Parathyroid Lesions: Our Single-Center Experience for the Last 5 Years

Paratiroid Lezyonları: Son 5 Yıllık Tek Merkez Deneyimimiz

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ABSTRACT

Objective: Parathyroid neoplasms are tumors seen in about 0.1% of the population. Although parathyroid adenomas are the most common, rarely carcinomas are also seen. Our aim in this study is to evaluate the clinical, laboratory and histopathological characteristics of patients who underwent parathyroidectomy in our hospital in the last 5 years.

Method: A total of 156 patients who underwent parathyroidectomy in our hospital and examined in the pathology department were included in the study. Cases were grouped according to the types of operations performed as those who underwent only parathyroid excision or partial/total thyroid excision with parathyroid excision. Age, gender, pre- and post-operative parathyroid hormone values, size, weight, pathological diagnosis of the parathyroid aland, presence of complications, comorbidities and their clinical follow-ups were evaluated.

Results: The 84% of 156 cases were female, and 16% were male. The mean age of the patients was 53.82±13.49 years. The mean pre-, and post-operative parathyroid hormone levels of the cases were 415.18±491.15 mg/dl, and 64.02±110.72 mg/dl, respectively. The mean volume of parathyroid tissues was calculated as 5.13±8.85 and the mean weight as 2.78±2.88 g. Pathological diagnoses were adenoma in 83.3%, hyperplasia in 10.9%, atypical adenoma in 2.6%, carcinoma in 1.9%, normal parathyroid gland in 0.6% and lymph node in 0.6%, of the cases. It was observed that as the postoperative PTH level increased, the weight of the parathyroid gland increased and the weight of the lesion was higher in males. The addition of thyroidectomy to the treatment, conventional parathyroidectomy instead of the minimally invasive method, and the high size and volume of the parathyroid gland were found to be associated with complications in the postoperative period.

Conclusion: In terms of thyroid pathologies that may accompany, it will be more appropriate to evaluate preoperative cases in detail and to continue the treatment with minimally invasive methods for the comfort of the patient in postoperative processes. It is highly important to always take a multidisciplinary management in the approach to parathyroid masses and to evaluate the clinical, laboratory, intraoperative and pathological findings of the cases in combination.

Keywords: Parathyroid, adenoma, atypical, parathyroid carcinoma, neoplasia, parathyroid hormone

ÖZ

Amaç: Paratiroid neoplaziler toplumda yaklaşık %0,1 oranında görülen tümörlerdir. En sık paratiroid adenomları görülmekle birlikte çok nadiren karsinomları da izlenmektedir. Bu çalışmada amacımız hastanemizde son 5 yılda paratiroidektomi yapılan olguların klinik, laboratuvar ve histopatolojik özelliklerini değerlendirmektir.

Yöntem: Çalışmaya hastanemizde paratiroidektomi yapılan ve patoloji bölümünde incelenen 156 olgu dahil edildi. Olgular uygulanan operasyon türleri yalnızca paratiroid eksizyonu yapılanlar ve paratiroid eksizyonu ile birlikte tiroid parsiyel/ total eksizyonu yapılanlar olarak gruplandırıldı. Olgulara ait yaş, cinsiyet, pre ve post operatatif parathormon değerleri, paratiroid bezinin boyut, ağırlık, patolojik tanısı, komplikasyon varlığı, eşlik eden ek hastalıklar ve klinik takipleri değerlendirilmiştir.

Bulgular: 156 olgunun %84'ü kadın, %16'sı erkek'tir. Ortalama yaş 53,82±13,49'dur. Olguların pre-operatif parathormon seviyeleri ortalaması 415,18±491,15 mg/dl, post-operatif parathormon seviyelerinin ortalama 64,02±110,72 mg/dl'dir. Paratiroid dokularının ortalama hacmi 5,13±8,85, ortalama ağırlık ise 2,78±2,88 gr olarak hesaplanmıştır. Patolojik tanıları %83,3'ü adenom, %10,9'u hiperplazi, %2,6'sı atipik adenom, %1,9'u karsinom, %0,6'sı normal paratiroid ve %0,6'sı lenf düğümüdür. Postoperatif PTH seviyesi arttıkça paratiroid bezi ağırlık artışı olduğu ve erkeklerde lezyon ağırlığının daha fazla olduğu gözlendi. Tedaviye tiroidektomi eklenmesi, minimal invaziv yöntem yerine konvansiyonel paratiroidektomi, paratiroid bezinin boyut ve hacminin yüksek olması postoperatif süreçte komplike komplikasyon ile ilişkili saptanmıştır.

Sonuç: Eşlik edebilecek tiroid patolojileri açısından preoperatif olguları iyi değerlendirmek ve tedaviyi minimal invaziv yöntemler ile sürdürmek hastanın postoperatif süreçlerde konforu için daha uygun olacaktır. Paratiroid kitlelerine yaklaşımda her zaman multidisipliner bir yaklaşım sergilemek, olgunun klinik, laboratuvar, intraoperatif ve patolojik bulgularının birlikte değerlendirilmesi çok önemlidir.

Anahtar kelimeler: Paratiroid, adenom, atipik, paratiroid karsinomu, neoplazi, parathormon

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INTRODUCTION

Normal parathyroid gland is generally 5x3x1 mm in size, and weighs less than 50 mg ⁽¹⁾. Five cell types were histologically determined in parathyroid tissue; chief cell, clear/vacuole chief cell, dark chief cell, oxyphil cell, transitional oxyphil cells. Adenomas occur as a result of hyperplasia of one or more of these cells ⁽²⁾.

Parathyroid tumors are heterogeneous tumors with an incidence of 0.1-0.3% in the general population ⁽³⁾. Generally, 85% of the cases have single parathyroid adenoma, 10% have hyperplasia and 3% have double adenoma. Atypical parathyroid adenomas (APAs) and parathyroid carcinomas (PCs) are extremely rare aggressive endocrine tumors, accounting for less than 1% of all cases with primary hyperparathyroidism ⁽³⁻⁵⁾. PCs occur less than 1 in 1 million people a year ⁽⁴⁾. In this study it is aimed to evaluate the clinical, laboratory and histopathological characteristics of patients who underwent parathyrodectomy in our hospital in the last 5 years.

MATERIAL and METHODS

A total of 156 patients who underwent parathyroidectomy and were evaluated in the pathology department between 2015-2020 at the University of Health Sciences Tepecik Training and Research Hospital were included in the study. Age, gender, parathyroid hormone results and pathology reports of the cases were obtained from the hospital information management system and patient files. The cases were grouped according to the ages of the cases as follows: Group 1, ≤59; Group 2, 60-69, nad Group 3, ≥70 years. The patients were grouped according to the types of operations performed as those who underwent only parathyroid excision or partial/total excision of the thyroid together with parathyroidectomy. Among resection materials containing fragmented and/or multiple parathyroid tissue particles, the largest specimen was included in the study, while the data concerning the weights of all specimens were included in the analysis. In order to ensure homogenization of the data concerning the size of the particles, data expressed in centimeters (cm) were converted into 3 dimensional measurements of the volume (cm³). VATS and TOEPVA performed were grouped as "other" category. Mediastinal, posterior tracheal and intrathyroidal parathyroid tissues were also grouped in the category of "other" localizations.

SPSS 15.0 Package program (SPSS Inc. Released 2006. SPSS for Windows, Version 15.0. Chicago, SPSS Inc.) was used for statistical analysis and analyzes were made within 95% confidence interval. One Way ANOVA and t test for independent variables were used in the analysis; p values less than 0.05 were considered to be statistically significant.

RESULTS

The study population consisted a total of 156 cases including 131 (84%) female and 25 (16%) patients. The mean age of the patients was 53.8±13.5 (18-92) years. Group 1 constituted of 110 (70.5%), Group 2, 26 (16.7%), and Group 3, 20 (12.8%) cases. Clinical diagnosis of adenoma was made in 144 (92.3%) and hyperparathyroidism in 12 (7.7%) patients. There is no additional disease in 75% (117) of the cases while there were concomitant thyroid follicular nodular disease in 21.1% (33, chronic renal disease in 1.9% (3), renal transplantation in 1.3% (2) and thyroid carcinoma in 0.6% of the cases (1).

When the cases were examined clinically, it is noteworthy that 14.8% (23) of the cases were ASA1, 69.9% (109) ASA2, 15.4% (24) ASA3 in the preoperative evaluation. The mean pre-operative parathyroid hormone levels of the cases were calculated as 415.2±491.2 mg/dl (min: 77.8 mg/dl, max: 2348.0 mg/dl), while the mean post-operative parathyroid hormone levels were 64.0±110.7 mg/dl (min: 0.7 mg/dl, max: 1163.0 mg/dl).

Regarding the operation type, 67.9% (106) of the cases underwent parathyroidectomy independent of the number of glands, and 31.1% of them

parathyroidectomy+hemi/total thyroidectomy operation. The operation type of the patients was minimally invasive parathyroidectomy in 19.2% (30), conventional parathyroidectomy in 78.2% (122), and the other surgeries in 2.6% (4) of the cases. Bilateral exploration was performed in 28.2% (44) of the cases. The excised parathyroid glands were located on the right side in 53.2% (83), left side in 38.5% (60) and bilaterally in 3.8% (6) of the cases. In the axial plane, it was observed that parathyroid glands were localized superiorly in 9.6% (15), inferiorly in 75.0% (115), superoinferiorly in 7.7% (12) of the cases. While 3.5% (5) of them were located in the middle of the thyroid gland, and 2.6% (4) of them were located outside these abovementioned regions (mediastinal,

posttracheal, intrathyroidal); It was also determined that localisations of 1.9% (3) of the lesions was unknown.

In the pathological examination of excised parathyroid tissues, the mean volume was calculated as 5.13±8.85 cm³ (min: 0.1 cm³, max: 67.4 cm³) and the mean weight as 2.78±2.88 g (min: 0.2 g, max: 14.0 g). When the pathology reports were examined, adenoma was detected in 83.3% (130), hyperplasia in 10.9% (17), atypical adenoma in 2.6% (4), carcinoma in 1.9% (3), normal parathyroid tissue in 0.6% (1) and lymph node in 0.6% (1) of the cases. The rates of adenoma, hyperplasia, atypical adenoma and carcinoma are demonstrated in Figure 1-4. Data

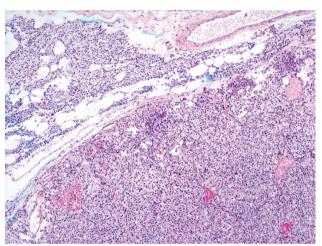


Figure 1. Parathyroid adenoma with normal parathyroid tissue at a rim (H&E, x100).

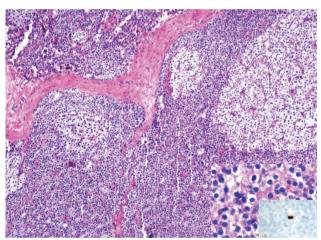


Figure 3. Increased mitosis in atypical parathyroid adenoma (H&E and PHH3 immunhistochemistry x400), and thick fibrous bands within the adenoma (H&E, x100).

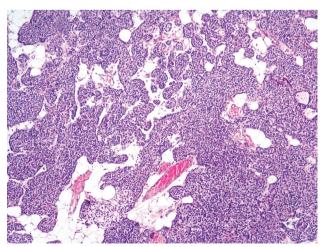


Figure 2. Parathyroid hyperplasia (H&E, x100).

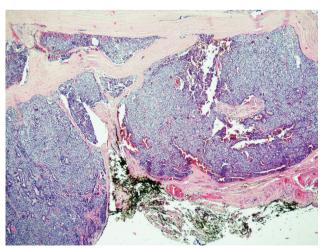


Figure 4. Parathyroid carcinoma (H&E, x40).

Table 1. Mean age, gender, size, weight, preoperative and postoperative PTH values according to parathyroid pathologies of the cases (* there is only one value in the group).

	Age	Gender F/M (%)	Size (cm³)	Weight (g)	Preoperative PTH (mg/dl)	Postopertative PTH (mg/dl)
Hyperplasia	44.6+13.9	76.5-23.5	3.8+4.3	2.7+2.1	864.7+816.0	114.0+292.0
Adenoma	54.8+12.9	85.4-14.4	4.1+5.5	2.6+2.6	232.3+355.5	54.6+56.4
Atypical adenoma	59.5+22.2	75.0-25.0	6.5+3.4	3.2*	828.7+689.4	65.7+107.9
Carcinoma	53.0+15.1	66.7-33.3	54.5+15.7	12.0+0.0	1319.7+760.0	115.6+163.7

concerning the mean age, gender, size, weight and PTH values of the cases with pathological parathyroid diagnoses are presented in Table 1. In addition to diagnoses of parathyroid pathologies, the cases that underwent partial/total thyroid excision had the diagnosis of thyroid follicular nodular disease in 9.6% (15), papillary microcarcinoma in 7.7% (12), papillary carcinoma in 3.2% (5), lymphocytic thyroiditis in 1.9% (3) of the cases .

When the postoperative processes of the cases were examined, it was determined that various complications developed in 13.5% (21) of the cases. The mean length of stay in the hospital was 4.9±4.3 (min: 1, max: 37) days. While no morbidity was observed in 81.4% (127) of the cases, unilateral vocal cord paralysis was detected in 6.4% (10), persistent hypercalcemia in 1.3% (2) and hypocalcemia in 1.3% (2) of the cases during clinical follow-up. In addition, it was reported that vision loss, leg contraction, bilateral vocal cord paralysis, recurrent nerve injury, neck hematoma, emphysema, bilateral periorbital edema, nasopharyngeal carcinoma, and vocal bifurcation developed despite normal ENT examination in one case (0.6%) in each. In the clinical follow-ups, it was determined that one patient had relapse 6 months later and 1 (0.6%) patient died.

Statistical analysis did not reveal any statistical significance between preoperative PTH levels and parathyroid weight and volume (p=0.19, p=1.00, respectively). Similarly, while there was no statistically significant difference between postoperative PTH values and volume (p=0.84), it was observed that weight of the parathyroid gland increased significantly as postoperative PTH level increased (p=0.007).

There was no significant correlation between age groups and parathyroid volume, weight, pre-and post-operative PTH levels (p=0.93, p=0.73, p=0.27, and p=0.74, respectively). Similarly there was no correlation between gender and lesion volume, pre-and post-operative PTH levels (p=0.07, p=0.68, and p=0.74, respectively). However, a significant relationship was found between gender and weight of the lesion (p=0.02), and it was noted that weight of the lesion was statistically higher in males.

When adenoma and hyperplasia were compared, no difference was found in terms of lesion volume and weight (p>0.05). On the other hand pre-, and post-operative PTH values were statistically significantly higher in the hyperplasia group (p=0.000, and p=0.047, respectively).

There was no statistically significant relationship between the complicated cases and gender (p=0.33), age group (p=0.17), comorbidity (p=0.71), pathological diagnosis (p=0.65), additional pathological diagnosis (p=0.13), ASA scores (p=0.80), preoperative PTH (p=0.65) and postoperative PTH levels (p=0.41). However, a statistically significant relationship was observed between complicated cases and operation types (p=0.005 and p=0.003) weight (p=0.009) and volume (p=0.044) of the gland. According to these data, it was revealed that the extend of the operation area and the increase in the size of the lesion significantly increased the risk of complications. It was observed that additional synchronous thyroidectomy and using conventional methods increased the risk of complications. Finally, it was noted that there was no statistically significant relationship between the pathological diagnoses of the cases and the duration of hospitalization (p=0.07).

DISCUSSION

Parathyroid adenoma is the most common cause of primary hyperparathyroidism (2,6). Adenomas usually occur in one gland (1,2) and although adenomas can originate from any of the 4 parathyroid glands, they most frequently originate from the lower glands (6). Although double adenomas have been reported, single gland involvement is usually seen (6). Adenomas seen with a female/male ratio of 3/1 are macroscopically in the form of nodular masses with or without a thin capsule (2,6). Adenomas can be in different sizes and weights (6). Adenomas with their largest diameters ranging from 1 to 3 cm, and wieghing more than approximately 150 mg have been reported (6). Unlike adenomas, parathyroid hyperplasia can be defined as the proliferation of parenchymal cells in multiple glands (1,6).

When pleomorphic and bizarre nuclei are seen in adenomas, and mitosis and lymphovascular invasion are not observed, this pathology is defined as atypical parathyroid adenoma (2). Atypical parathyroid adenomas are parathyroid neoplasms of uncertain malignant potential and include atypical histological findings that are histologically differentiated from parathyroid carcinomas (3). The question of whether atypical parathyroid adenomas could represent an early stage of a parathyroid carcinoma that was excised prior to the development of the molecular signature of the malignancy responsible for the invasive features, has not been clarified yet (3). According to the histopathological criteria recommended by WHO, the diagnosis of malignancy in the parathyroid gland is made based on the presence of clear and definite signs of invasive growth, vascular invasion, perineural invasion and/ or metastases in adjacent soft tissues or thyroid gland (3).

Parathyroid carcinomas, on the other hand, are extremely rare with an annual incidence of less than 1 in 1 million ^(4,6) and they are generally sporadic ⁽⁷⁾. Mutations of the CDC73 gene encoding parafibromin are the most common genetic changes ^(3,5) in these

tumors whose etiology is not clearly known (5,8,9). Although they can be seen clinically at any age, they peak around the age of 50 (2,10). They often occur equally in women and men (4). Most parathyroid carcinomas (>90%) secrete parathormone (4,6). The most important feature of PCs is their high recurrence rate (7) and 1/3 of them are known to metastasize (6). PCs are macroscopically large tumors; they usually involve one gland and the most important surgical finding is invasion into adjacent neck tissues (6). Levels of parathyroid hormone are 3 times higher upper limit of normal Tumors over 3 cm, prominent bone and/or kidney involvement, hoarseness and/or neck pain are clinically supporting findings for parathyroid carcinoma (4). However, the definitive diagnosis can be made by histopathological examination. When examining parathyroidectomy materials, detailed clinical information and careful pathological examination are required (7).

Observational studies are very important in terms of characterization of parathyroid lesions, which are not prevalent in the general population. In this context, in one of the studies conducted with a large number of cases, 375 cases who underwent parathyroidectomy were analyzed and 12 cases with adenoma or carcinoma were retrospectively screened (10). The pathological diagnoses of the cases included in the study were reported as PC in 4, parathyroid neoplasm in 5, and parathyroid neoplasm of undetermined malignant potential in 3 cases (10). The mean preoperative parathyroid hormone value of PC cases was stated to be 144.66 (±91.73) pg/mL in this case series with an age range reported as 41-68 years (10). In our study, the mean preoperative PTH values in parathyroid carcinoma (1319.7±760 mg/ dl), atypical adenoma (828.7±689.4 mg/dl), (323.3±355.5 mg/dl), and hyperplasia (864.7±816.0 mg/dl) were detrmined as indicated.

In another large case study, Kir et al. examined the clinical, demographic and laboratory findings of patients with primary hyperparathyroidism (11). In the study in which 217 cases were evaluated retrospectively, adenoma had been diagnosed in

74.2%, hyperplasia in 23%, while normal parathyroid tissue had been observed in 2.8% of the cases ⁽¹¹⁾. In this study group patients aged between 20 to 79 (median: 52 years) years and 85% of the cases consisted of female patients ⁽¹¹⁾. In the examination of 136 adenoma cases that were stated to meet the study criteria, it was reported that 29.4% of the patients were in the 6th decade of their lives and the median of preoperative PTH level was 163.4 pg/ml ⁽¹¹⁾. In our study, 30.1% of the patients with adenoma cases were in the 6th decade of their lives while the median preoperative PTH value was 224.9 mg/dl.

In a study involving 12 cases who underwent parathyrodectomy over a 2-year period, 9 (75%) of the patients were female and the mean age of the cases was 42.5 (12) years. In 91.6% of the cases histopathologically diagnosed as adenoma, the average pre-, and post-operative serum calcium (Ca) values were 12.62 mg/dl, and 9.54 mg/dl, and the corresponding mean values for serum phosphorus (P) were 2.39 mg/dl and 2.98 mg/dl, respectively (12). The limitation of our study is that the Ca and P values could not be included in the study, because they were not available in all cases. In our study, the mean pre-, and post-operative PTH values were 323.3±355.5 mg/dl, and 54.6±56.4 mg/dl, respectively Kanat et al. reported the average pre-, and postoperative PTH values of their study population as 276 mg/dl and 50.87mg/dl, respectively (12). In the same study, it was reported that the macroscopic diameters of pathological lesions ranged between 7-30 mm (median: 13.9 mm) (12). In our study, the volumes of the lesions were calculated in terms of homogeneous evaluation and the largest diameters of the lesions ranged from 0.1 mm to 42.0 mm with a mean volume of 4.1±5.5 cm³. Weight, another morphological criteria, was found to vary between 0.2-14.0 g (mean: 2.6±2.6 g) in the study.

Papillary carcinoma is the most common thyroid malignancy. It constitutes 85% of all thyroid carcinomas (13). Coexistence of synchronous parathyroid carcinoma and thyroid carcinoma is known to be extremely rare (13). Different opinions

are reported in the literature regarding the coexistence of parathyroid and thyroid pathologies. In one of the relevant studies, it was reported that non-medullary thyroid cancers accompanied primary hyperparathyroidism more frequently than the normal population (14). In addition, in this study in which 46 cases who underwent parathyroidectomy were evaluated retrospectively, 35 (76.1%) cases were reported to have simultaneous thyroidectomy. In the biochemical evaluation of the cases, preoperative serum P values increased more frequently in the group with microcarcinoma than the other group, and accompanying thyroid pathologies were microcarcinoma in 5 (10.9%), nodular colloidal goiter in 23, follicular adenoma in 3 and lymphocytic thyroiditis in 4 cases (14). Parathyroid pathologies observed in another series of 202 cases, and adenoma was reported in 93.5%, hyperplasia in 3.5%, carcinoma in 3% of the cases and synchronous thyroidectomy had been performed in 21% of the cases (15).

Parathyroid pathologies and co-thyroid pathology are observed in a wide range ⁽¹⁶⁾. Similarly, the rate of malignancy of the accompanying thyroid lesion is variable, and there is no guideline on how to treat these patients ⁽¹⁶⁾.

In a study evaluating 202 cases operated for parathyroid pathology, thyroid pathology was found in 117 (57.9%) cases in preoperative examinations (16). The preoperative fine needle aspiration biopsies of the cases were reported as malignant in 1.6%, benign in 85.7% and hurtle cell neoplasia in 9.5% of the cases (16). Concurrent thyroid surgery was also performed in 80.3% of the cases in the same study and the final pathology of all cases were reported as papillary microcarcinoma in 10.2%, papillary carcinoma in 2%, 5% Hashimoto thyroiditis in 5%, lymphocytic thyroiditis in 4%, hurtle cell adenoma in 1%, medullary thyroid carcinoma in 0.5%, well-differentiated thyroid tumor of uncertain malignant potential in 3% of the cases (16).

In a study including 83 cases who underwent

simultaneous parathyroid and thyroid operations, papillary carcinoma was found in 5 cases (6%) including 4 cases with microcarcinomas ⁽¹⁷⁾. In the abovementioned study, it was suggested that the surgical evaluation of the nodule in all parathyroidectomy procedures in the presence of preoperative thyroid nodule is important in terms of planning the concurrent surgical procedure ⁽¹⁷⁾.

In our study group, there were 2 cases of atypical parathyroid adenoma accompanying thyroid neoplasia, 1 papillary carcinoma and 1 papillary microcarcinoma. Although there was no accompanying thyroid neoplasia in our 3 cases with parathyroid carcinoma, the diagnosis of papillary microcarcinoma or papillary carcinoma was remarkable in 10.9% of our cases diagnosed with adenoma. Only papillary microcarcinoma of the thyroid gland accompanied parathyroid hyperplasia in 11.8% of the cases.

Due to the retrospective nature of our study, serum vitamin D, C and P levels could not be measured and radiological findings could not be evaluated in all cases. Although this constitutes an important limitation in our study, our case series study is considered to be an important trial in that it represents the general population of parathyroidectomy patients. In our study, it was found that as the weight of parathyroid gland increases, postoperative PTH values also increase and it was also noticed that the weight of the lesion was higher in males. When parathyroid adenoma and hyperplasia were compared, pre-and postoperative PTH values were found to be significantly higher in the hyperplasia group. It is thought that this situation is caused by the diffuse hyperplasia and the possibility of residual tissue remaining postoperatively. It is thought that the effect of the extend of the surgical field together with the size of the lesion determines the relationship between complications, weight, and volume of the parathyroid gland. Considering these data, it is suggested that the determination of the nature of the thyroid lesion by performing a detailed radiological examination,

and in case of need fine needle aspiration biopsy in the preoperative period and not resecting the thyroid gland during the parathyroidectomy-because benign lesions do not require intervention-will decrease the risk of complications.

In conclusion, a multidisciplinary management in the approach to parathyroid masses together with evaluation of the clinical, laboratory, intraoperative and pathological findings of the cases is critically important.

Ethics Committee Approval: Approval of the Ethics Committee of University of Health Sciences, Izmir Tepecik Research and Training Hospital was obtained (2021/1/4).

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Informed Consent: Since our study was retrospective, consent was not obtained from the patients.

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