

DOI: 10.5455/msm.2023.35.135-139

Received: Apr 15 2023; Accepted: May 26, 2023

© 2023 Almedina Ramas, Sekib Umihanic, Merima Kasumovic, Almir Salkic, Sabrina Uscuplic, Hasan Altumbabic

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORIGINAL PAPER

Mater Sociomed. 2023; 35(2): 135-139

# Hyperparathyroidism: Pathological Diagnosis and Association with Parathyroid Localization

Almedina Ramas<sup>1</sup>, Sekib Umihanic<sup>1</sup>, Merima Kasumovic<sup>2</sup>, Almir Salkic<sup>1</sup>, Sabrina Uscuplic<sup>1</sup>, Hasan Altumbabic<sup>1</sup>

<sup>1</sup>Otorhinolaryngology Clinic, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

<sup>2</sup>Plastic and Maxillofacial Clinic, University Clinical Center Tuzla, Bosnia and Herzegovina

## Corresponding author:

Merima Kasumović, Ph.D.  
Plastic and Maxillofacial Clinic, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina. Address: Mosnik 29, Tuzla 75000 Bosnia and Herzegovina Phone: 0038761146398, E-mail: merimamaxilo@gmail.com. ORCID ID: <https://orcid.org/0000-0002-0035-4744>.

## ABSTRACT

**Background:** The most common pathohistological finding in primary hyperparathyroidism is adenoma of the parathyroid gland, followed by hyperplasia and the rarest is carcinoma. However, hyperplasia of the parathyroid glands (PTG) is most commonly found in secondary and tertiary hyperparathyroidism. **Objective:** The aim of this study was to determine the relationship between the localization of the parathyroid glands and pathological diagnosis, as well as the prevalence of individual pathological diagnosis after surgery in patients with hyperparathyroidism. **Methods:** Analysis of retrospective-prospective database of 79 patients who underwent parathyroidectomy for hyperparathyroidism in the 7-year study period. Diagnostic methods were used to identify enlarged parathyroid glands as well as to determine their localization: ultrasound examination, scintigraphy and operative finding. Standard hematoxylin eosin staining was used for pathophysiological diagnosis. A correlation analysis between parathyroid gland localization and pathophysiological diagnosis was performed. **Results:** The median age of the patients were 51 age (range 20-73) and 67,1% of the patients were female. In the total number of surgically removed parathyroid glands (182), the most common pathophysiological diagnosis was hyperplasia. Parathyroid adenoma was found in 21 cases. Other diagnoses (thyroid nodule / tissue, lymph node, thymus, cancer) were found in 11 cases, while a normal finding was found in 12 glands. Pathophysiological diagnosis of hyperplasia and adenoma were more common in the lower parathyroid glands. Using the chi-square test, no association was found between pathophysiological diagnosis and localization of

enlarged parathyroid glands. **Conclusion:** The most common pathophysiological diagnosis in hyperparathyroidism was hyperplasia and was most commonly found in the inferior parathyroid glands. Adenoma as pathophysiological diagnosis is also most commonly found in the lower parathyroid glands, but without statistical significance.

**Keywords:** Hyperparathyroidism, parathyroid glands, hyperplasia, adenoma.

## 1. BACKGROUND

Parathyroid glands measure on average 2–4 mm in size and weigh 20–40 mg and are located on the posterior surface of the thyroid gland and are supplied by the inferior thyroid artery (1). Hyperparathyroidism occurs due to increased activity of the parathyroid glands, from an intrinsic abnormal change altering excretion of parathyroid hormone (primary or tertiary hyperparathyroidism) or from an extrinsic abnormal change affecting calcium homeostasis stimulating production of parathyroid hormone (secondary hyperparathyroidism) (2). Parathyroid gland anatomy is variable (PTG) in the population, four PTG are present, but some research reported fewer and cases of up to 12 glands per patient. Embryologically, parathyroid glands originate from endodermal tissue. The localization of the superior glands is usually on the upper pole of the thyroid gland, representing a short distance caudally from the intersection of the recurrent laryngeal nerve and inferior thyroid artery. The traveled distance of superior glands is shorter and their location is often more constant than the inferior glands. The

Location		Pathohistological diagnosis						
		Hyperplasia	Adenoma	Cancer	Thyroid node	Lymph node	Thymus	Normal tissue
Superior right	f	24	3	0	1	1	0	3
	% in location	75,0	9,4	0,0	3,1	3,1	0,0	9,4
	% in diagnosis	17,4	14,3	0,0	20,0	25,0	0,0	25,0
Inferior right	f	43	7	0	2	1	0	6
	% in location	72,9	11,9	0,0	3,4	1,7	0,0	10,2
	% in diagnosis	31,2	33,3	0,0	40,0	25,0	0,0	50,0
Superior left	f	33	2	0	1	0	0	0
	% in location	91,7	5,6	0,0	2,8	0,0	0,0	0,0
	% in diagnosis	23,9	9,5	0,0	20,0	0,0	0,0	0,0
Inferior left	f	38	8	0	1	2	1	3
	% in location	71,7	15,1	0,0	1,9	3,8	1,9	5,7
	% in diagnosis	27,5	38,1	0,0	20,0	50,0	100,0	25,0
Ectopic location	f	0	1	1	0	0	0	0
	% in location	0,0	50,0	50,0	0,0	0,0	0,0	0,0
	% in diagnosis	0,0	4,8	100,0	0,0	0,0	0,0	0,0
Total	f	138	21	1	5	4	1	12
	% in location	75,8	11,5	0,5	2,7	2,2	0,5	6,6
	% in diagnosis	100,0	100,0	100,0	100,0	100,0	100,0	100,0

Table 1. Pathohistological diagnosis of parathyroid glands diagnosed after surgery. Values are presented as number (%).

latter descend along with the thymus, which also originates from the third pharyngeal pouch and because of that fact the glands can often be found along the descent pathway in the neck or mediastinum. The inferior pole of the thyroid gland is their most common position, below the superior PTG (3).

*Clinicopathological primary hyperparathyroidism* includes parathyroid adenoma (80-85%), parathyroid hyperplasia (10-15%) and cancer (<1-5%). Secondary hyperparathyroidism is generally manifested with parathyroid hyperplasia, while tertiary hyperparathyroidism presents the onset of autonomic parathyroid hormone (PTH) production of neoplasm (s) from secondary parathyroid hyperplasia (4). Parathyroid adenoma and hyperplasia are the most common diagnoses, whereas parathyroid carcinomas and atypical adenomas are exceptional causes of hyperparathyroidism, the latter being purely a diagnosis by exclusion (5). When multiple glands are included, they may present a range of pathology from diffuse hyperplasia to asymmetric hyperplasia or multiple adenomas. The histological diagnosis of parathyroid cancer can be difficult and in some cases diagnosis can only be done following disclosure of distant metastases (6).

## 2. OBJECTIVE

To determine the relationship between the localization of the parathyroid glands and pathological diagnosis, as well as the prevalence of individual pathological diagnosis after surgery in patients with hyperparathyroidism.

## 3. MATERIALS AND METHODS

The study included 79 consecutive patients with hyperparathyroidism, who underwent total or partial parathyroidectomy in the period from January 2011 to February 2018. The inclusion criteria were patients with

primary, secondary and tertiary hyperparathyroidism who underwent parathyroidectomy, and excluding criteria were other tumor processes on the neck.

In this study, three diagnostic methods were used to diagnose enlarged parathyroid glands as well as to determine their localization: ultrasound examination, scintigraphy and operative finding. Standard HE (hematoxylin eosin) staining was used for pathophysiological diagnosis. Additional immunohistochemical analysis was used only in unclear cases of benign and malignant tumors.

### Ethical statement

This retrospective-prospective study was approved by the Ethics Committee, which is to be carried out in compliance with the International guidelines for human research protection of the Declaration of Helsinki and International Conference on Harmonization in Good Clinical Practical (ICH-GCP). Written informed consent was obtained from all individual participants included in the study.

### Statistical analysis

The data collected by the research were processed with the software package SPSS, version 20. Descriptive analysis was applied to the processing of all data. The distribution of frequencies and percentages was determined for categorical and ordinary variables and the basic statistical parameters for continuous variables. Independence testing, **that is** (i.e.), examination the correlation of variables, pathophysiological diagnosis and localization of parathyroid glands, due to the assumption that at least 80% of cells have a frequency of 5 or more, was performed only for diagnoses of hyperplasia and adenoma and individually combined upper and lower localizations. For this purpose, the chi-square test was also applied, and since no statistically significant correlation was confirmed, it was not necessary to check the strength of the bond with an appropriate measure of

association—Cramer's V correlation coefficient.

#### 4. RESULTS

This study included 79 patients with hyperparathyroidism who underwent total or partial parathyroidectomy in the period from January 2011 to February 2018, aged 20 to 73 years (mean  $51.13 \pm 11.83$ ). The majority of respondents were female (67%). In the examined group, the most common form of hyperparathyroidism is secondary, which was found in 41 (51.9%) cases. Primary hyperparathyroidism was found in 35 (44.3%) and tertiary in 3 (3.8%) patients. Eight total parathyroidectomies (10%), 32 subtotal parathyroidectomies (40.5%), 38 (48.1%) extirpations, (of which 2 operations with two glands and thyroid lobectomy on the same side) were performed in 79 subjects of our study, and one thoracotomy (1.3%). We analyzed the association between parathyroid localization and pathophysiological diagnosis. Of the total number of removed parathyroid glands found by surgery (182), the most common pathophysiological diagnosis was hyperplasia, which was found in 138 (75.8%) glands, as shown in Table 1.

Parathyroid adenoma was found in 21 (11.5%) cases. Other diagnoses (thyroid nodule / tissue, lymph node, thymus, cancer) were found in 11 (5.9%) cases, while a normal finding was found in 12 (6.6%) glands. Pathophysiological diagnosis of hyperplasia and adenoma were more common in the lower parathyroid glands. The total number of hyperplasia found in the lower right PTG was 43 (31.2%) while in the lower left was 38 (27.5%). Adenomas were found in 7 (33.3%) PTG localized in the lower poles on the left and in 8 (38.1%) localized in the lower poles on the right.

Using the chi-square test, no association was found between pathophysiological diagnosis and localization of enlarged parathyroid glands (noting that only diagnoses of hyperplasia and PTG adenoma were taken into account), no statistically significant difference in the frequency of these diagnoses was found according to localization ( $\chi^2 = 1.32$ ;  $df = 1$ ;  $p = 0.25$ ). This did not confirm our working hypothesis that there is a positive correlation between the localization of the parathyroid glands and the pathophysiological diagnosis. When it comes to their diagnoses, we had 1 cancer, 1 case of thymus tissue, then lymph nodes, thyroid nodes, and normal parathyroid tissue.

We also analyzed the relationship between pathophysiological diagnosis and forms of hyperparathyroidism, and we found out that of a total of 182 enlarged PTG, hyperplasia is the most common pathophysiological diagnosis and was found in 113 (90.4%) in secondary, 18 (13.7%) in primary and 7 (5.1%) in tertiary hyperparathyroidism. Adenoma was found in 17 (34.7%) in primary and 4 (3.2%) in secondary hyperparathyroidism.

#### 5. DISCUSSION

Lee JB et al (2015) examined 109 patients who underwent parathyroidectomy for secondary hyperparathyroidism from January 2003 to April 2014 (7). Pathological analysis showed nodular hyperplasia in 86 patients

(78.9%) and diffuse hyperplasia in 23 patients (21.1%). In a study involving 50 patients, a total of 199 glands were removed. Pathophysiological analysis showed that 183 glands were parathyroid lesions, where 4 glands were confirmed as normal parathyroid glands and 12 were lymph nodes. In cases of 183 confirmed pathological glands, 179 had parathyroid hyperplasia, and 4 lesions in 3 patients were parathyroid adenomas (8).

Parathyroidectomy (PTx) underwent 109 patients for secondary hyperparathyroidism (sHPT). Nodular hyperplasia was shown in 86 patients (78.9%) and diffuse hyperplasia in 23 patients (21.1%). Recurrent or persistent patients were 35 (32.1%). Four hundred twenty-three PTGs in the 109 patients were identified and surgically removed. Four hundred twenty-two parathyroid glands were found in typical sites as follows: 106 glands were right upper, 107 right lower, 105 left upper, and 104 left lower and 1 ectopic PTG in the upper mediastinum (7). Among 810 patients who underwent PTX for primary hyperparathyroidism (pHPT), single abnormal parathyroid glands were unevenly distributed among the four eutopic locations (left superior position, 15.7%; left inferior position, 31.3%; right superior position, 15.8%; right inferior position, 37.2%;  $P < 0.01$ ). According to this abnormal inferior parathyroid glands (68.5%) were significantly more common than abnormal superior glands (31.5%), respectively ( $P < 0.01$ ). This research indicates that single eutopic abnormal parathyroid glands are more likely to be inferior. Nevertheless, successful PTX remains predicated on knowledge of parathyroid anatomy, experience, and judgment of the surgeon (9).

The combined experience of three tertiary endocrine surgery centers with parathyroid adenoma (PTA) was described in the study Lee JC et al. (2015) (10). According to this study patients with adenomas  $> 1$  cm above the upper pole or other neck locations as a result of abnormal or incomplete descent were included for analysis. Ectopic adenoma was identified in 16 patients out of 5241 patients who underwent PTx in the 7-year study period (incidence 0.3%). Ectopic gland sites included the submandibular triangle, retropharyngeal space, carotid space, parapharyngeal space and cricothyroid space. This study indicates that a surgeon who performs parathyroidectomies can find incompletely or abnormally descended PTAs. In the Von Breitenbuch study (2007) the left side is the most common localization of the adenomas (11). Due to the obtained data, they recommend first exploration of the left side of the neck if the adenoma could not be localized preoperatively.

In our study of 79 patients, an ectopic parathyroid gland, localized in the upper mediastinum, was found in one patient. Pathophysiological diagnosis showed that it was adenoma. *Nodules corresponding to ectopic thyroid tissue* were found in three patients on pathophysiological analysis of the parathyroid glands, and thymus tissue was found in one patient in the analysis of the lower left parathyroid gland. The prevalence of ectopic localizations in our study with respect to the diverse results of other studies or a larger sample is consistent with most studies.

A rare cause of hyperparathyroidism are intrathyroid

parathyroid lesions, with an incidence of 1% to 3.4%. Therefore, exact diagnosis and preoperative localization of intrathyroid parathyroid lesions is very important for surgeons as an effective method to cure hyperparathyroidism. The differential diagnosis among rare intrathyroid parathyroid lesions and common thyroid nodules can be very difficult. A total of 15 patients with intrathyroid parathyroid lesions were enrolled in this study, including 11 females (73%, 11/15) and 4 males (27%, 4/15) and pathological diagnosis confirmed 12 cases of parathyroid adenoma (80%, 12/15), 1 case of parathyroid hyperplasia (6.7%, 1/15), and 2 cases of parathyroid adenocarcinoma (13.3%, 2/15) confirmed postoperatively. *The mean size* of the 15 lesions was  $2.1 \pm 1.1$  cm (12).

In our study, we had 5 cases of intrathyroid parathyroid lesions (4 women, 1 man), in two patients with primary hyperparathyroidism, nodules were found in the lower poles of the thyroid gland, 1 case was an atypical adenoma with unpredictable biological potential and the other hyperplasia of the parathyroid gland. In three patients with secondary hyperparathyroidism, lesions were found in the lower poles of the thyroid gland, two on the left side and one case on the right side and pathophysiological diagnosis confirmed the case of parathyroid hyperplasia. The results of our study showed that out of a total of 182 enlarged glands, the most common was hyperplasia, followed by parathyroid adenoma, while all other diagnoses were present in a total of 5.9% of cases and normal tissue in 6.6% of glands. Both hyperplasia and adenomas were more common in the lower glands. The prevalence of pathophysiological diagnoses according to the form of hyperparathyroidism in our paper showed that out of a total of 182 enlarged glands, hyperplasia was present in secondary form in 90.4%, primary 13.7% and tertiary hyperparathyroidism in 5.1% of glands, followed by adenoma, in the primary 34.7% and in the secondary in 3.2%. In this regard our findings are in agreement with previous studies. In a study performed on 121 patients, pathophysiological analysis showed adenoma in 3 cases, hyperplasia in 3 cases, and cancer in 1 (13). Other study described malignancy in 7 patients (6.8%) (14). Parathyroid cancer occurs in 1% to 3% patients with PTH, and in a study series of cases in two patients it was localized in the left lower parathyroid glands and in one in the upper (15).

In a 62-year-old patient, preoperative ultrasound examination of the neck showed an enlarged upper right parathyroid gland. Histopathological examination revealed parathyroid cancer. The majority of parathyroid neoplasms are found in the lower parathyroid glands, which is most likely related to the different embryonic descent pathways of the upper and lower glands (16). Of the 79 patients in our study, one patient was found to have parathyroid cancer. During surgery at the site of anatomical localization of the lower right parathyroid gland on frozen section preparations, first the lymph node is obtained, then the thyroid tissue, and the cancer is localized in the incorporated tissue of the lower half of the right lobe of the thyroid gland. Given the low prevalence in the general population, the data are in line

with the literature data.

A fact that is important to mention is that there are tumors with some features suggesting malignancy, but falling short of unequivocal histological diagnosis of malignancy, which are marked 'atypical adenoma' (6). Histopathological features include fibrous bands, pronounced trabecular growth, remarkable mitotic activity, tumor necrosis and incomplete invasion of the capsule. The importance of the remarkable mitotic activity is unclear, because their detection should encourage careful assessment, while searching for other features of malignancy (6).

In our study, 21 adenomas were diagnosed by pathophysiological analysis. In a patient who underwent total parathyroidectomy, pathophysiological diagnosis showed nodular hyperplasia of three parathyroid glands and in the projection of the right upper parathyroid gland one adenoma of the main cells, which according to the pathologist is found in 10% of cases according to the literature. Of the 21 adenomas, two adenomas were verified as atypical adenomas. In one patient, atypical adenoma was localized in the lower half of the right lobe of the thyroid gland, and at the same patient after three years, liver biopsy confirmed a diagnosis of a malignant epithelial tumor with neuroendocrine differentiation due to co-expression of galectin 3, cyclin D1 and pronounced proliferative activity cancer. Another atypical adenoma was diagnosed in a patient with localization of the lower left parathyroid gland, and within a year meta-changes in the liver were diagnosed. Pathophysiological analysis showed that it was a poorly differentiated cancer with extensive necrosis and a nonspecific immunophenotype (it cannot be ruled out that it was cholangiocarcinoma, but also other primary outcomes).

## 6. CONCLUSION

Hyperparathyroidism is a common endocrine disorder with potential complications. In a large number of cases, it requires surgical treatment, when the pathologist is often exposed to difficulties in reliably determining the true pathoanatomical substrate, due to the great variability and overlap in the microscopic finding.

In our study, the most common pathological diagnoses were hyperplasia (75.8%) and adenoma (21%). Both hyperplasia and adenoma were more common in the lower parathyroid glands, and most often in the lower right, but no statistically significant difference in frequency was found. Out of 182 glands, one cancer and 2 atypical adenomas were found, for which it is necessary to emphasize that they require special attention, i.e. such patients need to be seriously subjected to further diagnostic processing and monitoring.

- **Patient Consent Form:** All participants were informed about subject of the study.
- **Author's Contribution:** A.P. and E.M. gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. A.P, A.K., and E.M. had a part in article preparing for drafting or revising it critically for important intellectual content. A.P, A.K., and E.M. gave final approval of the

version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

- **Conflicts of interest:** There are no conflicts of interest.
- **Financial support and sponsorship:** None.

## REFERENCES

1. Islam AK. Advances in the diagnosis and the management of primary hyperparathyroidism. *Ther Adv Chronic Dis*. 2021; Jun 11.
2. Fraser WD. Hyperparathyroidism. *Lancet*. 2009; Jul 11; 374(9684): 145-158.
3. Tattera D, Wong LM, Vikse J, Sanna B, Pekala P, Walocha J, et al. The prevalence and anatomy of parathyroid glands: a meta-analysis with implications for parathyroid surgery. *Langenbecks Arch Surg*. 2019; 404(1): 63–70.
4. Duan K, Gomez Hernandez K, Mete O. Clinicopathological correlates of hyperparathyroidism. *J Clin Pathol*. 2015; Oct; 68(10): 771-787.
5. Grabelus SYS, Schmid KW. Pathology of parathyroid glands: Practical aspects four routine pathological investigations. *Pathologe*. 2015; May; 36(3): 229-236.
6. Mizamtsidi M, Nastos C, Mastorakos G, Dina R, Vassiliou I, Gazouli M, et al. Diagnosis, management, histology and genetics of sporadic primary hyperparathyroidism: old knowledge with new tricks. *Endocr Connect*. 2018; Feb; 7(2): R56-R68.
7. Lee JB, Kim WY, Lee YM. The role of preoperative ultrasonography, computed tomography, and sestamibi scintigraphy localization in secondary hyperparathyroidism. *Ann Surg Treat Res*. 2015; Dec; 89(6): 300–305.
8. Li W, Zhu Q, Lai X, Sun J, Jiang Y, Ren X, et al. Value of preoperative ultrasound-guided fine-needle aspiration for localization in Tc-99m MIBI-negative primary hyperparathyroidism patients. *Medicine (Baltimore)*. 2017; Dec; 96(49): e9051.
9. LoPinto M, Rubio GA, Khan ZF, Vaghaiwalla TM, Farra JC, Lew JI. Location of abnormal parathyroid glands: lessons from 810 parathyroidectomies. *J Surg Res*. 2017; Jan; 207: 22-26.
10. Lee JC, Mazeh H, Serpell J, Delbridge LW, Chen H, Sidhu S. Adenomas of cervical maldescended parathyroid glands: pearls and pitfalls. *ANZ J Surg*. 2015; Dec; 85(12): 957-961.
11. Von Breitttenbuch P, Iesalnieks I, Piso P, Schlitt HJ, Agha A. Primary hyperparathyroidism: clinical symptoms, diagnostic significance and localisation-a retrospective analysis. *Zentralbl Chir*. 2007; Dec; 132(66). 497-503.
12. Ye T, Huang X, Xia Y, Ma L, Wang L, Lai X, et al. Usefulness of preoperative ultrasonographic localization for diagnosis of a rare disease: Intrathyroid parathyroid lesions. *Medicine (Baltimore)*. 2008; Jun; 97(23).
13. Paillahueque G, Massardo T, Barberán M, Ocares G, Gallegos I, Toro L, et al. (False negative spect parathyroid scintigraphy with sestamibi in patients with primary hyperparathyroidism). *Rev Med Chil*. 2017; Aug; 145(8): 1021-1027.
14. Alkhalili E, Tasei Y, Askoy E, Aliyev S, Soundararajan S, Taskin E, et al. The utility of neck ultrasound and sestamibi scans in patients with secondary and tertiary hyperparathyroidism. *World J Surg*. 2015; Mar; 39(3): 701-705.
15. Cheah WK, Rauff A, Lee KO, Tan W. Parathyroid Carcinoma: A Case Series. *Ann Acad Med Singapore* 2005; 34: 443-446.
16. Kolluri S, Lal K, Cang R, Mandava N. Parathyroid carcinoma: a silent presentation. *Gland Surg*. 2014; Aug; 3(3): 211–214.