International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Histological Influence on Adenoma Localization Abstract

Ali Aktekin[1], Zuhal Özcan[2], Meryem Günay Gürleyik[3], Mehmet Torun[4], Abdullah Ramazan[5]

[1]General Surgeon, Giresun University, Medical Faculty, General Surgery Department, Giresun, Turkey.
[2]University of Health Haydarpasa Numune Education and Research Hospital, Pathology Deparment, Istanbul, Turkey.
[3,4]University of Health Haydarpasa Numune Education and Research Hospital, General Surgery Department, Istanbul, Turkey
[5]University of Health Haydarpasa Numune Education and Research Hospital, Radiology Department, Istanbul, Turkey.

Abstract

Introduction: Parathyroid scintigraphy and ultrasonography are the primary imaging methods used for localizing parathyroid adenomas. However, there remains a risk of missed or failed localization. This study aims to investigate the relationship between clinical and pathological findings in patients with parathyroid adenoma, focusing on the causes behind missed adenomas and localization failures.

Patients and Methods: We analyzed the demographic, clinical, laboratory, and radiological data of patients who underwent surgery for primary hyperparathyroidism due to adenomas. Additionally, we reassessed the adenomas' pathologic characteristics, including size, weight, dominant cell type, and the percentage of oxyphilic cells.

Results: A total of 115 patients were studied, with dominant cell types distributed as follows: 83 (71.6%) conventional chief cells, 15 (12.9%) water-clear cells, and 17 (14.7%) oxyphilic cells. The average percentage of oxyphilic cells was 21.15%. The localization rate via ultrasonography was significantly lower in the water-clear cell group ($p < 0.05$). While not statistically significant, the localization success using scintigraphy was lower in the oxyphilic cell group compared to others (58.8% vs. 80.7% and 86.7%). Our findings suggest that histological subtypes of parathyroid adenomas, particularly dominant cell content, may affect preoperative localization success.

Conclusion: Missed parathyroid adenomas may be attributed to their histological subtypes and dominant cell composition. These factors could influence the accuracy of preoperative localization with ultrasonography and scintigraphy.

Keywords: Parathyroid, ultrasonography, parathyroid scintigraphy, chief cells, water clear cells, oxyphilic cells

Introduction

The parathyroid glands (PGs) are small, nodular endocrine structures located behind the thyroid. The PG has two major types of cells: chief cells (ChC), which are most common, and oxyphilic cells (OxC). Chief

cells are further subdivided into conventional chief cells (CChC) and water-clear cells (WCC) which is less common. They generate and secrete parathyroid hormone (PTH), which influences calcium homeostasis **[1]**. Furthermore, any abnormalities in PTH production could lead to parathyroid diseases such as primary hyperparathyroidism (PHPT), which is characterized by excessive PTH release **[2]**. Increased circulating levels of PTH are primarily caused by single or multiple autonomously functioning parathyroid adenomas (PTA) in 80%–85% of cases but also by diffuse parathyroid hyperplasia in 15%–20% and parathyroid carcinoma in 1%–2% **[3,4]**.

PHPT is treated surgically, and because it is most often a single adenoma, preoperative localization of the adenomas allows a minimally invasive surgical approach. Preoperative imaging studies include ultrasonography (USG), ^{99} ^{m}Tc methoxyisobutylnitrile (MIBI) parathyroid scintigraphy, computed tomography, and magnetic resonance imaging (MRI), all of which carry the risk of missing and non-localization **[5-7]**.

Cell types and dominant ones could change the weight, size, echogenicity, and ^{99} ^{m}Tc methoxyisobutylnitrile uptake of a PTA. The purpose of this article was to document the relationship between clinical and pathological findings in patients with parathyroid adenoma in order to determine the causes of missing adenomas and non-localization. We also attempted to find some clues to persistent or recurring PHPT cases.

Patients and Methods

We gathered information from our computer data environment on patients who had PHPT operations between June 2017 and June 2019. The study designed in retrospective study with the permission of our hospital study committee on 30 July; 2019 (Number 771/07/2019) with obeying the Declaration of Helsinki. Patients' demographic characteristics such as age, gender, clinical findings, PTH values, and also whether the patient was a primary or recurrent case were all recorded. We also documented whether localization can be detected in all patients routinely using neck USG and/or double-phase MIBI parathyroid scintigraphy as imaging methods and whether these findings are accompanied by surgical findings. In suspicious patients, we performed a USG-guided PTH washout and fine-needle aspiration biopsy prior to surgery or an intraoperative rapid PTH assay. Pathologic size and weight of the lesions; whether the lesion is hyperplasia, adenoma, atypical adenoma, and carcinoma; OxC ratio; and dominant cell type (OxC, CChC, WCC, lipoadenoma, hamartoma) in each lesion were all reevaluated. In addition, we documented the end result of operations as a persistence or recurrence case. We only included the patients with PTAs who had a follow-up period of more than 6 months and excluded cases with hyperplasia and carcinoma and also if follow-up period of less than 6 months. The longest following time was 42 months.

***Ultrasonography*:** In supine position, the patients were examined with a 9Ghz high-resolution probe. Lesions were assessed in conjunction with scintigraphy. The sizes of the lesions were measured in two planes: craniocaudal and anteroposterior dimensions in the sagittal plane. Moreover, the location of the lesions to the thyroid gland, trachea, and carotid artery was noted. Contour features, shape, and echogenicity of the lesions were also specified.

***Scintigraphy*:** Dual-phase Tc-99m MIBI imaging was applied. Early-phase static images were obtained from the neck and mediastinum region 15 minutes after IV injection of 20 mCi Tc-99m MIBI, and late-phase static images were obtained 2–4 hours later. In addition, at approximately 1 hour, 64x64 matrix, 64 images/30 sec single-photon emission computed tomography (SPECT) images were taken to cover the

neck and mediastinum region.

***Interpretation*:** In terms of parathyroid adenoma/hyperplasia, the presence of non-focal thyroid Tc-99m MIBI involvement in early- or late-phase parathyroid images, focal nodular involvement extending up to the late phase, and focal involvement areas observed in parathyroid scintigraphies (static and SPECT) were considered significant. Furthermore, CT images of the patients' neck and upper mediastinum were combined with scintigraphic SPECT images to improve localization and visibility of the lesions.

***Surgery*:** After administering general anesthesia and positioning the patient, we incised the skin according to the orientation of preoperative localization. We all performed minimal invasive procedure. Following adenoma excision, we routinely examined the lesion with a frozen section in every patient. Moreover, we performed an intraoperative rapid PTH assay.

***Pathology*:** The parathyroid pathology reports were retrieved from the system database of our institution. Hematoxylin- and eosin-stained slides were analyzed again and classified based on size, weight, histopathologic diagnoses, percentage of OxC content, and dominant cell ratio. Size was calculated as the maximum diameter of the gland, as previously reported and verified by measurement on microscopic reexamination. On gross examination, the PGs were weighed and noted on the pathology reports. All histopathologic diagnoses were classified as hyperplasia, adenoma, atypical adenoma, and carcinoma categories. The cell morphology is subdivided into OxC, CChC, and WCC categories. Then, under a light microscope, OxC content in percentage and dominant cell ratio were determined by encircled OxC or dominant cell areas (magnification x200 and x400).

If the lesion was a circumscribed nodule with a well-defined intervening fibrous capsule and a rim of compressed parathyroid tissue at the periphery, PTA was diagnosed. Microscopically, PTA is predominantly composed of ChC intermingled with OxC. On the other hand, WCC adenomas are made up of nests of clear cells with a lot of foamy, granular cytoplasm. OxC adenomas were considered when the composition was at least 80%. If there was lymphatic or vascular invasion, extracapsular extension, pleomorphism, necrosis, or mitotic activity, we ruled out the lesion with the diagnosis of carcinoma**[8,9]**. If an immediate drop in PTH and alleviation of hypercalcemia were observed postoperatively and remained in normal range for more than 6 months, the diagnosis of PTA was also encouraged.

***Statistical Reviews*:** IBM SPSS Statistics 22 (IBM SPSS, Turkey) for statistical analysis programs was used to evaluate the findings of the study. While analyzing the study data, the Shapiro-Wilk test was used to assess the compliance of the parameters to the normal distribution, and descriptive statistical methods (mean, standard deviation, frequency) as well as the one-way ANOVA test were also used to compare the normally distributed parameters between groups. For intergroup comparisons of parameters that did not have a normal distribution, the Kruskal–Wallis test was used. Moreover, for comparisons of parameters with normal distribution between two groups, the student's t-test was used. On the other hand, for qualitative data comparison, the chi-square test and the Fisher–Freeman–Halton test were used. Pearson correlation analysis was used to investigate the relationships between parameters suitable for normal distribution, while Spearman's correlation analysis was used to examine the relations between parameters not suitable for normal distribution. The significance was determined at the $p < 0.05$ level.

Results

We discovered 22 (19%) men and 93 (81%) women among 115 PHPT patients with a mean age of 54.15 ± 12.03 years. The study was examined under three dominant cell groups: 83 (71.6%) CChC, 15 (12.9%) WCC, and 17 (14.7%) OxC. The average percentage of OxC was 21.15 ± 29.35.

There was no statistically significant difference between the dominant cell groups in terms of age, gender, PTH level, localization by scintigraphy, preoperative diagnosis as primary or recurrence, additional diseases in the thyroid gland, pathologic size, and weight of PHPT (for all of them, $p > 0.05$) (Tables 1 and 2).

In terms of PTA localization by USG, there is a statistically significant difference between the dominant cell groups ($p = 0.012$). The rate of localization of the OxC group by USG (94.1%) was significantly higher than the CChC (89.2%) and WCC (60%) dominant group ($p = 0.012$). In addition, the localization of the CChC group by USG was also statistically significantly higher than the WCC dominant group (Table 2).

There is no statistically significant relationship between the percentage of OxCs and age, gender, associated thyroid gland diseases, PTH level, localization by MIBI parathyroid scintigraphy and USG, preoperative diagnosis as primary or recurrence, pathologic size and weight of PTA, and end result of operation as recurrence, persistent, or resolved in PHPT (for all of them, $p > 0.05$). CChC dominant PTAs are heavier than WCC and OxC dominant PTAs without any statistically significant differences (Tables 2 and 3).

Only three patients were found to be recurrent, while three others remained persistent, and all six patients were in the CChC group. When we compared the oxyphilic cell ratio in the PTA, although all six patients were in the CChC group, we found that it was higher in the persistent cases (34, 25 ± 40, 97) than in the resolved cases (19, 31 ± 27, 44) but lower in the recurrent cases (7, 67 ± 12, 42) than in the resolved cases.

Discussion

PHPT is a common endocrine disorder that primarily affects women **[3,4]**. We also discovered that women outnumber men in PTA, with women being four times more affected than men in our study. Moreover, PHPT is treated surgically by removing enlarged glands. Bilateral neck exploration is considered the "gold standard" and has a 95% success rate, but it will be unnecessary in these patients due to precise preoperative localization of PTA **[10-12]**. Precise localization of PGs is difficult because the anatomy of PGs varies between individuals and less or excessive number of PGs could be present **[13,14]**.

Preoperative imaging studies such as USG, MIBI parathyroid scintigraphy, and MRI, as well as intraoperative rapid PTH assay and/or gamma probe, are now commonly used to localize adenomas in order to guide a minimally invasive surgical approach with varying success rates **[12,13,15,16]**. Furthermore, the main imaging modalities for preoperative localization of PTA are USG and MIBI parathyroid scintigraphy **[16, 17]**. In all patients, we used USG and MIBI parathyroid scintigraphy as double imaging modalities, but in suspicious cases, we also performed PTH washout, intraoperative rapid PTH assay, CT, or MRI.

The sensitivity of USG in detecting enlarged PGs was reported to be between 69% and 90%, with a specificity of 90%–98%. Some studies reported a correlation between the size of the PTA and the diagnostic accuracy of USG. Ectopic localization, localization in thyroid glands, nodular goiter, and enlarged lymph nodes may result in false-positive diagnosis **[16-18]**. We only found that PTA localization by USG was less successful in the WCC dominant group but most successful in the OxC group.

MIBI parathyroid scintigraphy localizes both the thyroid and PGs, but the thyroid gland has a faster washout time than the parathyroid **[13,21]**. MIBI parathyroid scintigraphy has a sensitivity of 62%–90% in patients with solitary PTA and 15%–50% in patients with multiglandular PTA **[21,22]**. Although MIBI parathyroid scintigraphy has a high sensitivity in patients with solitary PTA, false-negative and false-

positive results may occur due to thyroid nodules, metastatic lymph nodes, autoimmune thyroiditis, and Hurthle cell lesions of the thyroid gland **[11-13,19,21-23]**. Some previous articles stated that both high-weight and high OxC content increased the success of localization of PTA with MIBI parathyroid scintigraphy, while others stated that OxC content may cause the PTA to be missed with MIBI parathyroid scintigraphy **[13,22]**. In our study, PTA localizations by MIBI parathyroid scintigraphy were very low in the OxC groups, but we were unable to detect statistically significant differences between these three groups. In addition, we found no statistically significant relationship between the percentage of OxC content and localization by MIBI parathyroid scintigraphy. Our study found that if the OxC content of any PTA was high, localization by MIBI parathyroid scintigraphy could be difficult.

It is well known that CChC adenomas are the most common while WCC adenomas are rare. We also discovered that CChC adenomas are the dominant one, accounting for nearly 72% of patients. It was interesting to note that WCC adenomas accounted for nearly 13% of cases and were seen far more frequently than reported cases in the literature. WCCs are described as large polygonal cells with a small nucleus and large optically clear cytoplasm. In fact, WCCs are not seen in normal human PGs, and their presence is generally associated with hyperfunctioning parathyroid gland. These cells are thought to be the end stage of hyperplastic ChC and frequently appear as people get older **[26,27]**. Although parathyroid WCC hyperplasia and WCC adenoma are rare causes of primary hyperparathyroidism, hyperplasia has been found to be more common than adenoma **[26]**.

While ChC adenomas are known to secrete PTH, OxC adenomas have previously been considered as non-functional. However, several cases of PTH secreting OxC adenomas have been described and even reported to account for 3%–6.25% of all PTA **[28]**. The rate of 15% in our study is also higher than that of previous researches. In a recent study, OxC adenomas were associated with higher preoperative levels of serum calcium and PTH, as well as a higher rate of symptomatic disease **[29]**, but we found no laboratory differences between the three histopathologic groups. In fact, OxC adenomas are mostly composed of and more than 70% of OxCs, and adenomas that are exclusively composed of OxCs are rare (4.4%–8.4%) **[30]**.

Many pathologists are unable to distinguish between adenoma and hyperplasia. The most accepted criterion for adenoma is the involvement of a single gland. In addition to histopathologic examination of lesions diagnosed as PTA, we noticed an immediate decrease in PTH and serum calcium levels postoperatively. In our study, none of the WCC and OxC adenomas were persisted or recurred, demonstrating and providing clues to their real percentage in all PTAs. A longer follow-up, at least five years, may be advisable because we all performed minimal invasive surgery and we do not know other parathyroid glands.

In conclusion, localization of PTA is very important prior to surgical excision in order to perform a minimal surgical approach. USG and MIBI parathyroid scintigraphy are the primary imaging modalities to localize any PTA. Dominant cell content may influence the localization of PTA. Localization WCC dominant group with USG and localization of OxC dominant group with MIBI parathyroid scintigraphy were lower than the other groups. Knowing the dominant cell type and also OxC ratio could be help-full in choosing the imaging modalities in the persistent and recurrent patients in redo surgery. We also documented that the OxC and WCC produce and secrete PTH, as well as cause PHPT, with no clinical or hormonal activity differences when compared to CChC dominant PTAs. Although there were no statistically significant differences in the pathologic weights of PTA, we noticed that CChC dominant PTAs are heavier than WCC and OxC dominant PTAs.

References

1. Goltzman, D., Mannstadt, M., & Marcocci, C. (2018). Physiology of the Calcium-Parathyroid Hormone-Vitamin D Axis. *Frontiers of hormone research*, *50*, 1–13. https://doi.org/10.1159/000486060
2. Walker, M. D., & Silverberg, S. J. (2018). Primary hyperparathyroidism. *Nature reviews. Endocrinology*, *14*(2), 115–125. https://doi.org/10.1038/nrendo.2017.104
3. Bilezikian, J. P., & Silverberg, S. J. (2000). Clinical spectrum of primary hyperparathyroidism. *Reviews in endocrine & metabolic disorders*, *1*(4), 237–245. https://doi.org/10.1023/a:1026508829397
4. Melton L. J., 3rd (2002). The epidemiology of primary hyperparathyroidism in North America. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*, *17 Suppl 2*, N12–N17.
5. Solorzano, C. C., Carneiro-Pla, D. M., & Irvin, G. L., 3rd (2006). Surgeon-performed ultrasonography as the initial and only localizing study in sporadic primary hyperparathyroidism. *Journal of the American College of Surgeons*, *202*(1), 18–24. https://doi.org/10.1016/j.jamcollsurg.2005.08.014
6. Uludağ M. Preoperative Localization Studies in Primary Hyperparathyroidism. Med Bull Sisli Etfal Hosp 2019;53(1):7–15
7. Aygün N, İşgör A, Uludağ M. The Effectiveness of Preoperative Ultrasonography and Scintigraphy in the Pathological Gland Localization in Primary Hyperparathyroidism Patients. Med Bull Sisli Etfal Hosp 2019;53(4):379–384
8. Shakeel, S., & Mubarak, M. (2016). Proliferative Lesions of Parathyroid Glands: An Update for Practicing Pathologists. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP*, *26*(1), 51–59.
9. Wolpert, H. R., Vickery, A. L., Jr, & Wang, C. A. (1989). Functioning oxyphil cell adenomas of the parathyroid gland. A study of 15 cases. *The American journal of surgical pathology*, *13*(6), 500–504. https://doi.org/10.1097/00000478-198906000-00006
10. Ogilvie, J. B., & Clark, O. H. (2005). Parathyroid surgery: we still need traditional and selective approaches. *Journal of endocrinological investigation*, *28*(6), 566–569. https://doi.org/10.1007/BF03347248
11. Ruda, J. M., Hollenbeak, C. S., & Stack, B. C., Jr (2005). A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*, *132*(3), 359–372. https://doi.org/10.1016/j.otohns.2004.10.005
12. Sackett, W. R., Barraclough, B., Reeve, T. S., & Delbridge, L. W. (2002). Worldwide trends in the surgical treatment of primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. *Archives of surgery (Chicago, Ill.: 1960)*, *137*(9), 1055–1059. https://doi.org/10.1001/archsurg.137.9.1055
13. Yamaguchi, S., Yachiku, S., Hashimoto, H., Kaneko, S., Nishihara, M., Niibori, D., Shuke, N., & Aburano, T. (2002). Relation between technetium 99m-methoxyisobutylisonitrile accumulation and multidrug resistance protein in the parathyroid glands. *World journal of surgery*, *26*(1), 29–34. https://doi.org/10.1007/s00268-001-0177-2
14. Lumachi, F., Marzola, M. C., Zucchetta, P., Tregnaghi, A., Cecchin, D., & Bui, F. (2003). Hyperfunctioning parathyroid tumours in patients with thyroid nodules. Sensitivity and positive

predictive value of high-resolution ultrasonography and 99mTc-sestamibi scintigraphy. *Endocrine-related cancer*, *10*(3), 419–423. https://doi.org/10.1677/erc.0.0100419

15. Mihai, R., Gleeson, F., Buley, I. D., Roskell, D. E., & Sadler, G. P. (2006). Negative imaging studies for primary hyperparathyroidism are unavoidable: correlation of sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. *World journal of surgery*, *30*(5), 697–704. https://doi.org/10.1007/s00268-005-0338-9
16. Ozkaya, M., Elboga, U., Sahin, E., Kalender, E., Korkmaz, H., Demir, H. D., Celen, Y. Z., Erkılıç, S., Gökalp, A., & Maralcan, G. (2015). Evaluation of conventional imaging techniques on preoperative localization in primary hyperparathyroidism. *Bosnian journal of basic medical sciences*, *15*(1), 61–66. https://doi.org/10.17305/bjbms.2015.207
17. Acar, T., Ozbek, S. S., Ertan, Y., Kavukcu, G., Tuncyurek, M., Icoz, R. G., Akyildiz, M. M., Makay, O., & Acar, S. (2015). Variable sonographic spectrum of parathyroid adenoma with a novel ultrasound finding: dual concentric echo sign. *Medical ultrasonography*, *17*(2), 139–146. https://doi.org/10.11152/mu.2013.2066.172.tka
18. Nieciecki, M., Cacko, M., & Królicki, L. (2015). The role of ultrasound and nuclear medicine methods in the preoperative diagnostics of primary hyperparathyroidism. *Journal of ultrasonography*, *15*(63), 398–409. https://doi.org/10.15557/JoU.2015.0037
19. Rumack CM, Wilson SR, Charboneau JW, Levine D (2011). Diagnostic Ultrasound, 4th edition. Elsevier Mosby, Philadelphia
20. Goodman, A., Politz, D., Lopez, J., & Norman, J. (2011). Intrathyroid parathyroid adenoma: incidence and location--the case against thyroid lobectomy. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*, *144*(6), 867–871. https://doi.org/10.1177/0194599811400366
21. Palestro, C. J., Tomas, M. B., & Tronco, G. G. (2005). Radionuclide imaging of the parathyroid glands. *Seminars in nuclear medicine*, *35*(4), 266–276. https://doi.org/10.1053/j.semnuclmed.2005.06.001
22. Lumachi, F., Zucchetta, P., Marzola, M. C., Boccagni, P., Angelini, F., Bui, F., D'Amico, D. F., & Favia, G. (2000). Advantages of combined technetium-99m-sestamibi scintigraphy and high-resolution ultrasonography in parathyroid localization: comparative study in 91 patients with primary hyperparathyroidism. *European journal of endocrinology*, *143*(6), 755–760. https://doi.org/10.1530/eje.0.1430755
23. Erbil, Y., Kapran, Y., Işsever, H., Barbaros, U., Adalet, I., Dizdaroğlu, F., Bozbora, A., Ozarmağan, S., & Tezelman, S. (2008). The positive effect of adenoma weight and oxyphil cell content on preoperative localization with 99mTc-sestamibi scanning for primary hyperparathyroidism. *American journal of surgery*, *195*(1), 34–39. https://doi.org/10.1016/j.amjsurg.2007.01.040
24. Mehta, N. Y., Ruda, J. M., Kapadia, S., Boyer, P. J., Hollenbeak, C. S., & Stack, B. C., Jr (2005). Relationship of technetium Tc 99m sestamibi scans to histopathological features of hyperfunctioning parathyroid tissue. *Archives of otolaryngology--head & neck surgery*, *131*(6), 493–498. https://doi.org/10.1001/archotol.131.6.493
25. Krausz, Y., Lebensart, P. D., Klein, M., Weininger, J., Blachar, A., Chisin, R., & Shiloni, E. (2000). Preoperative localization of parathyroid adenoma in patients with concomitant thyroid nodular disease. *World journal of surgery*, *24*(12), 1573–1578. https://doi.org/10.1007/s002680010280

26. Boutzios, G., Sarlanis, H., Kolindou, A., Velidaki, A., & Karatzas, T. (2017). Primary hyperparathyroidism caused by enormous unilateral water-clear cell parathyroid hyperplasia. *BMC endocrine disorders*, *17*(1), 57. https://doi.org/10.1186/s12902-017-0207-1
27. Ezzat, T., Maclean, G. M., Parameswaran, R., Phillips, B., Komar, V., Mihai, R., Sadler, G., & Courtney, S. (2013). Primary hyperparathyroidism with water clear cell content: the impact of histological diagnosis on clinical management and outcome. *Annals of the Royal College of Surgeons of England*, *95*(3), e60–e62. https://doi.org/10.1308/003588413X13511609957533
28. Wolpert, H. R., Vickery, A. L., Jr, & Wang, C. A. (1989). Functioning oxyphil cell adenomas of the parathyroid gland. A study of 15 cases. *The American journal of surgical pathology*, *13*(6), 500–504. https://doi.org/10.1097/00000478-198906000-00006
29. Howson, P., Kruijff, S., Aniss, A., Pennington, T., Gill, A. J., Dodds, T., Delbridge, L. W., Sidhu, S. B., & Sywak, M. S. (2015). Oxyphil Cell Parathyroid Adenomas Causing Primary Hyperparathyroidism: a Clinico-Pathological Correlation. *Endocrine pathology*, *26*(3), 250–254. https://doi.org/10.1007/s12022-015-9378-3
30. Paul, A., Villepelet, A., Lefèvre, M., & Périé, S. (2015). Oncocytic parathyroid adenoma. *European annals of otorhinolaryngology, head and neck diseases*, *132*(5), 301–303. https://doi.org/10.1016/j.anorl.2015.08.033

Table 1: Comparisons of demographic and laboratory values of patients according to dominant cell types in PTA.

		Dominant Cell			*Total*	*p*
		Conventional Chief Cells	Water-Clear Cells	Oxyphilic Cells		
Age Mean±SD		54,06±11,96	50,33±9,36	57,76±14,25	*54,12±12,08*	[1]0,222
PTH Level Median(IQR)		186 (153,9)	182 (161)	205,2 (100)	*186 (119,5)*	[2]0,777
Pathologic Size (mm) Median(IQR)		14 (7,5)	15 (5)	14 (6,5)	*14 (7)*	[2]0,950
Pathologic Weight (mgr) Median(IQR)		130 (177)	100 (55)	128 (163,3)	*120 (130)*	[2]0,502
		n (%)	n (%)	n (%)	*n (%)*	
Gender	Man	17 (20,5%)	2 (13,3%)	3 (17,6%)	*22 (19,1%)*	[3]0,929
	Woman	66 (79,5%)	13 (86,7%)	14 (82,4%)	*93 (80,9%)*	
Diagnosis Before Surgery	Primary	80 (96,4%)	15 (100%)	17 (100%)	*112 (97,4%)*	[3]1,000
	Persistent or Recurrent	3 (3,6%)	0 (0%)	0 (0%)	*3 (2,6%)*	
Associated Thyroid Gland Diseases	No associated Diseases	49 (59%)	10 (66,7%)	9 (52,9%)	*68 (59,1%)*	[4]0,310
	MNG, not Hyper-Functioning	28 (33,7%)	5 (33,3%)	6 (35,3%)	*39 (33,9%)*	
	Papillary Thyroid Carcinoma	6 (7,2%)	0 (0%)	1 (5,9%)	*7 (6,1%)*	
	Follicular Thyroid Carcinoma	0 (0%)	0 (0%)	1 (5,9%)	*1 (0,9%)*	

*1Oneway Anova Test 2Kruskal Wallis Test 3Fisher FreemanHalton Test 4Chi-SquareTest *p<0.05*

Table 2: Successfully localization of PTA before surgery by scintigraphy and ultrasonography according to dominant cell type and percentage of oxyphilic cell ratio in adenoma**.**

		Dominant Cell			*Total*	p^1	Oxyphilic Cells Ratio (%)	p^2
		Conventional Chief Cells	Water-Clear Cells	Oxyphilic Cells				
		n (%)	n (%)	n (%)	n (%)		Median (IQR)	
Localization of Adenoma by Scintigraphy	**Localized**	67 (80,7%)	13 (86,7%)	10 (58,8%)	*90 (78,3%)*	**0,106**	5 (25)	**0,274**
	Not Localized	16 (19,3%)	2 (13,3%)	7 (41,2%)	*25 (21,7%)*		10 (51,5)	
Localization of Adenoma by USG	**Localized**	74 (89,2%)	9 (60%)	16 (94,1%)	*99 (86,1%)*	**0,012 ***	8 (36,2)	**0,550**
	Not Localized	9 (10,8%)	6 (40%)	1 (5,9%)	*16 (13,9%)*		2,5 (19,5)	

*1Fisher FreemanHalton Test, *p<0.05, 2Mann Whitney U Test*

Table 3: Comparisons of demographic and laboratory values of patients according to the oxyphilic cells ratio (in percentage) in PTA .

		Oxyphilic Cells Ratio (%)
		Median (IQR)
Gender	**Man**	7,5 (39,7)
	Woman	6 (26,5)
	p^1	**0,918**
Diagnosis Before Surgery	**Primary**	8 (27,7)
	Persistence, recurrence	1 (-)
	p^1	**0,545**
Associated Thyroid Gland Diseases	**No associated Diseases**	8 (34)
	MNG, not Hyper-Functioning	6 (20)
	Papillary Thyroid Carcinoma	1 (21)
	p^2	**0,783**
		Oxyphilic Cells Ratio (%)
Age	r	0,098
	p	0,296
PTH level+	r	0,042
	p	0,651
Pathologic Size (mm)+	r	-0,009
	p	0,921
Pathologic Weight (ngr)+	r	0,004
	p	0,966

1Mann Whitney U Test 2Kruskal Wallis Test
Note: Only one patient had accompanying Follicular CA and excluded at statistical analysis
Pearson Correlation Analysis +SpearmanRhoCorrelation Analysis

Table 4: Correlation of end results of diseases after surgery and histopthalogic results

		Dominant Cell				Oxyphilic Cells Ratio (%)
		Conventional Chief Cells (n=77)	Water-Clear Cells (n=13)	Oxyphilic Cells (n=14)	*Total (n=104)*	
		n (%)	n (%)	n (%)	n (%)	Median (IQR)
End Results of Diseases After Surgery	**Resolved**	71 (92,2%)	13 (100%)	14 (100%)	*98 (94,2%)*	5,5 (25)
	Persistent	3 (3,9%)	0 (0%)	0 (0%)	*3 (2,9%)*	22,5 (74,7)
	Recurrent	3 (3,9%)	0 (0%)	0 (0%)	*3 (2,9%)*	1 (-)
	p		[1]1,000			[2]0,434

1Fisher's Exact test *2Kruskal Wallis Test*