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TAČNOST ULTRASONOGRAFIJE U DETEKCIJI UVEĆANIH PARATIREOIDNIH ŽLEZDI KOD PACIJENATA SA RAZLIČITIM OBLICIMA HIPERPARATIREOIDIZMA

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UDC:

DOI: https://doi.org/10.2298/VSP181225015S

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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 ŽLEZDI KOD PACIJENATA SA RAZLIČITIM OB LICIMA HIPERPARATIREOIDIZMA

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Abstract

Background/Aim: Ultrasonography is a cheap, easily available and convenient method for diagnosis. The aim of this study was: 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 them with 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/$^{99}$mTc 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% positive cases ($p<0.05$). The total number of positive PTG detected by ultrasonography was 211 versus 225 detected by surgery (sensitivity- 95.9%; PPV- 99.4%). Histopathology confirmed the predominance of adenoma in A and D groups in comparison with B group of patients having PTG hyperplasia. Group C was characterized by the presence of adenomas in hyperplastic PTG. The mean size of PTG measured by ultrasonography was 17.59 ± 8.0mm (n=164) versus 18.36 ± 8.54mm (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 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/$^{99}$mTc scintigraphy. It can be also efficiently used for detection of PTG and diagnosis of HPT in patients previously not suspected for this disease.

Keywords: parathyroid glands; hyperparathyroidism; ultrasonography; scintigraphy; sensitivity
Apstrakt

Uvod/Cilj: Ultrasonografija je jeftina, lako dostupna i pogodna dijagnostička metoda. Cilj ove studije je bio: odrediti korisnost ultrasonografije kod preoperativne detekcije i lokalizacije uvećanih paratireoidnih žlezda (PTŽ) kod pacijenata sa različitim oblicima hiperparatireoidizma (HPT); odrediti učestalost detekcije uvećanih PTŽ kod pacijenata kod kojih se prethodno nije sumnjalo na ovo oboljenje ali koji su imali isimptome HPT; odrediti senzitivnost i pozitivnu prediktivnu vrednost (PPV) ultrasonografije u identifikaciji PTŽ kod HPT i uporediti ih sa scintigrafijom. Metode: Istraživanje je dizajnirano kao retrospektivno-prospektivna studija. Ukupan broj pacijenata kod kojih je urađena ultrasonografija pre hirurškog zahvata je iznosio 179 a broj pacijenata kod kojih je urađena scintigrafija, pretežno 201Tl/99mTc metodom, je iznosio 112. Pacijenti (52 muškaraca i 128 žena) su bili podeljeni u sledeće četirigrupe: grupa A-pacijenti sa primarnim (p)HPT (n=78); grupa B-pacijenti sa sekundarnim (s)HPT (n=47); grupa C- pacijenti sa tercijarnim (t)HPT (n=13); grupa D-pacijenti sa neprepoznatim HPT, ali čija anamneza ukazuje na ovo oboljenje (n=42). Visoko-rezoluciona ultrasonografija je korišćena za dijagnostiku od strane samo jednog iskusnog radiologa. Dijagnoza HPT je postavljena na osnovu karakterističnih kliničkih i biohemijskih parametara. Finalna potvrda je bazirana na hirurškom i patohistološkom nalazu. Uvećane PTŽ su detektovane kod 93.85% pacijenata pomoću ultrasonografije a kod 85.89% pacijenata pomoću scintigrafije (p<0.05). Ukupan broj pozitivnih PTŽ detektovanih ultrasonografijom je iznosio 211 u odnosu na 225 PTŽ detektovanih na osnovu hirurškog nalaza (senzitivnost-95.9%; PPV-99.4%). Histopatološkom analizom je potvrđena najveća zastupljenost adenoma u A i D grupi, u poređenju sa grupom B gde je dokazana hiperplazija. Grupu C je karakterisalo prisustvo adenoma u hiperplastičnim PTŽ. Prosečna veličina PTŽ izmerena ultrasonografijom je bila 17.59 ± 8.0mm (n=164) a veličina žlezda izmerenih nakon hirurgije je bila 18.36 ± 8.54mm (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 pouzdana u identifikaciji PTŽ između pacijenata kod kojih se na ovo oboljenje prethodno nije sumnjalo.

Zaključak: Ultrasonografija je senzitivnija i tačnija metoda za preoperativnu detekciju PTŽ kod HPT u poređenju sa 201Tl/99mTc scintigrafijom. Ova metoda se takođe može uspešno koristiti za detekciju uvećanih PTŽ a time i dijagnoze HPT u pacijenata kod kojih se na ovo oboljenje prethodno nije sumnjalo.

Ključnici: paratireoidna žležda; hiperparatireoidizam; ultrasonografija; scintigrafija; senzitivnost
Introduction

Normal-sized parathyroid glands (PTG) are very small; approximately 6 mm (craniocaudal) and 3-4 mm (transverse) dimension, 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 PTG 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 PTG due to renal insufficiency. A decrease of 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 excretion and by the 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 PTG by skilled surgeons provides a high rate of cure exceeding 95\(^8\). Parathyroid surgery was also indicated for patients with hipercalcemia, high PTH level and/or renal osteodystrophy in sPHP 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 PTG and are especially important for patients with solitary PT adenomas. The main reason for insufficiently successful surgical intervention is failure to localize the ectopic PTG and undiagnosed multiple PTG 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 PT adenoma and familiar HPT with multiglandular disease\(^10,12\).

Different methods for localization of PTG have been used in the last three decades, such as high-resolution ultrasonography, scintigraphy imaging, computerized tomography...
(conventional and new 4D), and magnetic resonance imaging\textsuperscript{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\textsuperscript{13-15}.

High-resolution ultrasonography was first described as a method for detection of PT tumours in 1979 by Edis and Evans\textsuperscript{16}. Subsequently, many studies have confirmed its efficacy for preoperative localization of abnormal PTG. 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\%.\textsuperscript{17} Among the PTG imaging techniques, ultrasonography has the advantage of convenience, easy availability and low cost, and is preferred by some authors\textsuperscript{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\textsuperscript{2-21}. PTG 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 PTG 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 PTG and in the hyperechoic capsule\textsuperscript{21}.

In 1989, a new approach using the radiopharmaceutical \textsuperscript{99m}Tc-MIBI was reported for identification and localization of PTG and this imaging method gradually replaced the previous subtraction method based on \textsuperscript{201}Tl/\textsuperscript{99m}Tc\textsuperscript{22}. Several investigators confirmed the use of this technique for the identification of abnormal PTG using either MIBI alone or with subtraction imaging. The sensitivity was in range of 71–93\%\textsuperscript{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\textsuperscript{25-27}. Both methods have significantly lower sensitivities in the detection of multiglandular disease\textsuperscript{27}. However, very often these methods are not comparable as suggested by meta-analyses based on a large number of publications\textsuperscript{26, 27}. It is generally suggested that a preoperative approach that combines both ultrasonography and scintigraphy is more accurate than technique alone\textsuperscript{11, 28, 29}.

There are many factors influencing the accuracy of ultrasonography for detection of pathological PTG, but it seems that the careful examination by a very experienced observer is of crucial importance\textsuperscript{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 aim of the study was: to determine the utility of ultrasonography in preoperative identification and localization of enlarged PTG in patients with different forms of 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 them with scintigraphy.

**Patients and Methods**

**Patients**

This is a retrospective – prospective study on patients with HPT, conducted at the Military Medical Academy (MMA) during the period between 1989 and 2014. The study was approved by the Ethical Committee of MMA. The number of patients was 180 and all of them were subjected to surgery in order to remove pathological PTG. There were 52 males
and 128 females. Their main age was 51.78 years (range, 18-79). Only one patient was false positive on surgery and thus excluded from the study. The patients were divided into four groups. Group A (n=78) was consisted of patients with primary HPT (pHPT), group B (n=47) and group C (n=13) included patients with secondary HPT (sHPT) and tertiary (tHPT), respectively. Group D (uHPT) consisted of patients with previously unrecognized HPT 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 PTG. This group consisted of 523 patients of which 124 had enlarged PTG. Of them only 42 were fully processed and included in the study. The main demographic characteristics of these subgroup patients were given in Table 1.

**Ultrasonography**

The ultrasonography of 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 apparatus 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 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. PTG 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 PTG. The size of the abnormal PTG was measured by taking the largest dimension.

**Scintigraphy**

In most patients subtraction scintigraphy by using $^{201}$Tl/$^{99m}$Tc was performed as described. In brief, scintigraphy of the neck region was done in dynamic mode during 25 min, after IV injection of 2 mCi (74 MBq) $^{201}$Tl. After Tl scintigraphy, dynamic scintigraphy during 25 min in the same position was done after IV injection 5 mCi (185 MBq) $^{99m}$Tc. A direct subtraction view was obtained by subtracting the $^{99m}$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. Scintigraphy was carried out at the Institute for Nuclear Medicine, MMA.

**Biochemical parameters**

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

All patients were operated on by a using classical bilateral neck exploration in the Clinic for Surgery, MMA. After removal, the size of PTG 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.

Statistical analysis

Data were expressed as mean ± Standard Deviation (SD) or mean ± Standard Error (SE). Comparisons between groups were analyzed by Student T-test, Mann-Whitney U test or Kruskal-Wallis test (multiple groups). Categorical data were compared by Chi-square test. Correlations were analyzed by 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 PTG 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 PTG were detected in 169 (93.9%) patients with HPT.

The total number of ultrasonographically-detected PTG 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% PTG. There was a statistically significant correlation between ultrasonography and surgery in the number of PTG (r=0.79; Spearmann range correlation; p<0.001). Histopathology confirmed 67.6% adenomas, 24.0% hyperplasia, 7.3% adenomas combined with hyperlasia and 1.1% 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 5mm x 3 mm x 1mm. Those PTG were located in the close proximity to the posterior capsule of the thyroid gland. The fibro-fatty capsule of PT adenomas has been usually presented as hyperechoic line separating them from the thyroid gland (Fig. 1). When combined with Power Doppler or Color Doppler, extrathyroidal feeding artery entering one pole of PT adenomas (Fig. 2A and2B, Fig.3) or diffuse blood flow within them were visible.

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%) PTG.

The mean size of PTG measured by ultrasonography was 17.59 ± 8.0mm (n=164) versus 18.36 ± 8.54mm (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 serum levels of PTH, Ca, P and ALP activity.

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

The concentration 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 (B and C groups, respectively) were higher than in the groups with primary HPT (A and D groups) (p<0.05).

The concentrations of Ca in plasma in A and B groups were higher than physiological concentrations and the differences, compared to C and D groups, were statistically significant (p<0.05). In contrast, the concentrations of P in B and C groups were statistically significantly higher (p<0.05) compared to A and D groups. Certain patients in the D group 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 groups A and D had dominant anamnestic and clinical signs of urinary system pathology, which were more frequent than in 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 groups B and C in comparison to the other two (p<0.05). It is interesting that the percentage of patients with positive EMNG results in groups A and C was higher in comparison to the group B (p<0.05). The percentage of patients with the anamnestic data of peptic ulcer was higher in group B than in group D (p<0.05). However, these differences were not confirmed by gastroscopy (Table 3).

Comparison of positive PTG findings between ultrasonography and scintigraphy

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

The number of patients with positive PTG findings detected by scintigraphy versus surgery was as follows: total number of patients – 85 vs 112; group A – 39 vs 50; group B – 19 vs 32; group C – 9 vs 10; group D – 18 vs 20.

When the success was analyzed according to the number of patients with positive PTG, it can be seen that in total group, groups A and B, ultrasonography was significantly superior to scintigraphy. In groups C and D, there were no statistically significant differences between these imaging methods.
The total number of PTG detected by ultrasonography versus surgery was: total group – 211 vs 255; group A – 77 vs 80; group B – 79 vs 141; group C – 20 vs 33; group D – 41 vs 44. The total number of PTG detected by scintigraphy versus surgery was: total group – 109 vs 133; group A – 49 vs 80; group B – 19 vs 96; group C – 9 vs 24; group D – 17 vs 20. 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 PTG**

Final aim of this study was to check sensitivity and PPV of ultrasonography and scintigraphy for detection of PTG 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 patients with detected PTG by ultrasonography, it can be seen that both parameters are 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 group B. In other groups (A, C, and D) PPV did not significantly differ compared to ultrasonography (Table 6, A imaging).

The sensitivity and PPV, calculated on the basis of total PTG number identified by ultrasonography, were similar to those analyzed by assessing the number of PTG positive patients. Similar to the previous results, sensitivity and PPV, determined according to 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 of pathological PTG in HPT patients. Although several hundred papers cover this topic, we wanted to present our experience in MMA 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 three forms of HPT and inclusion of one group of patients without prior unrecognized 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 main age of our patients was 51.8 years, suggesting that the evolution of the disease 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 circulating ionised 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.

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 absorption 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 by the gastrointestinal tract. 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 B and C groups compared to other two, suggesting higher
activity of PTG and more severe form of the disease. Although we found in most patients
that both PTH and Ca levels were increased, some inconsistency was observed, especially
in group D (unrecognized HPT), such that PTH is increased and Ca was normal or vice
versa. The literature data also suggest similar findings. We did not find any
differences between normocalcemic and hypercalcemic patients regarding
ultrasonographyc findings of PTG (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. 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 (Table 3) clearly indicate that diagnosis of HPT in our patients was established too
late.

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

The main aim of our study was to check the accuracy of ultrasonography for detection of
pathological PTG depending on the form of HPT. As already mentioned, several hundred
peer-reviewed papers have been published up to now on this topic. An enormous
heterogeneity exists between these publications which are dominantly related to pHPT.
Therefore, it was not possible to include all them in the analysis. To exclude bias, our
selection process was mainly focused to meta-analyses, reviews and papers similarly in design to our study. In the 1980s, sensitivity of ultrasonography for PTG localization in patients with pHPT without previous surgery ranged between 34% and 82%. However, since 1996 sensitivity of ultrasonography has been improved, especially in patients with solitary PT adenoma, reaching sensitivity of 77-91%. A meta-analysis based on 43 studies showed that ultrasound had pooled sensitivity and PPV of 76.1% and 93.2%, respectively, for preoperative localization of PTG in pHPT. Ruda et al. reviewed the literature from 1995 to 2003 and reported a sensitivity of 79% for ultrasound in PTG 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. demonstrated that ultrasonography correctly localized the adenoma in 76% 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. performed in 374 patients, neck ultrasound was able to detect adenomas only in 66.0% 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 et al. who showed that the sensitivity of neck ultrasonography in detecting PTG was 97.5% (number of adenomas) and 85% (localization). In addition, similarly with our results, image size of PTG 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. 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 Cheng et al. 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 PTG. 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 PTG. However, only few of them are relevant to our study, because the dominant 211Tl/99mTc scintigraphy method that we performed is no longer in use. In this context, Gooding et al. reported that parathyroid scintigraphy using a double-tracer (211Tl/99mTc) subtraction technique discovered 74% 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 PTG, but combined techniques were more effective than the use of a single modality. Roses et al. analyzed 36 patients with pHPT in whom either high-resolution real time ultrasonography, 211Tl/99mTc subtraction scintigraphy or CT scanning were performed. Overall sensitivity of correctly localizing the abnormal PTG with these techniques was relatively low: 34% for ultrasonography, 49% for the 211Tl/99mTc...
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. The results depend on many factors such as type of scintigraphy, localization and size of pathological PTG, form of HPT, histopathological characteristics of PTG and many others.

Haber et al. studied 120 patients with pHPT. Ultrasonography detected enlarged PTG in 77% of unselected patients and correctly predicted surgical findings in 74% patients undergoing surgery. Sestamibi scintigraphy was positive in 88% 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. 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. Lumachiet al. analyzed 22 papers published between 1996-2000 and showed that sensitivity detected by various scintigraphic methods varied between 56.9-100 for solitary adenomas but sensitivity was significantly lower when multiglandular PTG were analyzed (35.5-80). Gotthardt et al. 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. demonstrated that subtraction parathyroid scintigraphy (99mTc-MIBI followed by 99mTc-pertechnetate), is a reliable and very sensitive diagnostic tool in detecting abnormal PTG in parathyroid hyperplasia, reaching 100% sensitivity in detecting a “dominant gland” and sensitivity per localized gland of 70%.

Secondary HPT and tHPT are disease entities caused by diffuse or nodular hyperplasia of the parathyroid glands in patients with chronic renal failure. In these conditions, bilateral neck exploration is routinely done in all cases, with surgical options including subtotal parathyroidectomy or total parathyroidectomy with autotransplantation. In patients with secondary HPT, the four glands are not uniformly enlarged and therefore preoperative localization is difficult in comparison with primary HPT. In one study sensitivity and PPV, respectively, were 47.3% and 97.8% for MIBI scintigraphy, and 69.5% and 96.9% for ultrasonography. The sensitivity of combined techniques was 84.2%. In a recent meta-analysis, the pooled sensitivity of PTG scintigraphy in patients with sHPT was 53% and the pooled specificity was 93%. Based on a recent study, McHenry et al. 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 sHPT,
although slightly less sensitive in detection of hyperplastic PTG than PTG adenomas, is very accurate diagnostic procedure.

In our opinion, the inclusion of 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 PTG in 23.7% 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 PTG. Its high sensitivity and PPV, independently of the HPT forms, which were higher than those achieved by $^{201}\text{Tl}/^{99m}\text{Tc}$ scintigraphy, make it as reliable tool for preoperative surgical procedure. Ultrasonography can be also efficiently used for detection of PTG and diagnosis of HPT in patients previously not suspected for this disease.

References


Figure legends

Figure 1. Adenoma (pPTH). 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.

Figure 2. A) Adenoma (pPTH). 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).

Figure 3. Adenoma (pPTH). 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 intrathyroidal vascularization is visible above the parathyroid adenoma.

Figure 4. Biochemical parameters in patients with different forms of PTH

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, triangle = p<0.05 compared to A and D groups.
Fig. 1.
Fig. 2 B)
Fig. 4.
Table 1. Demographic characteristic of patients with HPT

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>Male</th>
<th>Female</th>
<th>Age (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (pHPT)</td>
<td>78</td>
<td>22</td>
<td>56</td>
<td>50.95 ± 12.39</td>
</tr>
<tr>
<td>B (sHPT)</td>
<td>47</td>
<td>17</td>
<td>30</td>
<td>51.09 ± 8.40</td>
</tr>
<tr>
<td>C (tHPT)</td>
<td>13</td>
<td>8</td>
<td>5</td>
<td>48.92 ± 9.78</td>
</tr>
<tr>
<td>D (uHPT)</td>
<td>42</td>
<td>5</td>
<td>37</td>
<td>55.00 ± 10.52</td>
</tr>
</tbody>
</table>

Table 2. Distribution of PTG detected by ultrasonography

<table>
<thead>
<tr>
<th>Localization</th>
<th>PTG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper</td>
<td>5.7</td>
</tr>
<tr>
<td>Left upper</td>
<td>6.6</td>
</tr>
<tr>
<td>Right lower</td>
<td>22.7</td>
</tr>
<tr>
<td>Left lower</td>
<td>38.2</td>
</tr>
<tr>
<td>Multiple</td>
<td>18.2</td>
</tr>
<tr>
<td>Topic atypic</td>
<td>6.2</td>
</tr>
<tr>
<td>Ectopic</td>
<td>2.4</td>
</tr>
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</table>

Table 3. Dominant anamnestic and clinical parameters in patients with different forms of HPT
### Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Group A (n=78)</th>
<th>Group B (n=47)</th>
<th>Group C (n=13)</th>
<th>Group D (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal colica</td>
<td>72&lt;sup&gt;B,C&lt;/sup&gt;</td>
<td>11</td>
<td>8</td>
<td>76&lt;sup&gt;B,C&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kidney stone</td>
<td>71&lt;sup&gt;B,C&lt;/sup&gt;</td>
<td>14</td>
<td>8</td>
<td>69&lt;sup&gt;B,C&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peptic ulcus</td>
<td>30</td>
<td>51&lt;sup&gt;D&lt;/sup&gt;</td>
<td>46</td>
<td>21</td>
</tr>
<tr>
<td>Bladder stone</td>
<td>12</td>
<td>15</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Bone pain</td>
<td>63</td>
<td>96&lt;sup&gt;A,D&lt;/sup&gt;</td>
<td>100&lt;sup&gt;A,D&lt;/sup&gt;</td>
<td>45</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>34</td>
<td>60&lt;sup&gt;A,D&lt;/sup&gt;</td>
<td>92&lt;sup&gt;A,D&lt;/sup&gt;</td>
<td>22</td>
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<tr>
<td>Bone fracture</td>
<td>11</td>
<td>23</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Psych. symptoms</td>
<td>49</td>
<td>64&lt;sup&gt;D&lt;/sup&gt;</td>
<td>92&lt;sup&gt;A,D&lt;/sup&gt;</td>
<td>34</td>
</tr>
<tr>
<td>Neurol. sympt.</td>
<td>32</td>
<td>94&lt;sup&gt;A,D&lt;/sup&gt;</td>
<td>100&lt;sup&gt;A,D&lt;/sup&gt;</td>
<td>24</td>
</tr>
</tbody>
</table>

### Clinical Signs

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>Group A (n=78)</th>
<th>Group B (n=47)</th>
<th>Group C (n=13)</th>
<th>Group D (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>75</td>
<td>100</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>Positive EMNG</td>
<td>58</td>
<td>14&lt;sup&gt;A,C&lt;/sup&gt;</td>
<td>61</td>
<td>ND</td>
</tr>
<tr>
<td>Posit. findings of urin. system</td>
<td>73</td>
<td>100</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>Posit. findings of gastroduod. syst.</td>
<td>45</td>
<td>40</td>
<td>38</td>
<td>16</td>
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</tbody>
</table>

Superscript letters point out statistically significant differences ($\chi^2$ test; p<0.05). <sup>A</sup> in relation to group A; <sup>B</sup> in relation to group B, <sup>C</sup> in relation to group C, and <sup>D</sup> in relation to group D.

---

Table 4. Comparison of positive PTG findings between ultrasonography and scintigraphy in patients with different forms of HPT

<table>
<thead>
<tr>
<th>Group</th>
<th>Imaging method</th>
<th>Total No. of patients *</th>
<th>No. of patients with pos. PTG</th>
<th>$\chi^2$ value</th>
<th>p</th>
</tr>
</thead>
</table>

---

24
The analysis was performed by χ² test. Statistically significant differences between imagings methods are bolded.

*=total number of patients with positive PTG detected by surgery/pathology

<table>
<thead>
<tr>
<th>Group</th>
<th>Imaging method</th>
<th>Total No. of PTG*</th>
<th>No. of positive PTG</th>
<th>χ² value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ultrasonography Scintigraphy</td>
<td>225</td>
<td>211</td>
<td>12.31</td>
<td>=0.0004</td>
</tr>
<tr>
<td>A (pPTH)</td>
<td>Ultrasonography Scintigraphy</td>
<td>80</td>
<td>77</td>
<td>29.28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>B (sPTH)</td>
<td>Ultrasonography Scintigraphy</td>
<td>141</td>
<td>79</td>
<td>30.92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C (tPTH)</td>
<td>Ultrasonography Scintigraphy</td>
<td>33</td>
<td>20</td>
<td>2.97</td>
<td>=0.0849</td>
</tr>
<tr>
<td>D (uPTH)</td>
<td>Ultrasonography Scintigraphy</td>
<td>44</td>
<td>41</td>
<td>1.083</td>
<td>=0.298</td>
</tr>
</tbody>
</table>

The analysis was performed by χ² test. Statistically significant differences between imagings methods are bolded.

*=total number of PTG detected by surgery/pathology
Table 6. Comparison of sensitivity and PPV in detection of positive PTG (A imaging) or total number of PTG (B imaging) between ultrasonography and scintigraphy

<table>
<thead>
<tr>
<th>A) imaging</th>
<th>Parameters</th>
<th>Total group</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
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</thead>
<tbody>
<tr>
<td>Ultrason.</td>
<td>Sensit. (%)</td>
<td>96.4</td>
<td>91.0</td>
<td>93.6</td>
<td>100</td>
<td>100</td>
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<tr>
<td></td>
<td>PPV (%)</td>
<td>99.3</td>
<td>98.6</td>
<td>95.6</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Scintigraphy</td>
<td>Sensit. (%)</td>
<td>74.6*</td>
<td>78.0*</td>
<td>59.3***</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>PPV (%)</td>
<td>94.6</td>
<td>93.9</td>
<td>79.2*</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B) imaging</th>
<th>Parameters</th>
<th>Total group</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrason.</td>
<td>Sensit. (%)</td>
<td>95.9</td>
<td>94.5</td>
<td>93.6</td>
<td>100</td>
<td>100</td>
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<tr>
<td></td>
<td>PPV (%)</td>
<td>99.4</td>
<td>97.4</td>
<td>98.7</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Scintigraphy</td>
<td>Sensit. (%)</td>
<td>80.2*</td>
<td>77.7*</td>
<td>51.7***</td>
<td>88.8</td>
<td>88.8</td>
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<tr>
<td></td>
<td>PPV (%)</td>
<td>89.6</td>
<td>87.3</td>
<td>78.4*</td>
<td>93.4</td>
<td>80.9*</td>
</tr>
</tbody>
</table>

* = p<0.05; *** =p<0.001 compared to corresponding parameters of ultrasonography