonography and scintigraphy

One of the aims of the study was to compare the accuracy of ultrasonography and scintigraphy for abnormal PTGs detection, in patients with different clinical forms of HPT. Results are given in Table 4. The number of patients with positive PTGs detected by ultrasonography *vs* surgery was as follows: total number of patients – 169 *vs* 179, respectively; the group A – 71 *vs* 78, respectively; the group B – 44 *vs* 47, respectively; the group C – 13 *vs* 13, respectively; the group D – 41 *vs* 42, respectively.

The number of patients with positive PTG findings detected by scintigraphy *vs* surgery was as follows: total number of patients – 85 *vs* 112, respectively; the group A – 39 *vs* 50, respectively; the group B – 19 *vs* 32, respectively;

Table 5

Comparison of detected parathyroid glands (PTGs) numbers between ultrasonography and scintigraphy in patients with different forms of hyperparathyroidism (HPT)

Group*	Imaging method	Total number of PTGs**	Number of positive PTGs	χ^2 value	*p*
Total	Ultrasonography	225	211	12.31	0.0004
	Scintigraphy	133	109		
A (pHPT)	Ultrasonography	80	77	29.28	< 0.0001
	Scintigraphy	80	49		
B (sHPT)	Ultrasonography	141	79	30.92	< 0.0001
	Scintigraphy	96	19		
C (tHPT)	Ultrasonography	33	20	2.97	0.0849
	Scintigraphy	24	9		
D (uHPT)	Ultrasonography	44	41	1.083	0.298
	Scintigraphy	20	17		

***For explanation see under Table 1;**Total number of PTGs detected by surgery/pathology.**

the group C – 9 *vs* 10, respectively; the group D – 18 *vs* 20, respectively.

When the success was analyzed according to the number of patients with positive PTGs, it can be seen that in total group, the groups A and B, ultrasonography was significantly superior to scintigraphy. In the groups C and D, there were no statistically significant differences between these two imaging methods.

The total number of PTGs detected by ultrasonography *vs* surgery was: total group – 211 *vs* 255, respectively; the group A – 77 *vs* 80, respectively; the group B – 79 *vs* 141, respectively; the group C – 20 *vs* 33, respectively; the group D – 41 *vs* 44, respectively. The total number of PTGs detected by scintigraphy *vs* surgery was: total group – 109 *vs* 133, respectively; the group A – 49 *vs* 80, respectively; the group B – 19 *vs* 96, respectively; the group C – 9 *vs* 24, respectively; the group D – 17 *vs* 20, respectively. The results are presented in Table 5. When the results were calculated in this way, they were very similar as those presented in Table 4.

Comparison of sensitivity and positive predictive values between ultrasonography and scintigraphy in detection of PTGs

The final aim of this study was to check sensitivity and PPV of ultrasonography and scintigraphy for detection of pathological PTGs in different groups of HPT patients. The results are summarized in Table 6. When sensitivity and PPV were analyzed by assessing the number (percentage) of the patients with detected PTGs by ultrasonography, it can be seen that both parameters were very high in all groups of HPT patients (sensitivity: range, 91.0–100%; PPV: range, 95.6–100%). In the total group, sensitivity was 96.4% and PPV was 99.3%.

Scintigraphy results showed lesser sensitivity. In the total group, sensitivity was 74.6% and PPV 94.6%. The lowest sensitivity (59.3%) and PPV (72.2%) was detected in the group B. In other groups (A, C, and D) PPV did not significantly differ compared to ultrasonogrpahy (Table 6, A imaging).

The sensitivity and PPV, calculated on the basis of total PTGs number identified by ultrasonography, were similar to those analyzed by assessing the number of PTGs positive patients. Similar to the previous results, sensitivity and PPV, determined by scintigraphy, were lower compared to ultrasonographic findings, while being lowest in the group B (Table 6, B imaging).

Discussion

This clinical study was designed with the aim to analyze the accuracy of ultrasonography for pre-operative detection

Table 6

Comparison of sensitivity and positive predictive value (PPV) in detection of positive parathyroid glands (PTGs) (A imaging) or total number of PTGs (B imaging) between ultrasonography and scintigraphy

Imaging method	Parameters	Total groups	Group A	Group B	Group C	Group D
Detection of positive PTGs						
ultrasononography	Sensit. (%)	96.4	91.0	93.6	100	100
	PPV (%)	99.3	98.6	95.6	100	100
scintigraphy	Sensit. (%)	74.6*	78.0*	59.3***	90	90
	PPV (%)	94.6	93.9	79.2*	100	100
Detection of total number of PTGs						
ultrasonography	Sensit. (%)	95.9	94.5	93.6	100	100
	PPV (%)	99.4	97.4	98.7	100	100
scintigraphy	Sensit. (%)	80.2*	77.7*	51.7***	88.8	88.8
	PPV (%)	89.6	87.3	78.4*	93.4	80.9*

***Note*: For explanation about groups see under Table 3.**
***$p < 0.05$; ***$p < 0.001$ compared to corresponding parameters of ultrasonography.**

of pathological PTGs in HPT patients. Although several hundred papers cover this topic, we wanted to present our experience in the MMA, Belgrade and to show some specificities. The study included ultrasound imaging of a relative large cohort of patients (n = 179) performed by only one radiologist, simultaneous comparison of all tree forms of HPT and inclusion of one group of patients with no prior recognized HPT. However, as many other studies, its limitation is related to the relatively small number of patients in the tHPT group, unequal number of patients imaged with ultrasonography in comparison with scintigraphy and the fact that scintigraphy was performed in most patients with an old $^{201}Tl/^{99m}Tc$ method. In addition, the investigation was a retrospective-prospective study.

Our cohort consisted of 71.0% female and 29.0% male, which is in agreement with the literature data reporting a female-to-male ratio in pHPT of approximately 3–4:1 [32]. The prevalence of pHPT in female is most probably associated with estrogens, but their role in pathogenesis of HPT is still unclear. The average age of our patients was 51.8 years, suggesting that the disease evolution is slow and thus its detection is late.

The analysis of diagnostic parameters in our study was aimed just to illustrate their differences between groups, but not comparison with imaging data, since they are explored too much in literature. The increased serum level of PTH is a hallmark of HPT. It is known that the secretion and synthesis of PTH is controlled by the ambient of circulating ionized Ca concentration. Under normal conditions, an increase in serum Ca concentration, which might not be detected by biochemical methods, will instantly suppress PTH secretion. Similarly, a reduction in serum Ca concentration will immediately simulate PTH secretion. This inverse sigmoidal association between these two parameters is regulated by the calcium-sensing receptor. The other principal regulator of PTH secretion is 1,25-dihydroxyvitamin D concentration, which also inversely correlates with PTH concentration [4].

Primary HPT in our groups of patients was characterized by both increased levels of serum concentrations of PTH and Ca, simultaneously with reduction of serum P levels. Abnormal secretion of PTH raises the serum Ca level by promoting the renal tubular reabsorption of Ca, decreasing tubular reabsorption of phosphate, and stimulating osteoclasts. In addition, PTH stimulates vitamin D production, which, in turn, raises serum Ca by promoting its absorption in the gastrointestinal tract [4, 32]. We found elevated concentrations of PTH in almost all groups of HPT patients and less than 5% of them have normal values. The concentrations were higher in the groups B and C compared to other two groups, suggesting higher activity of PTGs and more severe form of the disease. Although we found that both PTH and Ca levels were increased in most patients, some inconsistency was observed, especially in the group D (unrecognized HPT), such that PTH is increased and Ca was normal or *vice versa*. The literature data also suggest similar findings [4, 6, 32]. We did not find any differences between normocalcemic and hypercalcemic patients regarding ultrasonographic findings of abnormal PTGs (data not shown).

In our study we observed much higher number of patients having symptoms and clinical signs of HPT than others did. For example, Reid et al. [8] showed that a history of nephrolithiasis was present in 10.0% of their patients with pHPT in contrast to 90% in our study. It is interesting that the anamnestic data about bone fracture were very similar (15–16%). However, symptoms and clinical parameters of skeletal system in our patients were very often and the results correlated with increased ALP activity. These and other clinical findings clearly indicate that diagnosis of HPT in our patients was established too late.

Histopathology of PTGs in our patients from different HPT groups did not significantly differ from published results [1, 2, 7, 9], showing the predominance of adenomas in the groups A and D (pPTH), hyperplasia in the group with sPTH and combination of adenomas with hyperplasia in the group with tPTH. In addition, we also found the predominant localization of pathological changes in the inferior PTGs, predominantly in the left lower quadrant. Some authors reported predominant right lower localization [8, 33], or equal right-left lower localization [34]. The exact localization of abnormal PTGs is of particular importance for planning the adequate surgical procedure [35].

In the 1980s, sensitivity of ultrasonography for PTGs localization in patients with pHPT without previous surgery ranged between 34% and 82% [17]. However, since 1996, sensitivity of ultrasonography has been improved, especially in patients with solitary PT adenoma, reaching sensitivity of 77–91% [13]. A meta-analysis [36] based on 43 studies showed that ultrasound had pooled sensitivity and PPV of 76.1% and 93.2%, respectively, for preoperative localization of abnormal PTGs in pHPT. Ruda et al. [37] reviewed the literature from 1995 to 2003 and reported a sensitivity of 79% for ultrasound in PTGs detection. A limitation of this study was the inclusion of reoperative patients with persistent disease. In another meta-analysis, sensitivity of ultrasound ranged from 48.3% to 96.2%. In a retrospective cohort study on 477 patients, Stern et al. [34] demonstrated that ultrasonography correctly localized the adenoma in 76% of patients with pHPT, with a sensitivity of 76.2% and PPV of 86.8%. Measurements were least accurate for adenomas measuring less than 1 cm in diameter. In a recent study of Reid et al. [8], performed in 374 patients, neck ultrasound was able to detect adenomas only in 66.0% of patients with pHPT. The failure in adenoma detection was associated with older age, lower peak Ca, lower PTH and higher creatinine levels. However, when an adenoma was identified on ultrasound, the laterality was confirmed to be correct at surgery in 94.5% of cases, which is very similar to our results.

Our results are closest to those published by Bradley and Knodle [18] who showed that the sensitivity of neck ultrasonography in detecting pathological PTGs was 97.5% (number of adenomas) and 85% (localization). In addition, similarly with our results, image size of PTGs correlated

well with the measured size of the adenoma on final pathological examination.

It is obvious that our results regarding sensitivity (96.4%) and PPV (99.3%) are better than most results published to date. We think that the main reason for such a success is careful ultrasound examination by only one radiologist with long-term experience in the neck ultrasound diagnostics. This assumption is supported by many publications. For example, Stern et al. [34] showed that ultrasound scans made by a single senior operator specializing in neck had a higher sensitivity than scans made by multiple examiners. The operator dependence of ultrasound is also recognized through meta-analysis of Cheung et al. [36]. It is interesting that experienced surgeon-performed ultrasound may be comparable or superior to radiologist-performed ultrasound.

One aim of our study was to compare the sensitivity and PPV of ultrasonography and scintigraphy in detecting abnormal PTGs. We showed that ultrasonography is more reliable method than scintigraphy and this is especially important for sHPT. There are many papers which compared the accuracy of ultrasonography and scintigraphy in detecting pathological PTGs [13–15, 24, 28, 38, 39]. However, only few of them are relevant to our study, because the dominant ^{211}Tl/^{99m}Tc scintigraphy method that we performed is no longer in use. In this context, Gooding et al. [30] reported that parathyroid scintigraphy using a double-tracer (^{211}Tl/^{99m}Tc) subtraction technique discovered 74% of parathyroid adenomas in patients with and without previous neck operations. High-resolution (10-MHz) ultrasound depicted 78% of these adenomas. Alone, neither modality was particularly sensitive in the detection of primary hyperplasia of PTGs, but combined techniques were more effective than the use of a single modality. Roses et al. [38] analyzed 36 patients with pHPT in whom either high-resolution real time ultrasonography, ^{211}Tl/^{99m}Tc subtraction scintigraphy or CT scaning were performed. Overall sensitivity of correctly localizing the abnormal PTGs with these techniques was relatively low: 34% for ultrasonography, 49% for the ^{211}Tl/^{99m}Tc scintigraphy, and 41% for CT scanning. The authors concluded that these three imaging techniques did not provide reliable information for initial bilateral exploration of the neck.

Most comparisons in literature refer to scintigraphic methods that are now in use. As one can see from several selected publications, mainly related to pHPT, results are very variable indicating that scintigraphy is superior, inferior or equivalent to ultrasonography [13–15, 24, 28, 38–40]. The results depends on many factors such as type of scintigraphy, localization and size of pathological PTGs, form of HPT, histopathological characteristics of PTGs and many others.

Haber et al. [28] studied 120 patients with pHPT. Ultrasonography detected enlarged PTGs in 77% of unselected patients and correctly predicted surgical findings in 74% of patients undergoing surgery. Sestamibi scintigraphy was positive in 88% of unselected patients and the difference, compared to ultrasonography, was statistically significant. Sestamibi scintigraphy was clearly more sensitive for ectopic parathyroid adenomas, providing correct localization in all 8 cases. When one test was negative, testing with the second method was usually positive, improving the likelihood of a positive result to 98% when both tests were employed. Equal sensitivity and PPV between these methods were demonstrated in a meta- analysis of Cheung et al. [36]. They showed that ultrasound had pooled sensitivity and PPV of 76.1% (70.4–81.4%) and 93.2% (90.7–95.3%), respectively. Sestamibi-SPECT had pooled sensitivity and PPV of 78.9% (64–90.6%) and 90.7% (83.5–96.0%), respectively. Lumachi et al. [41] analyzed 22 papers published between 1996 and 2000, and showed that sensitivity detected by various scintigrafic methods varied between 56.9% and 100% for solitary adenomas but sensitivity was significantly lower when multiglandular PTGs were analyzed (35.5–80%). Gotthardt et al. [26] found median sensitivity of 72% (range 39–92.5%) of sestamibi-SPECT in a meta-analysis that was not limited to pHPT patients undergoing initial parathyroidectomy since studies included patients with secondary HPT, as well as those with persistent and recurrent disease. Our results are comparable to those and pointed out that the reliability of scintigraphy is lowest in the group of sHPT, manifested by PTG hyperplasia. However, recent results from our hospital show how new scintigraphic methods can improve the detection of hyperplastic PTG. Namely, Dugonjic et al. [42] demonstrated that subtraction parathyroid scintigraphy (^{99m}Tc-MIBI followed by ^{99m}Tc-pertechnetate) is a reliable and very sensitive diagnostic tool in detecting abnormal PTGs in parathyroid hyperplasia, reaching 100% sensitivity in detecting a “dominant gland” and sensitivity *per* localized gland of 70%.

In patients with sHPT, the four glands are not uniformly enlarged and therefore preoperative localization is difficult in comparison with pHPT. In one study, sensitivity and PPV, were 47.3% and 97.8%, respectively for MIBIscintigraphy, and 69.5% and 96.9%, respectively for ultrasonography. The sensitivity of combined techniques was 84.2% [43]. In a recent meta-analysis, the pooled sensitivity of PTG scintigraphy in patients with sHPT was 53% and the pooled specificity was 93% [27]. Based on a recent study, McHenry and Shi [44] concluded that, compared to patients with a single adenoma, patients with hyperplasia were more likely to have negative sestamibi, ultrasound or both exams and lower gland weights. Therefore, parathyroid hyperplasia should be suspected in patients with lower gland weights and negative imaging. Our findings showed that ultrasonography in patients with sHPT, although slightly less sensitive in detection of hyperplastic PTGs than PTG adenomas, is very accurate diagnostic procedure.

In our opinion, the inclusion of the group D in this study is of great importance in order to show that ultrasonography could be the first diagnostic option for

pHPT. This group represented patients without prior suspicion to HPT. The patients were examined ultrasonographically mainly due to the renal stone. After careful analysis of their symptoms, the patients gave consent for neck ultrasound. We detected abnormal PTGs in 23.7% of the patients. Therefore, this group, although very similar by ultrasonography parameters to the group A (pHPT), deserves more careful analysis.

Conclusion

Ultrasonography is an accurate imaging method for detection of pathological PTGs. Its high sensitivity and PPV, independently of the HPT forms, which were higher than those achieved by $^{201}Tl/^{99m}Tc$ scintigraphy, make it as reliable tool for preoperative surgical procedure. Ultrasonography can be also efficiently used for detection of PTGs and diagnosis of HPT in patients previously not suspected for this disease.

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