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# Parathyroidectomy Outcomes in Patients with Primary Hyperparathyroidism: Impact of Patient Factors, Preoperative Localization, and Surgical Characteristics

# Primer Hiperparatiroidili Hastalarda Paratiroidektomi Sonuçları: Hasta İlişkili Faktörler, Preoperatif Lokalizasyon ve Cerrahi Özelliklerin Etkisi

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**ÖZET**

**AMAÇ:** Primer hiperparatiroidizmde (PHPT) cerrahi başarısını etkileyebilecek faktörlerin daha iyi anlaşılması, olumsuz sonuçlarla ilişkilendirilen reoperasyonların önlenmesine katkı sağlayabilir. Bu çalışma, PHPT'de cerrahi başarıyı etkileyen faktörleri belirlemeye odaklanmakta olup, özellikle preoperatif lokalizasyon yöntemlerine vurgu yapmaktadır.

**GEREÇ VE YÖNTEM:** PHPT nedeniyle paratiroidektomi (PTx) uygulanan 191 hasta çalışmaya dahil edildi. Demografik, klinik ve laboratuvar verileri ile cerrahi özellikler ve preoperatif lokalizasyon bulguları kaydedildi. Hastalar cerrahi sonuçlarına göre "başarılı PTx" ve "başarısız PTx" olmak üzere iki gruba ayrılarak karşılaştırmalar yapıldı. Ayrıca başarılı PTx grubunda preoperatif lokalizasyon bulguları ile intraoperatif bulgular arasındaki uyum da değerlendirildi.

**BULGULAR:** Çalışmamızda cerrahi başarı oranı %84,29 ve minimal invaziv PTx (MIP) oranı %75,39 olarak saptandı. Ultrasonografide paratiroid adenomunun (PA) saptanması, başarılı PTx'i öngörmede en yüksek duyarlılığa (%92,55), düşük serum kreatinin düzeyi (<0,65 mg/dL) ise en yüksek özgüllüğe (%93,33) sahipti. Çok değişkenli analizde MIP (p<0,001) ve düşük serum kreatinin düzeyi (p=0,008), başarılı PTx'in bağımsız belirleyicileri olarak belirlendi; diyabetes mellitus (p=0,023) ise başarısız PTx için bir öngördürücü olarak saptandı. Ayrıca ultrasonografinin hem kesin (65,84% vs. 57,76%) hem de taraf bazlı (80,12% vs. 72,67%) lokalizasyonda sintigrafiye göre intraoperatif bulgularla daha yüksek uyum gösterdiği bulundu.

**SONUÇ:** Daha genç yaş, ultrasonografide PA saptanması, MIP uygulanması ve komorbidite olmaması (özellikle diyabetes mellitusun bulunmaması), PHPT'de cerrahi başarı oranını artırabilir. Ayrıca, PHPT'de preoperatif lokalizasyonda ultrasonografinin sintigrafiye göre daha üstün olduğunu düşünmekteyiz. Bu bağlamda, daha geniş örneklemli prospektif çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler**: Primer hiperparatiroidizm, paratiroidektomi, cerrahi başarı, preoperatif lokalizasyon

**ABSTRACT**

**AIM:** A better understanding of the factors that may affect surgical success in primary hyperparathyroidism (PHPT) may prevent reoperations, which are known to be associated with more adverse outcomes. This study focuses on identifying the factors influencing surgical success in PHPT, with particular attention to preoperative localization techniques.

**MATERIAL and METHODS:** We included 191 patients who underwent parathyroidectomy (PTx) for PHPT. Demographic, clinical and laboratory data, surgical characteristics, and preoperative localization findings were obtained. Comparisons were made by dividing patients into two groups, successful PTx or failed PTx, according to surgical outcomes. In addition, the correlation between preoperative localization findings and intraoperative findings in the successful PTx group was also evaluated.

**RESULTS:** In our study (with a surgical success rate of 84.29% and a minimally invasive PTx [MIP] rate of 75.39%), parathyroid adenoma (PA) detection on ultrasonography had the highest sensitivity (92.55%) and low serum creatinine (<0.65mg/dL) had the highest specificity (93.33%) in predicting successful PTx. In multivariate analysis, MIP (p<0.001) and low serum creatinine (p=0.008) emerged as independent predictors of successful PTx, whereas diabetes mellitus (p=0.023) was identified as a predictor of failed PTx. We also found that ultrasonography was more concordant with intraoperative findings than was scintigraphy in both exact (65.84% vs. 57.76%) and side-only (80.12% vs. 72.67%) localization.

**CONCLUSION:** Younger age, PA detection on ultrasonography, MIP, and absence of comorbidities (especially diabetes mellitus) may increase the surgical success rate in PHPT. We also think that ultrasonography is superior to scintigraphy for preoperative localization in PHPT. In this context, prospective studies with larger sample sizes are needed.

**Key words:** Primary hyperparathyroidism, parathyroidectomy, surgical success, preoperative localization

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## INTRODUCTION

Primary hyperparathyroidism (PHPT) is characterized by hypercalcemia and concurrent high or inappropriately normal serum parathyroid hormone (PTH) levels, caused by excessive PTH secretion by one or more uncontrolled parathyroid glands. It is one of the most common endocrine disorders with widely variable prevalence estimates of 1–7 cases per 1000 adults and is the leading cause of hypercalcemia (1 - 5). It is caused by a single parathyroid adenoma (PA) in the vast majority of cases (80-85%), less frequently by multiglandular disease (MGD) (15-20%), which usually develops due to multiple hyperplastic parathyroid glands, and extremely rarely by parathyroid carcinoma (<1%) (3, 4).

The classical phenotype of this disease, which was first recognized as a multisystem symptomatic disease and was called "a disease of bones, stones, moans, and groans" by Fuller Albright (6), evolved from overt kidney and bone disease to asymptomatic chronic hypercalcemia with the introduction of biochemical tests in the 1970s and their increasing widespread use in recent decades (5, 7).

The only curative treatment for PHPT is surgical removal of the diseased parathyroid gland or glands. There is no controversy regarding surgical treatment in symptomatic PHPT and parathyroidectomy (PTx) should be offered to all patients with symptomatic disease except those whose general medical condition is unfavorable. However, surgical treatment recommendations in asymptomatic PHPT have not been generalized to all patients, and criteria for surgical treatment recommendations have been developed in light of evidence obtained from studies on target organ damages of the disease and the benefits of curative surgery (4, 8). In patients who meet the criteria, PTx remains the preferred therapeutic approach for PHPT. Although the traditional surgical method for these patients is bilateral neck exploration (BNE), with the development and widespread use of preoperative localization methods, in recent decades, minimally invasive PTx (MIP), also known as focused PTx, has largely replaced BNE with comparable success rates. Considering that the vast majority of these patients (80-85%) have a single PA, it seems logical to prefer the MIP method instead of extensive exploration, but for a successful MIP, it is absolutely necessary to precisely localize the PA using appropriate preoperative localization methods (5, 8, 9).

Successful PTx in PHPT is the maintenance of normal serum Ca levels for at least 6 months after PTx. Failed PTx (i.e. unsuccessful surgery) is defined as the failure to achieve normal serum Ca levels within 6 months after PTx (8). Repeated surgical treatments for persistent or recurrent PHPT increase the risk of complications, mainly recurrent laryngeal nerve injury and hypocalcemia, so it is important to predict and prevent failed PTx. Some previous studies have investigated demographic, clinical, radiological and biochemical features that may predict failed PTx (10 - 12).

For a successful PTx, the localization of the adenoma or adenomas must be determined preoperatively. Providing precise localization before surgery with the selection of appropriate imaging methods allows the surgeon to apply a more focused and less invasive surgical method with a high success rate. There are many imaging methods available for preoperative localization in PHPT, the most commonly used being ultrasonography (US), 99mtechnetium-sestamibi (99mTc-MIBI) scintigraphy and single photon emission computed tomography (SPECT). The results of previous studies on the superiority of these methods over each other in terms of success rates are contradictory. The choice of imaging modalities ultimately depends on availability, costs, preference of specialists such as surgeons and endocrinologists, experience of radiologists, and patient-related factors (5, 7, 8, 13, 14).

In this study, we aimed to investigate the surgical success rate, the factors associated with surgical success, and the concordance of preoperative localization modalities with intraoperative findings in patients who underwent surgical treatment for PHPT.

## MATERIALS AND METHODS

This retrospective study included 191 patients who were diagnosed with PHPT and recommended surgical treatment at the Department of Endocrinology and Metabolism of Necmettin Erbakan University (NEU) Medical School between January 2020 and January 2024. The Ethics Committee of the NEU Medical School approved the study (decision no: 2024/5200 and date: 20.09.2024). The study was conducted in accordance with the Ethical Principles of the World Medical Association Declaration of Helsinki. Study investigators obtained informed consent from all subjects prior to start of the study. Patients with PHPT whose surgical treatment decision was made by the Multidisciplinary Team (MDT) in accordance with the criteria recommended by current guidelines at that time were included in the study (15). Subjects with other causes of hypercalcemia, such as cancer-related hypercalcemia, those diagnosed with familial hypocalciuric hypercalcemia and secondary or tertiary hyperparathyroidism, and those lost to follow-up after PTx were excluded from the study. Additionally, being younger than 18 years of age and being pregnant were also exclusion criteria.

Demographic data (age and gender), past medical history (comorbidities such as diabetes mellitus [DM], hypertension [HT], goiter, malignancy, osteoporosis and nephrolithiasis), anthropometric measurements (height, weight and body mass index [BMI]), laboratory measurements (Ca, albumin, phosphorus, PTH, Cr and 24-hour urinary Ca excretion), preoperative imaging results (99mTc-MIBI SPECT, neck US and parathyroid fine-needle aspiration with PTH washout findings), type of surgery, intraoperative findings (such as adenoma localization and size) and postoperative histopathology results of the patients included in the study were recorded from the patient files. Since the routine parathyroid scintigraphy method available in our institution is 99mTc-MIBI SPECT, all parathyroid scintigraphy results included in the study were 99mTc-MIBI SPECT results. Ultrasonographic localization of PA was performed by experienced endocrinologists using a high-resolution US device.

PTH washout method was not performed in all cases. This procedure was preferred in cases with US and 99mTc-MIBI SPECT incompatibility or in cases with US appearance not typical for PA. A PTH washout level higher than the patient's serum PTH level was considered "positive", a PTH washout level lower than the upper limit of normal according to the institutional laboratory PTH reference range was considered "negative", and the values between these two were considered as "gray zone".

Operative success was defined as maintaining normal serum Ca levels for 6 months or more after PTx, and failed PTx was defined as failure to maintain normal serum Ca levels within 6 months after PTx (16). Patients were divided into surgical outcome groups as successful PTx and failed PTx. Parameters such as demographic, clinical and laboratory data, preoperative localization findings, surgical data (such as type of surgery, adenoma size and histopathological findings) were compared among surgical outcome groups and the predictive values of these parameters for successful PTx were investigated.

The concordance of the findings of preoperative localization modalities with intraoperative findings was investigated. This concordance investigation was first performed in terms of exact localization (such as right lower, right upper, left lower). Then, all different localizations on the same side were categorized together and the "side-only" (such as right, left) concordance of the preoperative localization findings with intraoperative findings was investigated. Surgical, i.e. intraoperative, localization was used as the standard. Sensitivity, specificity, area under the curve (AUC), positive predictive value (PPV), negative predictive value (NPV), and kappa-values were determined for each method.

### Statistical Analysis

IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium) were used for statistical analysis. Continuous variables with a normal distribution were expressed as mean ± standard deviation, whereas those without a normal distribution were summarized as median (interquartile range). Categorical data were presented as counts and percentages. Comparisons between pre- and postoperative laboratory values were carried out using the paired t-test or Wilcoxon signed-rank test, based on whether the data followed a normal distribution. Continuous variables were examined using either the Student's t-test or the Mann–Whitney U test, chosen according to the distribution pattern of the data. Categorical variables were compared by means of the chi-square test, Fisher's exact test, or Fisher–Freeman–Halton test, as appropriate. The predictive ability of the variables for surgical outcomes was evaluated through receiver operating characteristic (ROC) curve analysis, and the Youden index was used to identify optimal cut-off values. Concordances of localization between intraoperative findings and preoperative localization methods were evaluated using the kappa coefficient. $p<0.05$ values were accepted as statistically significant results.

## RESULTS

We included 191 patients with PHPT (25 males and 166 females) into the study, mean age was 53.38 ± 11.65 (range 25 - 75) years. 29 (15.18%) patients had papillary thyroid carcinoma (PTC), 37

(19.37%) patients had DM, 62 (32.46%) patients had osteoporosis and 30 (15.71%) patients had nephrolithiasis (Table 1).

**Table 1.** Summary of demographics, comorbidities, preoperative laboratory findings, and characteristics of PHPT and surgical treatment

| | |
|---|---|
| Age (n=191) | 53.38 ± 11.65 |
| Sex (n=191) | |
| Male | 25 (13.09%) |
| Female | 166 (86.91%) |
| Height, cm (n=191) | 164.07 ± 6.44 |
| Weight, kg (n=191) | 74.48 ± 11.54 |
| BMI, kg/m$^2$ (n=191) | 27.55 ± 3.04 |
| Comorbidities (n=191) | |
| DM | 37 (19.37%) |
| HT | 61 (31.94%) |
| MNG | 50 (26.18%) |
| Hypothyroidism | 17 (8.90%) |
| PTC | 29 (15.18%) |
| Other malignancies | 10 (5.24%) |
| Osteoporosis | 62 (32.46%) |
| Nephrolithiasis | 30 (15.71%) |
| Surgery outcome (n=191) | |
| Failed PTx | 30 (15.71%) |
| Successful PTx | 161 (84.29%) |
| Type of surgery (n=191) | |
| MIP | 144 (75.39%) |
| BNE | 47 (24.61%) |
| Intraoperative localization (n=161) | |
| Right inferior | 60 (37.27%) |
| Left inferior | 49 (30.43%) |
| Other localizations | 52 (32.30%) |
| Parathyroid pathology (n=161) | |
| Negative | 1 (0.62%) |
| Adenoma | 148 (91.93%) |
| Hyperplasia | 12 (7.45%) |
| Positive $^{99m}$Tc-MIBI SPECT (n=191) | 163 (85.34%) |
| Parathyroid adenoma on US (n=191) | 169 (88.48%) |
| Adenoma size, mm (n=169) | 9.8 (8 - 14) |
| PTH washout, ng/L (n=117) | 856 (30 - 2543) |
| Negative | 33 (28.21%) |
| Gray zone | 3 (2.56%) |
| Positive | 81 (69.23%) |
| PHPT type (n=191) | |
| Typical | 161 (84.29%) |
| Normocalcemic | 22 (11.52%) |
| Normohormonal | 8 (4.19%) |
| Serum PTH, ng/L (n=191) | 131 (96 - 190) |
| Normal (15-65) | 8 (4.19%) |
| High (>65) | 183 (95.81%) |
| Serum Ca, mg/dL (n=191) | 10.60 (10.35 - 11.03) |
| Normal (8.4-10.2) | 22 (11.52%) |
| High (>10.2) | 169 (88.48%) |
| Urinary Ca excretion, mg/24 h (n=191) | 355.83 ± 132.08 |
| Normal (<400) | 128 (67.02%) |
| High (≥400) | 63 (32.98%) |
| Serum P, mg/dL (n=191) (Normal range, 0.50-0.90) | 2.54 ± 0.54 |
| Serum 25(OH)D, ug/L (n=191) (Normal range, 30-100) | 13.72 (9.17 - 17.00) |
| Serum Cr, mg/dL (n=191) (Normal range, 0.50-0.90) | 0.72 ± 0.18 |
| ALP, U/L (n=191) (Normal range, 35-104) | 109 (83 - 144) |

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.
ALP, alkaline phosphatase; BMI, body mass index; BNE, bilateral neck exploration; Ca, calcium; Cr, creatinine; DM, diabetes mellitus; HT, hypertension; MIP, minimally invasive parathyroidectomy; MNG, multinodular goiter; P, phosphorus; PHPT, primary hyperparathyroidism; PTC, papillary thyroid carcinoma; PTH, parathyroid hormone; PTx, parathyroidectomy; US, ultrasonography; 25(OH)D, 25-hydroxyvitamin D; $^{99m}$Tc-MIBI SPECT, $^{99m}$Technetium-sestamibi single-photon emission computerized tomography.

Surgery was successful in 161 (84.29%) patients. 144 (75.39%) patients underwent MIP and 47 (24.61%) patients underwent BNE. Most common locations were right inferior (37.27%) and left inferior (30.43%). Parathyroid pathology was adenoma in 148 (91.93%) patients and was hyperplasia in 12 (7.45%) patients. 163 (85.34%) patients had uptake on 99mTc-MIBI SPECT scintigraphy and US detected adenoma in 169 (88.48%) patients. Of the 117 patients who underwent PTH washout, 81 (69.23%) had positive PTH washout results

Age (p=0.032) was significantly lower in the successful PTx group than in the failed PTx group. The frequency of DM (p=0.004), HT (p=0.036) and osteoporosis (p=0.043) was significantly lower in the successful PTx group than in the failed PTx group

**Table 2.** Comparison of demographic and clinical data, characteristics of PHPT and surgical treatment, and preoperative laboratory findings between surgical outcome groups.

| | Surgery outcome | | |
|---|---|---|---|
| | Failed PTx (n=30) | Successful PTx (n=161) | p |
| Age | 57.57 ± 10.90 | 52.60 ± 11.65 | **0.032†** |
| Sex | | | |
| Male | 6 (20.00%) | 19 (11.80%) | 0.240§ |
| Female | 24 (80.00%) | 142 (88.20%) | |
| Height, cm | 164.97 ± 7.62 | 163.90 ± 6.21 | 0.407† |
| Weight, kg | 76.37 ± 12.18 | 74.13 ± 11.42 | 0.331† |
| BMI, kg/m$^2$ | 27.92 ± 2.93 | 27.48 ± 3.06 | 0.467† |
| Comorbidities | | | |
| DM | 12 (40.00%) | 25 (15.53%) | **0.004#** |
| HT | 15 (50.00%) | 46 (28.57%) | **0.036#** |
| MNG | 9 (30.00%) | 41 (25.47%) | 0.770# |
| Hypothyroidism | 3 (10.00%) | 14 (8.70%) | 0.734§ |
| PTC | 5 (16.67%) | 24 (14.91%) | 0.784§ |
| Other malignancies | 3 (10.00%) | 7 (4.35%) | 0.194§ |
| Osteoporosis | 15 (50.00%) | 47 (29.19%) | **0.043#** |
| Nephrolithiasis | 5 (16.67%) | 25 (15.53%) | 0.791§ |
| Type of surgery | | | |
| MIP | 9 (30.00%) | 135 (83.85%) | **<0.001#** |
| BNE | 21 (70.00%) | 26 (16.15%) | |
| Patients with positive $^{99m}$Tc-MIBI SPECT | 23 (76.67%) | 140 (86.96%) | 0.161§ |
| Patients with parathyroid adenoma on US | 20 (66.67%) | 149 (92.55%) | **<0.001§** |
| Adenoma size, mm | 8 (6.8 - 10) | 10 (8 - 15) | **0.009‡** |
| PTH washout, ng/L | 30 (16 - 746) | 952.5 (208 - 2698) | **0.012‡** |
| Negative | 10 (66.67%) | 23 (22.55%) | **0.004¶** |
| Gray zone | 0 (0.00%) | 3 (2.94%) | |
| Positive | 5 (33.33%) | 76 (74.51%) | |
| PHPT type | | | |
| Typical | 27 (90.00%) | 134 (83.23%) | 0.239¶ |
| Normocalcemic | 1 (3.33%) | 21 (13.04%) | |
| Normohormonal | 2 (6.67%) | 6 (3.73%) | |
| Serum PTH, ng/L | 127.5 (96 - 156) | 135 (96.6 - 198) | 0.455‡ |
| Low (<15) | 0 (0.00%) | 0 (0.00%) | 0.614§ |
| Normal (15-65) | 2 (6.67%) | 6 (3.73%) | |
| High (>65) | 28 (93.33%) | 155 (96.27%) | |
| Serum Ca, mg/dL | 10.95 (10.49 - 11.26) | 10.59 (10.32 - 10.95) | **0.045‡** |
| Low (<8.4) | 0 (0.00%) | 0 (0.00%) | 0.210§ |
| Normal (8.4-10.2) | 1 (3.33%) | 21 (13.04%) | |
| High (>10.2) | 29 (96.67%) | 140 (86.96%) | |
| Serum P, mg/dL | 2.67 ± 0.51 | 2.52 ± 0.55 | 0.163† |
| Low (<2.5) | 13 (43.33%) | 87 (54.04%) | 0.380# |
| Normal (2.5-4.5) | 17 (56.67%) | 74 (45.96%) | |
| High (>4.5) | 0 (0.00%) | 0 (0.00%) | |
| Serum 25(OH)D, ug/L | 13.34 (9.50 - 18.00) | 13.72 (9.17 - 16.60) | 0.768‡ |
| Low (<30) | 26 (86.67%) | 151 (93.79%) | 0.242§ |
| Normal (30-100) | 4 (13.33%) | 10 (6.21%) | |
| High (>100) | 0 (0.00%) | 0 (0.00%) | |
| Urinary Ca excretion, mg/24 h | 343.63 ± 121.82 | 358.11 ± 134.14 | 0.583† |
| Normal (<400) | 19 (63.33%) | 109 (67.70%) | 0.798# |
| High (≥400) | 11 (36.67%) | 52 (32.30%) | |
| Serum Cr, mg/dL | 0.82 ± 0.22 | 0.70 ± 0.17 | **0.008†** |
| Low (<0.50) | 1 (3.33%) | 9 (5.59%) | **0.003¶** |
| Normal (0.50-0.90) | 19 (63.33%) | 138 (85.71%) | |
| High (>0.90) | 10 (33.33%) | 14 (8.70%) | |
| ALP, U/L | 105 (78 - 133) | 110 (84 - 144) | 0.436‡ |
| Low (<35) | 0 (0.00%) | 0 (0.00%) | 0.787# |
| Normal (35-104) | 15 (50.00%) | 73 (45.34%) | |
| High (>104) | 15 (50.00%) | 88 (54.66%) | |

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.
ALP, alkaline phosphatase; BMI, body mass index; BNE, bilateral neck exploration; Ca, calcium; Cr, creatinine; DM, diabetes mellitus; HT, hypertension; MIP, minimally invasive parathyroidectomy; MNG, multinodular goiter; P, phosphorus; PHPT, primary hyperparathyroidism; PTC, papillary thyroid carcinoma; PTH, parathyroid hormone; PTx, parathyroidectomy; US, ultrasonography; 25(OH)D, 25-hydroxyvitamin D; $^{99m}$Tc-MIBI SPECT, $^{99m}$Technetium-sestamibi single-photon emission computerized tomography.
† Student's t test, ‡ Mann Whitney U test, # Chi-square test, § Fisher's exact test, ¶ Fisher-Freeman Halton test

83.85% (135/161) of patients in the successful PTx group and 30.00% (9/30) of patients in the failed PTx group underwent MIP, and the frequency of MIP was significantly higher in the successful PTx group (p<0.001). The frequency of PA detection on US (p<0.001), size of PA (p=0.009), PTH washout level (p=0.012) and the frequency of PTH washout positivity (p=0.004) were significantly higher in the successful PTx group than in the failed PTx group (Table 2).

Preoperative serum Ca (p=0.045) and Cr (p=0.008) levels and the frequency of high (>0.90ng/dL) preoperative serum Cr (p=0.003) were significantly lower in the successful PTx group than in the failed PTx group (Table 2).

Detection of PA on US had the highest sensitivity (92.55%), accuracy (83.25%) and NPV (45.45%) to predict successful PTx (Figure 1). Low serum Cr had the highest specificity (93.33%) and PPV (96.77%) for the cut-off point of 0.65mg/dL to predict successful

PTx (Figure 2).

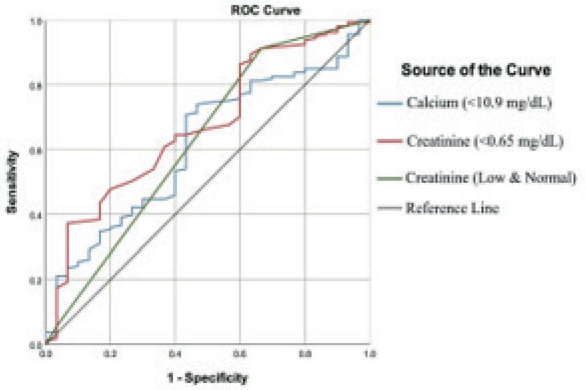


**Figure 2.** ROC curves of factors (preoperative serum Ca and Cr levels) that may predict successful surgery in patients with PHPT.

*Ca, calcium; Cr, creatinine; PHPT, primary hyperparathyroidism; US, ultrasonography.*

On the other hand, gray zone or positive PTH washout had the highest area under ROC curve (AUC: 0.716, 95% CI: 0.567 - 0.864, p=0.007) (Figure 1).

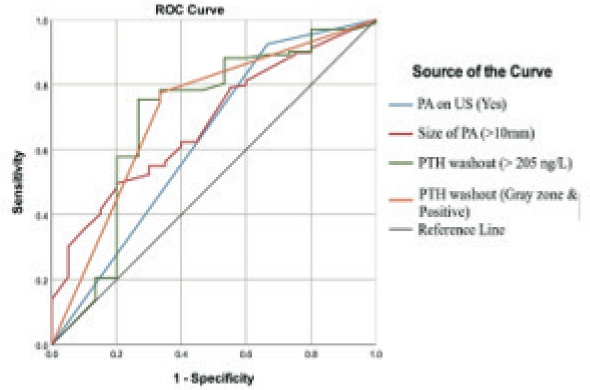


**Figure 1.** ROC curves of factors (PA detection on US, size of PA and PTH washout results) that may predict successful surgery in patients with PHPT.

*PA, parathyroid adenoma; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; US, ultrasonography.*

The results of ROC curve analysis to determine the performance of variables to predict successful PTx are given in Table 3.

**Table 3.** Performance of variables to predict successful PTx, ROC curve analysis

| | Cut-off | Sensitivity | Specificity | Accuracy | PPV | NPV | AUC (95% CI) | p |
|---|---|---|---|---|---|---|---|---|
| PA on US | Yes | 92.55% | 33.33% | 83.25% | 88.17% | 45.45% | 0.629 (0.509 - 0.750) | **0.025** |
| Adenoma size | >10 mm | 49.66% | 80.00% | 53.25% | 94.87% | 17.58% | 0.681 (0.568 - 0.793) | **0.009** |
| PTH washout | >205 ng/L | 75.49% | 73.33% | 75.21% | 95.06% | 30.56% | 0.702 (0.537 - 0.866) | **0.012** |
| PTH washout | Gray zone & Positive | 77.45% | 66.67% | 76.07% | 94.05% | 30.30% | 0.716 (0.567 - 0.864) | **0.007** |
| Serum Ca | <10.9 mg/dL | 70.81% | 56.67% | 68.59% | 89.76% | 26.56% | 0.615 (0.511 - 0.719) | **0.045** |
| Serum Cr | <0.65 mg/dL | 37.27% | 93.33% | 46.07% | 96.77% | 21.71% | 0.676 (0.574 - 0.777) | **0.002** |
| Serum Cr | Low & Normal | 91.30% | 33.33% | 82.20% | 88.02% | 41.67% | 0.627 (0.507 - 0.746) | **0.028** |

AUC, area under ROC curve; Ca, calcium; CI, confidence interval; Cr, creatinine; NPV, negative predictive value; PA, parathyroid adenoma; PPV, positive predictive value; PTH, parathyroid hormone; PTx, parathyroidectomy; ROC, receiver operating characteristic; US, ultrasonography.

According to multivariable logistic regression analysis results, MIP (OR: 13.436, 95% CI: 5.112 - 35.312, p<0.001) and low (<0.65mg/dL) preoperative serum Cr (OR: 8.350, 95% CI: 1.731 - 40.266, p=0.008) were independently associated with the successful PTx while DM (OR: 0.304, 95% CI: 0.109 - 0.849, p=0.023) was independently associated with the failed PTx (Table 4).

**Table 4.** Significant factors independently associated with the surgery outcome (successful), multivariable logistic regression analysis

| | β coefficient | Standard error | p | Exp(β) | 95% CI for Exp(β) | |
|---|---|---|---|---|---|---|
| DM | -1.190 | 0.524 | **0.023** | 0.304 | 0.109 | 0.849 |
| Type of surgery, MIP | 2.598 | 0.493 | **<0.001** | 13.436 | 5.112 | 35.312 |
| Serum Cr, <0.65 mg/dL | 2.122 | 0.803 | **0.008** | 8.350 | 1.731 | 40.266 |
| Constant | 0.085 | 0.367 | 0.816 | 1.089 | | |

CI, confidence interval; Cr, creatinine; DM, diabetes mellitus; MIP, minimally invasive parathyroidectomy; Nagelkerke $R^2$=0.406

In addition, we evaluated location prediction performance of the 99mTc-MIBI SPECT and US in the patients with successful PTx (n=161). 99mTc-MIBI SPECT predicted exact localization accurately in 93/161 (57.76%) cases, kappa coefficient was 0.463 (95% CI: 0.372 - 0.553, p<0.001). US predicted exact localization accurately in 106/161 (65.84%) cases, kappa coefficient was 0.544 (95% CI: 0.453 - 0.634, p<0.001). 99mTc-MIBI SPECT predicted side-only localization accurately in 117/161 (72.67%) cases, kappa coefficient was 0.578 (95% CI: 0.482 - 0.673, p<0.001). US predicted side-only localization accurately in 129/161 (80.12%) cases, kappa coefficient was 0.668 (95% CI: 0.577 - 0.759, p<0.001) (Table 5)

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**Table 5.** Concordance between intraoperative location and preoperative diagnostic methods in the patients with successful PTx (n=161)

| | Intraoperative | 99mTc-MIBI SPECT | US |
|---|---|---|---|
| Location | | | |
| None | 0 (0.00%) | 21 (13.04%) | 12 (7.45%) |
| Right inferior | 60 (37.27%) | 49 (30.43%) | 66 (40.99%) |
| Left inferior | 49 (30.43%) | 46 (28.57%) | 46 (28.57%) |
| Right superior | 5 (3.11%) | 10 (6.21%) | 7 (4.35%) |
| Left superior | 7 (4.35%) | 8 (4.97%) | 8 (4.97%) |
| Right-unspecified | 12 (7.45%) | 6 (3.73%) | 9 (5.59%) |
| Left-unspecified | 9 (5.59%) | 5 (3.11%) | 7 (4.35%) |
| Multiple | 12 (7.45%) | 10 (6.21%) | 3 (1.86%) |
| Intrathymic | 2 (1.24%) | 2 (1.24%) | 0 (0.00%) |
| Mediastinal | 2 (1.24%) | 2 (1.24%) | 0 (0.00%) |
| Intrathyroidal | 3 (1.86%) | 2 (1.24%) | 2 (1.24%) |
| Isthmus inferior | 0 (0.00%) | 0 (0.00%) | 1 (0.62%) |
| Proportion of agreement (1) | - | 93 (57.76%) | 106 (65.84%) |
| Kappa coefficient (95% CI) (1) | - | 0.463 (0.372 - 0.553) | 0.544 (0.453 - 0.634) |
| p | - | **<0.001** | **<0.001** |
| Side | | | |
| None | 0 (0.00%) | 21 (13.04%) | 12 (7.45%) |
| Right | 77 (47.83%) | 65 (40.37%) | 82 (50.93%) |
| Left | 65 (40.37%) | 59 (36.65%) | 61 (37.89%) |
| Other | 19 (11.80%) | 16 (9.94%) | 6 (3.73%) |
| Proportion of agreement (1) | - | 117 (72.67%) | 129 (80.12%) |
| Kappa coefficient (95% CI) (1) | - | 0.578 (0.482 - 0.673) | 0.668 (0.577 - 0.759) |
| p | - | **<0.001** | **<0.001** |

Descriptive statistics were presented using frequency (percentage). (1) Concordance between intraoperative findings.
CI, confidence interval; PTx, parathyroidectomy; US, ultrasonography; 99mTc-MIBI SPECT, 99mTechnetium-sestamibi single-photon emission computerized tomography.

## DISCUSSION

This study investigated the factors that may be associated with surgical success in PHPT. First of all, detection of PA on US was shown to have the highest sensitivity in predicting successful PTx. MIP and low preoperative serum Cr were independently associated with successful PTx, while DM was independently associated with failed PTx. We also evaluated the concordance of preoperative localization methods with intraoperative findings in the successful PTx group and found that US was superior to 99mTc-MIBI SPECT.

The only curative treatment option for PHPT is surgery, and all symptomatic patients and asymptomatic patients who meet the criteria recommended by the guidelines should be treated surgically (4). Surgical success rate in PHPT has been reported to be over 95%, regardless of surgical technique and preoperative localization (4, 8, 16, 17). Unfortunately, the successful PTx rate of our cohort (84.29%) was lower than previous studies. We think that the low surgical success rate in our study may be due to the retrospective design of our study and the inclusion of only patients who applied to the endocrinology department for follow-up after PTx.

Some previous studies investigated demographic, clinical, radiological and biochemical characteristics to predict failed PTx. In a multicenter study that included a total of 1190 patients from 14 hospitals, with an overall success rate of 92%, age ≥70 years was reported as one of the predictors of persistent PHPT (10). On the other hand, there are also previous studies that have shown that age is not associated with persistent hypercalcemia (18). In our study, age was significantly higher in the failed PTx group but was not found to be an independent predictor in multivariate analysis.

Although there are previous studies reporting that conditions such as older age, multiple comorbidities, and frailty were associated with the preference for nonoperative management instead of definitive treatment with PTx, there is insufficient evidence in the literature regarding the effect of comorbidities (such as DM and HT) on surgical success in PHPT (19). Lew JI et al. reported that 21 (2.9%) of 723 patients who were followed for at least 6 months after surgery had failed PTx, and in 3 of those 21 patients, the reason for the failed PTx was that BNE could not be performed because of comorbidities (cardiac or pulmonary) (16). We found that the frequencies of comorbidities such as DM, HT and osteoporosis were lower in the successful PTx group than in the failed PTx group. However, in the multivariate analysis, we found that only DM was an independent predictor of failed PTx among these comorbidities. Although there are not enough previous studies to support our findings, we think that this relationship between DM and failed PTx may be due to the surgeon's possible inertia in performing adequate exploration due to comorbidities.

Two different methods, BNE and MIP, are used in the surgical treatment of PHPT. With the effective use of imaging methods and the introduction of new imaging modalities in recent decades, MIP has become the preferred surgical procedure for PHPT in many institutions. However, it should be kept in mind that some patients may still need the traditional BNE method. There is no consensus yet on which method is superior to the other. The advantages of MIP over the traditional BNE approach are fewer complications, reduced operation time and hospital stay, the potential to be performed in outpatient settings, and reduced costs. Furthermore, MIP has a success rate of over 95%, similar to BNE, and randomized prospective studies have not shown a difference in cure rate between MIP and BNE (7, 20 - 23). In our study, we found that the frequency of MIP was significantly higher in the successful PTx group than in the failed PTx group. We also found that MIP was an independent predictor of successful PTx in multivariate analysis.

US and 99mTc-MIBI are frequently used as primary imaging modalities for PA localization in PHPT. There is evidence to suggest that US and 99mTc-MIBI have similar performance for PA localization (24), and there is also ample evidence to suggest that US is superior to 99mTc-MIBI (18, 25 - 27). In a study including 58 patients who underwent PTx, sensitivity for detection of PA were found to be 80.4% for 99mTc-MIBI planar imaging, and 88.2% for US (25). In a study including 107 patients who underwent PTx for PHPT, Lu R et al. reported that the sensitivity and accuracy of US for detection of PA were significantly higher than 99mTc-MIBI SPECT/CT (93.0% vs. 63.0% and 88.0% vs. 63.0% respectively) (26). In the current study, US localized PA in 88.48% and 99mTc-MIBI SPECT in 85.34% of all patients with PHPT, regardless of surgical outcomes. In the analysis performed according to surgical outcomes, the PA detection rates of US and 99mTc-MIBI SPECT in the successful PTx group increased to 92.55% and 86.96%, respectively, and these results suggest that US is superior to 99mTc-MIBI SPECT in PA detection.

A multicenter study investigating the outcomes of initial surgery for PHPT across Europe reported that detection of PA on 99mTc-MIBI and US was associated with a reduced risk of persistent hypercalcaemia (RR 0.66 and 0.40, respectively), whereas negative 99mTc-MIBI and negative US were associated with an increased risk of persistent hypercalcaemia (RR 1.58 and 2.54, respectively) (18). In our study, detection of PA on US had the highest sensitivity, accuracy and NPV to predict successful PTx. However, it was not found to be an independent predictor in multivariate analysis.

Another reason that makes our study important is that the relationship between the size of PA and PTx outcomes, which has not been addressed much in previous studies, was also investigated. In a study of 1745 patients who underwent MIP, PA weight ≤ 200 mg was reported to be associated with a higher frequency of failed PTx (28). In our study, although no evaluation was made in terms of weight, the size of PA was found to be significantly lower in the failed PTx group than in the successful PTx group.

Another method used for preoperative localization in patients with PHPT is PTH washout, which is generally preferred when US and 99mTc-MIBI are inadequate. Some previous studies reported the sensitivity of PTH washout to be 84 - 90.7% (29, 30). According to our findings, the performance of PTH washout was found to be lower than other localization methods evaluated in the current study, such as US and 99mTc-MIBI SPECT, and also lower than the performance suggested for PTH washout in previous studies. We think that this may be due to the fact that we used this method only in difficult cases where US and 99mTc-MIBI SPECT results were unclear or inconsistent. In addition, because only patients who presented to the endocrinology clinic for postoperative follow-up were included, our study population inherently consisted of more complex and equivocal cases, in whom PTH washout was more frequently performed. This selection bias may have contributed both to the higher-than-expected use of this technique and to its lower diagnostic yield in our cohort. Taken together, these findings indicate that although PTH washout can still be useful in selected equivocal cases, its routine use may not provide substantial additional benefit, and a more selective and judicious application of this minimally invasive procedure appears appropriate.

Some other noteworthy results of our study are that preoperative serum Cr levels were lower in the successful PTx group and that low serum Cr was found to be an independent predictor of successful PTx in multivariate analysis. Our study is the first to suggest that preoperative serum Cr levels may be associated with PTx outcomes. One possible explanation is that patients with lower Cr levels may represent a healthier and younger subgroup with fewer comorbidities, which has been consistently associated with better surgical outcomes. Therefore, the observed relationship between low Cr and successful PTx is biologically plausible and underscores the importance of renal function status in the perioperative management of PHPT.

There are not enough studies in the literature investigating the concordance of preoperative localization findings with intraoperative findings, and the results of the studies on the superiority of USG and 99mTc-MIBI over each other in this regard are contradictory. While there are studies reporting that 99mTc-MIBI and US are similar in terms of concordance with surgical localization, there are also studies reporting that either 99mTc-MIBI or US is superior to the other in this context (13, 31, 32). In our study, the concordance of US with intraoperative PA localization was found to be higher than 99mTc-MIBI SPECT. In addition, when we evaluated side-only prediction, the concordance of US with intraoperative findings increased from 65.84% to 80.12%. One of the reasons why the results of our study are inconsistent with some previous studies may be the difference in the scintigraphy modalities used (such as 99mTc-MIBI SPECT or SPECT/CT).

The most important limitations of our study are its retrospective design and small sample size. In addition, the fact that only patients who applied to the endocrinology department for follow-up after PTx were included in the study is an important limitation resulting from the retrospective design of our study.

In conclusion, based on the results of our study, we think that the most important factors associated with successful surgery in patients with PHPT are younger age, detection of PA on US, preference for MIP as the surgical approach, low preoperative serum Cr level, and absence of comorbidities, especially DM. We also demonstrated that US is superior to 99mTc-MIBI SPECT for preoperative localization in PHPT. However, our findings need to be confirmed by future prospective studies with larger sample sizes.

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Author's contribution:
Conceptualization: MK, Formal analysis: MK, YÖ, Investigation: MK, Methodology: YÖ, MK, Project administration: YÖ, Resources: MK, Software: MK, YÖ, Supervision: MK, Validation: MK, YÖ,Visualization: MK, YÖ, Writing – original draft: MK, Writing – review & editing: MK, YÖ

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