ORIGINAL ARTICLE

Correlation of localization and size of the parathyroid glands by ultrasound and intraoperative findings in hyperparathyroidism

Almedina Ramaš[1], Sabrina Uščuplić[1], Šekib Umihanić[1], Hasan Altumbabić[1], Almir Salkić[1], Merima Kasumović[2]

[1]Department of Otorhinolaryngology, Head and Neck Surgery, [2]Clinic for Plastic and Maxillofacial Surgery; University Clinical Centre, Tuzla, Bosnia and Herzegovina

ABSTRACT

Aim To determine a correlation between the localization of the parathyroid gland (PTG), based on ultrasound (US) examination and the operative findings, as well as the correlation between the size of the parathyroid glands measured by ultrasonography (USG) with pathological findings+, and prevalence of enlarged parathyroid glands in various forms of hyperparathyroidism.

Methods A total of 83 patients with hyperparathyroidism who had undergone parathyroidectomy over a period of seven years were included in the study. US examinations of the neck and scintigraphy were performed before surgery in 83 and 42 patients, respectively. In the pathohistological analysis, in addition to diagnosis, the size and weight of the parathyroid gland were measured.

Results US examination revealed 125 enlarged parathyroid glands and two normal-sized glands. Scintigraphy revealed 52 enlarged and three normal-sized parathyroid glands. Enlarged parathyroid glands were more frequently found in the projection of the lower pole thyroid glands. A significantly higher number of enlarged upper parathyroid glands were found by the operative findings than by US. There was no statistically significant difference in the diagnosis of enlarged parathyroid glands in all three forms of hyperparathyroidism. There was a positive correlation between the size of the parathyroid glands obtained by US and the size of the operative finding (κ=0.51; p=0.00 and p<0.0005, respectively). The relationship between parathyroid gland size measured by ultrasound and pathological analysis showed a positive correlation.

Conclusion Ultrasound was useful in evaluating enlarged parathyroid glands, especially in combination with scintigraphy.

Key words: intraoperative identification, parathyroid localization, parathyroidectomy, scintigraphy, surgeon

Corresponding author:
Ramaš Almedina
Department of Otorhinolaryngology,
Head and Neck Surgery,
University Clinical Centre Tuzla
Ul Prof dr Ibre Pašića bb, 75000 Tuzla,
Bosnia and Herzegovina
Phone: +387 35 303 193;
E-mail: almedinaramas10@gmail.com
ORCID iD: https://orcid.org/0000-0002-6843-3166

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INTRODUCTION

Hyperparathyroidism is defined as excessive secretion of the parathyroid hormone (PTH), and it may be primary (PHPT), secondary (sHPT) or tertiary (tHPT) (1) hyperparathyroidism. Indications for surgery in secondary hyperparathyroidism are: osteodystrophy, calcifications in soft tissue, calciphylaxis, severe vascular calcifications, bone pain and itching, medically refractory hypercalcemia, hyperphosphatemia, and if the patient's calcium and phosphorus product is greater than 70 and PTH greater than 800 pg/mL (2). Palumbo et al. state that surgery is the main treatment for tertiary hyperparathyroidism, and that the main indications for treatment are persistent hypercalcemia and/or increased PTH (3).

Total parathyroidectomy with or without autotransplantation, subtotal parathyroidectomy, and limited parathyroidectomy are the three operations that are frequently carried out (4). The localization of pathological parathyroid tissue can be difficult for the surgeon because the localization of the gland can be very unpredictable compared to the normal anatomical localization (4). It is important to develop a strategy for the systematic location of the parathyroid glands (5). It is essential to identify the parathyroid gland (PTG) before surgery, especially in patients with PHPT who require excision of only one or a few PTG, and this allows for a less invasive approach (6). PTG can be detected preoperatively using computed tomography, technetium-99m scintigraphy, or ultrasonography (USG) (6). Knowledge of the prevalence, location, and anatomy of the PTG is essential for surgeons planning for and carrying out parathyroidectomies (6).

Today, the most widely used approach is minimally invasive parathyroidectomy, which is associated with fewer postoperative complications and a shorter procedure (7). The goal is to reduce the size and length of the operative incision, which is associated with greater pain and longer hospitalization (7). In order for these procedures to be successful, it is necessary to provide the surgeon with information on the precise localization of the pathological parathyroid gland (7). Because of that, preoperative imaging and radiological diagnostics are extremely important (4). According to Abruzzo et al. diagnostic radiological processing plays a significant role because it helps during the initial intervention to find the possible gland location and thus avoid the risk of recurrence and relapse due to ectopic or excess tissue (8).

According to Li et al. most surgeons prefer studious preoperative localization before parathyroidectomy (9). A two-phase Tc-99m MIBI scan is most commonly used in preoperative determination of parathyroid gland localization, and ultrasound is commonly used in preoperative determination of the localization of the parathyroid gland, and is more sensitive than scintigraphy. Although it is operator dependent, ultrasound offers a rapid and safe imaging method, free from ionizing radiation. A sestamibi scan has sensitivity that is comparable to ultrasound and is enhanced by tomographic imaging (10). According to Sys et al. in order to identify and localize hyperfunctioning parathyroid glands prior to surgery, methionine PET/CT has been shown to be comparable to sestamibi SPECT/CT (11). The United Kingdom guidelines recommend ultrasound scanning in combination with sestamibi scintigraphy or alone to guide surgery in patients with primary hyperparathyroidism (12).

^{18}F-fluorocholine positron emission tomography/computed tomography (^{18}F-FCH PET/CT) is the most sensitive method for the detection of parathyroid adenomas that can be combined with 4D-CT, but results in a higher dose exposure for the patient and it is a preferred imaging technique in patients with tertiary hyperparathyroidism (13). Preoperative localization of abnormal parathyroid glands can be performed with a variety of modalities and inconsistency in preoperative imaging recommendations even extends to within an individual surgeon's practice (14). Recently, new methods have been developed, such as endoscopic or robot-assisted parathyroid surgery without direct neck incision (15).

Hyperparathyroidism is a serious disease. Our experience has shown that surgical treatment is necessary in the most cases, since medical treatment is often not enough. It is significant to point out that there is an agreement that a good preoperative preparation of the location of the parotid gland is of great importance because otherwise the work of the surgeon is made more difficult and the time of the operation extended. This kind of the study has not been conducted so far in Bosnia and Herzegovina.

The aim of this study was to determine the association of parathyroid gland localization determined by ultrasound examination and the operative finding, as well as a correlation between the size of the parathyroid glands measured by ultrasonography and the pathological finding, and the prevalence of enlarged parathyroid glands in various forms of hyperparathyroidism.

PATIENTS AND METHODS

Patients and study design

The study included 83 patients with hyperparathyroidism who underwent total or partial parathyroidectomy in the period of seven years from January 2011 to January 2020, aged 20 to 73 years (mean 51.13±11.83).

The inclusion criteria were patients with primary, secondary and tertiary hyperparathyroidism who underwent parathyroidectomy. Exclusion criteria were patients with other tumour processes on the neck.

This retrospective-prospective study was approved by the Ethics Committee of the University Clinical Centre Tuzla (Nr. 02-09/2-81/17), and it was carried out in compliance with the International Guidelines for Human Research Protection of the Declaration of Helsinki and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP) (16).

Methods

Ultrasound (US) examinations of the neck and scintigraphy (MIBI) were performed preoperatively by a nuclear medicine specialist. Ultrasound examinations were performed using a real-time ultrasound machine, with the 7.5 MHz linear probe (Toshiba SSA-220A, Japan). The size, echostructure, and localization were determined for each enlarged parathyroid gland. Two categories of classification were used, enlarged PTGs accurately localized and non-localized by this method. Also, the values of gland size (mm) were measured using an assessment scale, and all the glands were divided into three groups: <10 mm, 10-15 mm and >15mm, and values of gland weight (g) were measured using the assessment scale, and all the glands were divided into three groups <1g, 1-1.5, >1.5g.

Data were collected from protocols, medical documentation, and records of the Clinic for Ear, Throat and Nose Diseases, the Clinic for Radiology and Nuclear Medicine and Polyclinics for laboratory diagnostics, Department of Pathology of the University Clinical Centre Tuzla. In the pathohistological analysis (standard haematoxylin and eosin staining), in addition to diagnosis, size and weight of the parathyroid gland were measured. Additional immunohistochemical analysis was used only in obscure cases of benign and malignant tumours.

Statistical analysis

Descriptive analysis was applied to the processing of all the data. The distribution of frequencies and percentages was determined for categorical and ordinary variables and the basic statistical parameters for continuous variables. The relationship between the dichotomous variable of the localization of parathyroid glands (localized and non-localized glands) obtained by ultrasound examination and operative findings was verified by McNemar's test, and the strength of the relationship by calculating an appropriate measure of the association, i.e. the Fi correlation coefficient. To check the degree of agreement between these variables, the Kappa (κ) coefficient was calculated. The difference in the frequency of parathyroid glands localized by US examination and operative findings according to forms of hyperparathyroidism was tested with the $\chi 2$ test. The Kolmogorov-Smirnov test was used to make a decision on the adequate verification of the association of continuous variables. The size, that is the circumference of the gland, as a continuous variable, was calculated on the basis of the two largest actual measurements (length and width) of the localized gland, expressed in millimetres. Matching glands are glands localized in the same place by ultrasound examination and pathohistological findings. A significant deviation was found in all continuous variables from normality of distribution. The relationship between the size of the corresponding parathyroid glands assessed by ultrasound examination and pathohistological findings was tested by calculating the Spearman correlation coefficient.

RESULTS

The study included 83 patients (226 glands) with hyperparathyroidism who underwent total or partial parathyroidectomy. Three methods were

used to localize the parathyroid glands: US, scintigraphy and surgery. Ultrasound examination revealed 125 enlarged and two normal-sized parathyroid glands. Scintigraphy revealed 52 enlarged and three normal-sized parathyroid glands. Surgery found 186 enlarged parathyroid glands.

US examination revealed 54 (out of 127; 42.5%) enlarged lower right PTGs, while 60 (out of 186; 32.3%) were found in operative findings. Ultrasound revealed 47 (out of 127; 37.0 %) enlarged lower left parathyroid glands (localized in the lower end in the projection of the left lobe), while 56 (out of 186; 30.1%) were found by surgery. MIBI showed an equal representation of enlarged lower parathyroid glands, 20 (out of 55; 36.4 %) (Table 1).

Table 1. Prevalence of the localization of enlarged parathyroid glands according to the diagnostic method

Localization	No (%) of glands		
	Ultrasound examination	Scintigraphy	Operative finding
Right upper	14 (11.0)	3 (5.4)	32 (17.2)
Right lower	54 (42.5)	20 (36.4)	60 (32.3)
Left upper	8 (6.3)	5 (9.1)	36 (19.4)
Left lower	47 (37.0)	20 (36.4)	56 (30.1)
Ectopic localization	2 (1.6)	4 (7.3)	2 (1.0)
Normal results	2 (1.6)	3 (5.4)	0 (0.0)
Total	**127 (100.0)**	**55 (100.0)**	**186 (100.0)**

US revealed 14 (out of 127; 11.2%) enlarged upper right PTGs, while 32 (out of 186; 17.2%) were found in operative findings. The total number of enlarged upper left PTGs found by ultrasound examination was eight (out of 127; 6.2%), while 36 (out of 186; 19.3%) were found in operative findings (Table 1).

By analysing the localization of enlarged parathyroid glands, using all three methods, enlarged parathyroid glands were found most frequently in the projection of the lower thyroid glands (lower PTG). The most common localization of enlarged lower parathyroid glands was in the projection of the right lower pole of the thyroid gland.

Of a total of 186 enlarged glands found by operative findings, 108 were accurately localized by US examination. Out of a total of 226 glands examined, which were not localized as enlarged by operative findings, 205 were not localized even by US examination (Table 2).

Statistically significant difference was found in the determination of the location of enlarged parathyroid glands by US examination and operative findings ($p=0.00$ and $p<0.0005$, respectively). The values of the Fi correlation coefficient showed that, according to the Cohen criterion, there was a strong relationship between the method of the diagnosis and the localization of enlarged parathyroid glands ($\varphi=0.54$; $p=0.00$ and $p<0.0005$, respectively). The Kappa coefficient of agreement ($\kappa = 0.51$; $p=0.00$ and $p<0.0005$, respectively) showed a moderate degree of agreement of the compared methods in determining the location of glands, found by US examination and operative findings, which confirmed our hypothesis. There was a positive correlation between the size of the parathyroid glands obtained by US examination and the size of the operative finding.

Table 2. Comparison of the localization of enlarged parathyroid glands

Examination	No (%) of glands		
	Localized	Nonlocalized	Total
Ultrasound	108 (58.0)	17 (7.7)	125 (30.0)
Operative finding	78 (42.0)	205 (92.3)	283 (70.0)
Total	186 (100.0)	226 (100.0)	408 (100.0)

The calculated sensitivity of the ultrasound method in relation to the operative finding was 57.1%, and the specificity 92.3%, while the sensitivity of the scintigraphy in relation to the operative finding was 49.5%, and the specificity 93.3%.

Out of a total of 125 enlarged PTGs found by ultrasound examination, 45 (36.0%) were found to be related to primary hyperparathyroidism, 75 (60.0 %) to secondary, and five (4.0 %) to tertiary. By operative findings, out of a total of 186 enlarged glands, 53 (28.5%) were related to primary hyperparathyroidism, 125 (67.2%) to secondary and eight (4.3%) to tertiary (Table 3).

Table 3. Enlarged parathyroid glands in relation to the form of hyperparathyroidism

Type of hyperparathyroidism	No (%) of glands	
	Ultrasound examination	Operative finding
Primary	45 (36.0)	53 (28.5)
Secondary	75 (60.0)	125 (67.2)
Tertiary	5 (4.0)	8 (4.3)
Total	125 (100.0)	186 (100.0)

No statistically significant difference was found in the diagnosis of enlarged parathyroid glands in relation to all three forms of hyperparathyroidism ($p=0.43$), nor individually between the primary ($p=0.24$) or secondary ($p=0.28$) form.

Dimensions of the enlarged parathyroid glands were larger in the pathohistological findings compared to the ultrasound findings. The average sum of values of the size of the enlarged pa-

rathyroid glands determined by US examination was 264.0 mm, and in the pathohistological findings, 618.6 mm. The sum of the average sizes of matching glands was 165.9 mm by ultrasound and 300.4 mm by pathohistology.

On US, enlarged parathyroid glands (size range 10-15 mm) were the most frequent (67; 53.6%). In the pathohistological findings, parathyroid glands sized >15 mm were the most frequent (87; 47.3%) (Table 4).

Table 4. The ratio of the size of enlarged parathyroid glands evaluated in ultrasound and histopathological findings

Gland size (cm)	No (%) of glands	
	Ultrasound examination	Pathohistological findings
<1	22 (17.6)	36 (19.6)
1– 1.5	67 (53.6)	61 (33.1)
>1.5	36 (28.8)	87 (47.3)
Total	125 (100.0)	184 (100.0)

The ratio of the sizes of the matching parathyroid glands was investigated and assessed using both methods. The highest number of PTGs in ultrasound findings, 57 (54.8 %) were 10-15 mm, while in the pathohistological findings the highest number of PTGs, 56 (53.8 %), were >15 mm.

A statistically significant mild correlation was found between the actual sizes of the matched parathyroid glands using ultrasound and pathohistological findings ($p=0.27$; $p=0.01$- $p<0.01$), as well as the sizes obtained using the established assessment scale ($p=0.20$; $p= 0.04$- $p<0.01$). This confirmed that there is a positive correlation between the size of the parathyroid glands determined by the ultrasound findings and the size measured in the pathohistological analysis.

Based on the established scale obtained by pathohistological findings, it was observed that more than half, 98 (out of 186; 52.7%) glands were <1g, while other glands, on two levels of the scale, were almost equal in weight, 1-1.5 g, 46 (24.7%) glands, while 42 (22.6%) glands weighed >1.5 g (Table 5).

Table 5. Representation of the weight of the parathyroid glands according to the established scale

Gland weight (g)	No (%) of glands
< 1	98 (52.7)
1 – 1.5	46 (24.7)
>1.5	42 (22.6)
Total	186 (100.0)

There was one patient with ectopic parathyroid gland in upper mediastinum and he was referred to a thoracic surgeon for further treatment. This case was excluded from the study.

DISCUSSION

The main finding of the study is that the largest number of enlarged parathyroid glands were found in the projection of the lower pole thyroid glands, mostly the lower right parathyroid glands and a significantly higher number of enlarged upper parathyroid glands were found by the operative findings than by ultrasound.

Once the biochemical diagnosis has been established and the decision to proceed with surgery has been made, the next step is imaging to help the surgeon to plan the operation (2). Surgery of parathyroid glands is generally reserved for patients with symptomatic PHPT (17). To localize the parathyroid adenoma, 99mTc MIBI scintigraphy and neck ultrasonography are usually adequate (18). In Chen et al. study preoperative ultrasound was used to locate and measure the bilateral inferior parathyroid glands, assisting surgeons in identifying and protecting the parathyroid glands during surgery (19). A meta-analysis that included 24 studies showed that lower PTGs were detected more frequently than the upper ones (5). Upper PTGs may be seen more inferiorly, deep relative to the middle part of the thyroid gland (4%), or may be located at or above the uppermost part of the thyroid gland (3%) (5). Rarely, upper glands can be found in the retropharyngeal (1%) or retroesophageal (1%) space, or in the thyroid gland itself (0.2%) (5). This probably makes identification by radiological methods more difficult (5). A study by Lo Pinto et al. determined the anatomical localization of individual pathological parathyroid glands. Among the 810 patients who underwent parathyroidectomy, individual pathological parathyroid glands were unevenly distributed between four ectopic localizations (left upper, 15.7%; left lower, 31.3%; right upper, 15.8%; right lower, 37.2%); pathological lower parathyroid glands (68.5%) were significantly more common than pathological upper glands (31.5%), respectively (20).

In our study, to determine the localization of parathyroid glands, operative finding, the US finding (done in 79 patients) and the scintigraphy finding (done in 42 patients) were taken into account. Through all three modes of diagnosis, the lower parathyroid glands were localized most often, and of these, more were found to the lower right than the lower left. Also, a significantly higher number

of enlarged upper parathyroid glands were found by the operative findings than by ultrasound. On the basis of the obtained results, this research fully conforms to the data obtained by other research from the world literature.

Lee et al. investigated the sensitivity of three methods for preoperative diagnosis, USG, MIBI and CT and found out USG had the highest sensitivity (91.5%) and MIBI the lowest one (56.1%) among the 3 modalities (5). Study by Perie et al. showed that USG detected 75% of hyperplastic glands, while MIBI identified 66% (21). In a prospective study by Mohammadi et al. the sensitivity of USG and MIBI, and the combination of USG and MIBI was 54%, 25%, and 45%, respectively (22). According to a study by Iwen et al. (23) the preoperative sensitivity of sonography were higher at lower left glands and the results of this study agree with our results.

USG alone is usually efficient enough to localize parathyroid adenoma preoperatively, and MIBI is proposed for patients with nonlocalizing USG (24), which is in concordance with our results. Given the different ranges of sensitivity and specificity of ultrasound and scintigraphy in different studies, it may be concluded that our study does not differ from other results, and even corresponds to the findings of most authors showing higher values of gland size determined by pathohistological findings than by US examination; there was no statistically significant difference in the diagnosis of enlarged parathyroid glands in all three forms of hyperparathyroidism.

Simple neck ultrasounds are the most extensively used and economical localization studies. If the ultrasound is non-localizing, radionuclide imaging with a ^{99m}Tc-sestamibi scan can help detect an abnormal parathyroid gland (2). The limitation of this study is that the examination of a larger number of patients could possibly give better results. Larger studies are needed to provide stronger conclusions.

In conclusion, because in most cases, hyperparathyroidism requires surgical treatment, intraoperative identification of the parathyroid glands is not always simple or quick. This prolongs the time of the operation and increases the possibility of complications, as well as the cost of treatment, and makes the work of the surgeon more difficult. Therefore, a good preoperative diagnostic evaluation is a necessary prerequisite for a successful operation.

Ultrasound is a simple, rapid, safe imaging method, free from ionizing radiation and inexpensive diagnostic method that gives the surgeon an insight into the localization of the glands and facilitates their work, especially in combination with scintigraphy.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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