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RESEARCH ARTICLE

Diagnostic Value of Preoperative Imaging Modalities and Their Association with Clinical Parameters in Lesion Localization in Primary Hyperparathyroidism

Primer Hiperparatiroidizmde Preoperatif Görüntüleme Yöntemlerinin Tanısal Değeri ve Klinik Parametrelerle İlişkisi

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ABSTRACT

Objective: The aim of the study was to assess the diagnostic value of preoperative imaging modalities for identifying primary hyperparathyroidism (PHPT) and to examine the clinical and biochemical characteristics associated with successful lesion localization.

Materials and Methods: Data from 216 patients who underwent parathyroidectomy for PHPT and had successful preoperative localization from neck ultrasonography (USG) and Tc-99m sestamibi scintigraphy were analyzed retrospectively. Cases that were not initially localized by imaging were evaluated based on 4D-CT or 18F-fluorocholine PET/CT reports. The associations between accurate localization with imaging modalities and the clinical and biochemical characteristics were investigated.

Results: The combined use of neck USG and Tc-99m sestamibi scintigraphy had a sensitivity of 55.1% and a positive predictive value of 96.3% for detecting hyperfunctional lesions. Multivariable analysis revealed that a parathyroid gland size greater than 1 cm (odds ratio [OR]=2.521, p=0.002), serum intact parathyroid hormone (iPTH) concentration greater than 134 ng/L (OR=2.270, p=0.007), and the presence of normocalcemic PHPT (OR=2.546, p=0.023) were independently associated with successful localization when using USG and sestamibi scintigraphy together.

Conclusions: Combined neck USG and Tc-99m sestamibi scintigraphy are particularly effective for localizing of PHPT in patients with larger glands, higher iPTH levels, and normocalcemic PHPT, potentially obviating the need for advanced imaging in selected cases.

Keywords: Primary hyperparathyroidism, neck ultrasonography, Tc-99m sestamibi scintigraphy, 4D-CT, 18F-fluorocholine PET/CT

ÖZET

Amaç: Primer hiperparatiroidizmde preoperatif görüntüleme yöntemlerinin tanısal değerini değerlendirmek ve lokalizasyon başarısı ile klinik ve biyokimyasal özellikler arasındaki ilişkiyi incelemek.

Gereç ve Yöntemler: Primer hiperparatiroidizm nedeniyle paratiroidektomiye giden ve preoperatif dönemde başlangıçta lokalizasyon amaçlı boyun ultrasonografisi ve Tc-99m sestamibi sintigrafisi yapılmış 216 hastanın verileri retrospektif olarak analiz edildi. Başlangıç görüntüleme yöntemleriyle lokalize edilemeyen olgular, 4-boyutlu BT ve/veya 18F-kolin PET-BT raporları temel alınarak değerlendirildi. Görüntüleme yöntemlerinin doğru lokalizasyon sonuçları ile klinik ve biyokimyasal özellikler arasındaki ilişkiler analiz edildi.

Bulgular: Boyun ultrasonografisi ve Tc-99m sestamibi sintigrafisinin kombine kullanımı, hiperfonksiyonel lezyonların saptanmasında %55,1 duyarlılık ve %96,3 pozitif prediktif değer göstermiştir. Çok değişkenli analizde ise, paratiroid bez boyutunun >1 cm olması (OR=2,521, p=0,002), serum iPTH düzeyinin >134 ng/L olması (OR=2,270, p=0,007) ve normokalsemik primer hiperparatiroidizm varlığı (OR=2,546, p=0,023), kombine USG ve sestamibi sintigrafisi ile başarılı lokalizasyonun bağımsız belirleyicileri olarak saptanmıştır.

Sonuç: Kombine boyun ultrasonografisi ve Tc-99m sestamibi sintigrafisi, özellikle daha büyük bez boyutu, yüksek iPTH düzeyleri ve normokalsemik primer hiperparatiroidizm varlığında etkili olup, seçilmiş hastalarda ileri görüntüleme yöntemlerine olan gereksinimi ortadan kaldırabilir.

Anahtar Kelimeler: Primer hiperparatiroidizm, boyun ultrasonografisi, Tc-99m sestamibi sintigrafisi, 4-boyutlu BT, 18F-kolin PET/BT

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by autonomous overproduction of parathyroid hormone (PTH), leading to disturbances in calcium–phosphate homeostasis (1). The clinical presentation of PHPT ranges from an asymptomatic state to severe disease involving multiple organ systems (2). PHPT can result in nephrolithiasis, impaired renal function, osteoporosis or fragility fractures, neurocognitive or gastrointestinal dysfunction, and increased cardiovascular morbidity (3,4). In clinical practice, approximately 80% of patients with PHPT are asymptomatic, with diagnosis often incidental during routine measurements of serum calcium and PTH levels (2). The most common cause of PHPT is a solitary adenoma (75–85%), followed by multiglandular hyperplasia (10%), double adenomas (4%), and, rarely, parathyroid carcinoma (1%) (5).

Treatment decisions for PHPT are based on the presence of symptoms and evidence of skeletal demineralization or renal involvement. Surgical removal of the hyperfunctioning gland is considered the definitive treatment for PHPT, whereas monitoring and follow-up are recommended for asymptomatic patients who do not meet the surgical criteria (5). Preoperative localization of the responsible parathyroid tissue is crucial for treatment planning. In recent years, the standard surgical approach has advanced from bilateral neck exploration, in which all four glands are examined, to minimally invasive parathyroidectomy (MIP), which involves targeted removal of the affected gland following unilateral exploration (6).

Currently, neck ultrasonography (USG) and technetium-99m sestamibi scintigraphy are the standard first-line imaging modalities for preoperative lesion localization in PHPT (1). The reported sensitivity of USG for lesion localization ranges 29–73%, while Tc-99m sestamibi scintigraphy has a sensitivity of 50–70% and a specificity of 77–87%. Several studies have shown that combining sestamibi scintigraphy with single-photon emission CT (SPECT) improves sensitivity (3). However, each imaging modality has inherent strengths and limitations, and diagnostic performance can vary depending on patient-related and gland-related factors (1,5).

In cases where USG and sestamibi scintigraphy yield negative or discordant results, 4D-CT has been shown to be an effective alternative for preoperative localization (7). By providing detailed anatomical information on the size and location of abnormally positioned parathyroid glands, 4D-CT has emerged as potentially more sensitive and accurate, with reported sensitivities ranging 70–92% (3). Fine-needle aspiration biopsy (FNAB) with PTH washout is also increasingly used in clinical practice to differentiate parathyroid lesions from other suspicious lesions detected on imaging and to aid with localization; however, there is no current consensus regarding the optimal cutoff value for PTH washout in parathyroid tissue (8). Another imaging modality used in cases of uncertain localization is 18F-fluorocholine PET/CT, which has shown higher sensitivity than USG and scintigraphy. Nevertheless, due to limited availability and high cost, 18F-fluorocholine PET/CT has yet to be adopted for routine use (1).

In this study, we aimed to evaluate the diagnostic value of imaging modalities for localizing parathyroids in PHPT preoperatively and to investigate the relationship between localization success in patients requiring advanced imaging after failed initial localization studies and clinical and biochemical characteristics.

MATERIALS AND METHODS

Patients

This retrospective cohort study included patients aged 18 years and older diagnosed with PHPT at the Endocrinology Clinic of Ankara Training and Research Hospital between January 2020 and June 2025. These patients met the surgical criteria according to the report of the 5th International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, and subsequently underwent parathyroidectomy (9). In our center, the diagnosis of PHPT was established by the presence of hypercalcemia on at least two separate occasions in conjunction with inappropriately elevated serum intact PTH (iPTH) levels (reference ranges: serum calcium 8.5–10.5 mg/dL and PTH 15–65 ng/L).

The exclusion criteria were the presence of secondary or tertiary hyperparathyroidism, absence of at least two preoperative imaging studies, detection of malignancy on postoperative histopathological examination, a history of previous central neck surgery, persistent or recurrent PHPT, hereditary or lithium-associated hyperparathyroidism, and incomplete medical records.

Preoperative Imaging Studies

All patients underwent neck USG and Tc-99m sestamibi scintigraphy to localize the pathological parathyroid gland. Tc-99m sestamibi scintigraphy was performed using a dual-phase protocol with early and delayed imaging, and SPECT/CT was used when considered necessary by the nuclear medicine physician. Images were interpreted by nuclear medicine physicians. Neck USG was performed by an endocrinologist with at least 5 years of experience in parathyroid USG using a high-resolution linear transducer (7–12 MHz). In patients where imaging failed to localize the lesion, further evaluation was conducted with 4D-CT and 18F-fluorocholine PET/CT. Data for USG, Tc-99m sestamibi scintigraphy, and 4D-CT were obtained from the hospital imaging database, while 18F-fluorocholine PET/CT reports were retrieved from patient medical records. 18F-fluorocholine PET/CT findings were evaluated based on the reports of experienced nuclear medicine specialists. The accuracy of radiological localization was assessed in comparison with intraoperative surgical findings. Lesions that were suspicious for adenoma or hyperplasia on initial neck USG but not visualized on Tc-99m sestamibi scintigraphy or lesions detected on repeat USG guided by findings from advanced imaging modalities, underwent ultrasound-guided FNAB. PTH washout analysis was performed on the aspirated material, and a washout PTH level higher than the corresponding serum iPTH level was considered a positive result.

In our clinical practice, the two primary imaging modalities requested for lesion localization in patients with PHPT and

to indicate surgery are neck USG and Tc-99m sestamibi scintigraphy. The addition of low-resolution SPECT is decided by the nuclear medicine department. If the lesion could not be detected by either imaging methods or the PTH washout result of a suspicious ultrasonographic lesion was negative, 4D-CT was requested provided that there were no contraindications. Patients in whom lesion localization was unsuccessful despite the use of these imaging modalities were referred to external centers for 18F-fluorocholine PET/CT, and evaluation was based on radiology reports. Regardless of whether patients presented with previous USG reports, all were re-evaluated with neck USG at our clinic for their parathyroid gland. Patients with localized hyperfunctioning parathyroid lesions were referred for MIP whereas those without successful localization underwent surgical neck exploration.

During data collection, the localization of the hyperfunctioning parathyroid lesion (ie, right superior, right inferior, left superior, left inferior, or ectopic) and the presence of concomitant thyroid nodules were recorded. For each imaging modality, sensitivity and positive predictive value (PPV) were calculated.

Assessment Parameters

Normocalcemic PHPT (NPHPT) was defined as persistently normal albumin-corrected serum calcium levels in the presence of elevated PTH concentrations, after exclusion of secondary causes of hyperparathyroidism (10). Patients' demographic characteristics and clinical status were recorded. The presence of symptoms was defined as the occurrence of at least one complaint related to hyperparathyroidism, including fatigue, constipation, weakness, muscle or bone pain, and depressive symptoms. Bone mineral densitometry results were evaluated as normal bone density, osteopenia, or osteoporosis in individuals aged 50 years and older, and as bone mass lower than expected for age or normal bone mass for age in individuals older than 50 years. Each condition constituting an indication for surgery was assigned 1 point, and the total score (range: 0–5 points) was calculated accordingly. Preoperative laboratory parameters, including serum iPTH, albumin-corrected calcium, phosphorus, 25-hydroxyvitamin D [25(OH)D], glomerular filtration rate (GFR), thyroid-stimulating hormone (TSH), free thyroxine (FT4), anti-thyroid peroxidase antibody (anti-TPO), and 24-hour urinary calcium excretion were evaluated by reviewing electronic medical records. When available, tissue PTH washout values and pathology report data were also recorded. Anti-TPO positivity was defined as the presence of autoimmune thyroid disease. The maximum diameter of the excised parathyroid lesion was recorded from the surgical specimen. Based on histopathological examination, lesions were classified as either adenoma, hyperplasia, atypical adenoma, or carcinoma. A successful surgical outcome was defined as the normalization of serum iPTH and calcium levels within the first 24 hours postoperatively, along with histopathological confirmation that the excised tissue was consistent with parathyroid tissue.

Ethical Approval

The study was approved by the local ethics committee (January 14, 2026/687) and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed using SPSS v.20 software. The normality of distribution was tested using the Kolmogorov–Smirnov test. Data showing a normal distribution are presented as mean ± standard deviation (SD), while data not showing a normal distribution are presented as median (min–max). Categorical variables are expressed as n (%). The Mann–Whitney U test was used for comparisons between continuous variables that did not show a normal distribution. Comparisons between categorical variables were made using the Chi-squared ($\chi 2$) or Fisher's exact tests. The localization rates (sensitivity) and PPVs of imaging methods for parathyroid lesions were calculated. Additionally, the evaluation of independent variables affecting the localization of imaging methods was performed using logistic regression analysis. Sensitivity was defined as the proportion of hyperfunctioning glands correctly localized by imaging. The specificity represented the proportion of non-localized cases correctly identified as negative within the parathyroid gland localization framework. The PPV indicated the probability that a lesion identified by imaging corresponded to the surgically confirmed pathological gland, whereas negative predictive value (NPV) reflected the probability that a non-localizing result truly corresponded to the failure to localize the lesion. Additionally, independent predictors of localization success were evaluated using multivariable logistic regression analysis. Variables with $p<0.20$ in univariate analysis were considered for inclusion in the multivariable model. The Enter method was used for multivariable logistic regression analysis. Since all included patients had surgically confirmed PHPT, specificity and NPV could not be calculated within the classical disease-present or disease-absent framework. Therefore, additional receiver operating characteristic analyses were performed by defining imaging outcome as localized versus non-localized lesions. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 216 patients who underwent parathyroidectomy for PHPT and had preoperative lesion localization with neck USG and Tc-99m sestamibi scintigraphy were included in the study. Of the patients, 86.1% were female and 75.9% were asymptomatic. The demographic and laboratory characteristics of the patients are presented in Table 1. The median albumin-corrected serum calcium level was 11.1 mg/dL (range: 9.3–14), and the median iPTH level was 125.5 ng/L (range: 25–531). According to preoperative imaging results, the most common lesion localizations responsible for PHPT were the right superior (43.1%) and right inferior (28.2%) glands. In seven patients, preoperative localization findings were not concordant with intraoperative surgical findings. Postoperative histopathological examination revealed adenoma as the cause of PHPT in 90.3% of cases. The localization performance of initial conventional preoperative imaging modalities is shown in Table 2. The combined use of neck USG and sestamibi

Table 1. Demographic and clinical characteristics of patients with PHPT

Variables		Patients with PHPT (n=216)
Age (years)		55 (23–81)
Sex (n, %)		
	Female	186 (86.1%)
	Male	30 (13.9%)
PHPT according to serum calcium levels (n, %)		
	Hypercalcemic	38 (17.6%)
	Normocalcemic	178 (82.4%)
Symptoms (n, %)		
	Absent	164 (75.9%)
	Present	52 (24.1%)
Nephrolithiasis (n, %)		
	Absent	158 (73.1%)
	Present	58 (26.9%)
Bone mineral density (n, %)		
	≥50 years	164 (75.9%)
	Normal	28 (17.1%)
	Osteopenia	51 (31.1%)
	Osteoporosis	85 (51.8%)
	<50 years	52 (24.1%)
	Low bone mass for age	35 (67.3%)
	Normal bone mass for age	17 (32.7%)
Indications for surgery		
	Symptomatic (n, %)	52 (24.1%)
	Asymptomatic (n, %)	164 (75.9%)
	<50 years	36 (21.9%)
	Serum Ca ≥mg/dl above the limit of normal	30 (1.8%)
	Skeletal involvement	77 (46.9%)
	Renal involvement	177 (81.9%)
Number of surgical indications (n)		2 (0–5)
Autoimmune thyroid disease (n, %)		
	Absent	86 (39.8%)
	Present	130 (60.2%)
Thyroid nodule (n, %)		
	Absent	74 (34.3%)
	Present	142 (65.7%)
eGFR (ml/min/1.73m^2)		94 (46–126%)
TSH (mIU/L)		1.69 (0.2–8)
Alb-sCa (mg/dl)		11.1 (9.3–14)
P (mg/dl)		2.7 (1–4.4)
CaxP (mg^2/dl^2)		29.75 (12.8–46.33)
iPTH (ng/L)		125.5 (25–531)
24-hour urinary calcium (mg/day)		359 (28.2–1254)
25 (OH) vitamin D (µ/L)		19.65 (3–52)
Parathyroid gland localization (n, %)		
	Right superior	93 (43.1%)
	Right inferior	61 (28.2%)
	Left supeior	18 (8.3%)
	Left inferior	39 (18.1%)
	Ectopic (mediastinal)	5 (2.3%)
Parathyroid gland size (cm)		1 (0.4–5)
Histopathology (n, %)		
	Adenoma	195 (90.3%)
	Hyperplasia	16 (7.4%)
	Atypical adenoma	5 (2.3%)
	Carcinoma	0 (0%)

eGFR=estimated glomerular filtration rate. Alb-sCa=albumin-corrected serum calcium. Ca=calcium. P=phosphorus. CaxP=calcium–phosphorus product. iPTH=intact parathyroid hormone. PHPT=primary hyperparathyroidism. TSH=thyroid-stimulating hormone. Symptomatic status was defined as the presence of at least one hyperparathyroidism-related complaint (eg, fatigue, constipation, weakness, musculoskeletal pain, or depressive symptoms). Renal involvement was defined as the presence of nephrolithiasis or nephrocalcinosis.
Skeletal involvement was defined as a history of fragility fracture or osteoporosis on bone mineral density assessment (DXA T-score ≤−2.5). Data are presented as median (min–max) for non-normally distributed variables and as n (%) for categorical variables.

Table 2. Localization rates of parathyroid lesions using preoperative imaging modalities in patients with PHPT

Imaging modality	Number of examinations (n)	Localization rate (n, %)	PPV (n, %)
USG	216	171/216 (79.2%)	164/171 (95.9%)
Sestamibi	216	131/216 (60.6%)	127/131 (96.9%)
USG and sestamibi	216	119/216 (55.1%)	115/119 (96.63%)
4D-CT	104	69/104 (66.3%)	63/69 (91.3%)
18F-fluorocholine PET/CT	16	11/16 (68.7%)	11/11 (100%)
USG/sestamibi	216	183/216 (84.7%)	176/183 (96.2%)
USG/sestamibi/4D-CT	104	88/104 (84.6%)	82/88 (93.2%)
USG/sestamibi/18F-fluorocholine PET/CT	16	12/16 (75%)	12/12 (100%)
Triple-modality imaging	104	88/104 (84.6%)	82/88 (93.2%)
Quadruple-modality imaging	16	12/16 (75%)	12/12 (100%)

USG=ultrasonography. 4D-CT=4-dimensional computed tomography. ^{18}F-fluorocholine PET/CT=fluorine-18 fluorocholine positron emission tomography/computed tomography. PPV=positive predictive value. Triple-modality imaging=USG/sestamibi/4D-CT. Quadruple-modality imaging=USg/sestamibi/4D-CT/^{18}F-fluorocholine PET/CT. Categorical variables are presented as n (%).

Table 3. Localization rates and positive predictive values of imaging modalities according to quartiles of preoperative serum calcium and parathyroid hormone levels

Alb-sCa vs iPTH	USG (n=216)		Sestamibi (n=216)		USG with sestamibi (n=216)		4D-CT (n=104)		^{18}F-fluorocholine PET/CT (n=16)	
	Localizasion (n, %)	PPV (n, %)	Localization (n, %)	PPV (n, %)	Localization (n, %)	PPV (n, %)	Localization (n, %)	PPV (n, %)	Localization (n, %)	PPV (n, %)
Alb-sCa (mg/dl)										
<10.7	44/50 (88%)	43/44 (97.7%)	36/50 (72%)	35/36 (97.2%)	33/50 (66%)	32/33 (96.9%)	18/23 (78.3%%)	17/18 (94.4%)	1/1 (100%)	1/1 (100%)
10.7–11	42/57 (73.7%)	40/42 (95.2%)	32/57 (56.1%)	31/32 (96.9%)	29/57 (50.9%)	28/29 (96.5%)	17/26 (65.4%)	15/17 (88.2%)	2/5 (40%)	2/2 (100%)
11.1–11.4	45/54 (83.3%)	41/45 (91.1%)	32/54 (59.3%)	30/32 (93.7%)	29/54 (53.7%)	27/29 (93.1%)	20/28 (71.4%)	17/20 (85%)	2/2 (100%)	2/2 (100%)
>11.4	40/55 (72.7%)	40/40 (100%)	31/55 (56.4%)	31/31 (100%)	28/55 (50.9%)	28/28 (100%)	14/27 (51.9%)	14/14 (100%)	6/8 (75%)	6/6 (100%)
iPTH (ng/L)										
<96	38/54 (70.4%)	35/38 (92.1%)	29/54 (53.7%)	27/29 (93.1%)	26/54 (48.1%)	24/26 (92.3%)	13/27 (48.1%)	9/13 (69.2%)	6/9 (66.7%)	6/6 (100%)
96–125	41/54 (75.9%)	40/41 (97.6%)	29/54 (53.7%)	28/29 (96.5%)	26/54 (48.1%)	25/26 (96.1%)	21/28 (75%)	21/21 (100%)	2/2 (100%)	2/2 (100%)
126–172	44/54 (81.5%)	42/44 (95.4%)	36/54 (66.7%)	35/36 (97.2%)	33/54 (61.1%)	32/33 (96.9%)	20/27 (74.1%)	18/20 (90%)	0/1 (0%)	N/A
>172	48/54 (79.2%)	47/48 (97.9%)	37/54 (68.5%)	37/37 (100%)	34/54 (63%)	34/34 (100%)	15/22 (68.2%)	15/15 (100%)	3/4 (75%)	3/3 (100%)

Alb-sCa=albumin-corrected serum calcium. iPTH=intact parathyroid hormone. USG=ultrasonography. 4D-CT=4-dimensional computed tomography. PPV=positive predictive value. NA=not applicable.

scintigraphy yielded a sensitivity of 55.1% and a PPV of 96.3% for detecting hyperfunctioning parathyroid lesions. In patients with unsuccessful localization with initial imaging and who subsequently underwent advanced imaging, the sensitivity of localization was 66.3% for 4D-CT and 68.7% for 18F-fluorocholine PET/CT, with PPVs of 91.3% and 100%, respectively. Figure 1 illustrates the localization outcomes of lesions that could not be identified by either neck USG or sestamibi scintigraphy during the initial preoperative evaluation in patients with PHPT following additional imaging modalities.

The localization rates and PPVs of imaging modalities according to quartiles of preoperative serum calcium and iPTH levels are presented in Table 3. When serum calcium levels exceeded 11.4 mg/dL, the PPV of all four imaging modalities was 100%. Similarly, when iPTH levels were greater than 172 ng/L, the PPV reached 100% in patients whose lesions were localized by both neck USG and sestamibi scintigraphy. Comparisons of demographic and clinical characteristics according to localization status of preoperative imaging modalities are summarized in Table 4. Patients whose lesions were localized by either neck USG or sestamibi scintigraphy had significantly higher median iPTH levels compared with those without successful localization (p=0.024 and p=0.049, respectively). A comparison of demographic and clinical characteristics between patients whose parathyroid lesions were localized by USG and sestamibi scintigraphy combined versus those who were not is presented in Table 5. Significant

Table 4. Comparison of demographic and clinical characteristics of patients according to localization status of preoperative imaging modalities in PHPT

Variables	USG (n=216)			Sestamibi (n=216)			4D-CT (n=104)			18F-fluorocholine PET/CT (n=16)		
	(+) (n=171)	(-) (n=45)	p value	(+) (n=131)	(-) (n=85)	p value	(+) (n=69)	(-) (n=35)	p value	(+) (n=11)	(-) (n=5	p value
Age (years	55 (25–81)	57 (23–79)	0.168	55 (25–77)	57 (23–81)	0.205	59 (25–79)	54 (23–77)	0.018*	49 (23–58)	54 (40–59)	0.364
Sex (n, %)			0.183			0.746			0.825			1.000
Female	150 (87.7%)	36 (80%)		112 (85.5%)	74 (87.1%)		58 (84.1%)	30 (85.7%)		7 (63.6%)	4 (80%)	
Male	21 (12.3%)	9 (20%)		19 (14.5%)	11 (12.9%)		11 (15.9%)	5 (14.3%)		4 (36.4%)	1 (20%)	
PHPT according to serum calcium levels (n, %)			0.085			0.070			0.686			1.000
Hypercalcemic	137 (80.1%)	41 (91.1%)		103 (78.6%)	75 (88.2%)		57 (82.6%)	30 (85.7%)		10 (90.9%)	5 (100%)	
Normocalcemic	34 (19.9%)	4 (8.9%)		28 (21.4%)	10 (11.8%)		12 (17.4%)	5 (14.3%)		1 (9.1%)	0 (0%)	
Symptoms (n, %)			0.133			0.075			0.259			0.509
Absent	126 (73.7%)	38 (84.4%)		94 (71.8%)	70 (82.4%)		56 (81.2%)	25 (71.4%)		5 (72.7%)	8 (100%)	
Present	45 (26.3%)	7 (15.6%)		37 (28.2%)	15 (17.6%)		13 (18.8%)	10 (28.6%)		3 (27.3%)	0 (0%)	
Number of surgical indications	2 (0–5)	2 (0–5)	0.577	2 (0–5)	2 (0–5)	0.579	2 (0–4)	2 (0–5)	0.328	2 (0–5)	2 (1–2)	0.137
Target organ involvement												
Skeletal involvement	83 (48.5%)	25 (55.6%)	0.402	64 (48.9%)	44 (51.8%)	0.676	39 (56.5%)	20 (57.1%)	0.952	6 (54.5%)	2 (40%)	1.000
Renal involvement	139 (81.3%)	38 (84.4%)	0.624	108 (82.4%)	69 (81.2%)	0.813	60 (87%)	29 (82.9%)	0.574	9 (81.8%)	4 (80%)	1.000
Autoimmune thyroid disease (n, %)			0.512			0.168			0.845			1.000
Absent	70 (40.9%)	16 (35.6%)		57 (43.5%)	29 (34.1%)		25 (36.2%)	12 (34.3%)		6 (54.5%)	2 (40%)	
Present	101 (59.1%)	29 (64.4%)		74 (56.5%)	56 (65.9%)		44 (63.8%)	23 (65.7%)		5 (45.5%)	3 (60%)	
Thyroid nodule (n, %)			0.883			0.084			0.288			0.299
Absent	59 (34.5%)	15 (33.3%)		39 (29.8%)	35 (41.2%)		27 (39.1%)	10 (28.6%)		3 (27.3%)	3 (60%)	
Present	112 (65.5%)	30 (66.7%)		92 (70.2%)	50 (58.8%)		42 (60.9%)	25 (71.4%)		8 (72.7%)	2 (40%)	
eGFR (ml/min/1.73m^2)	95 (46–126)	89 (51–124)	0.080	96 (48–124)	90 (46–126)	0.071	89 (51–126)	94 (46–124)	0.609	95 (77–124)	100 (95–118)	0.173
TSH (mIU/L)	1.78 (0.2–8)	1.6 (0.42–5.4)	0.490	1.69 (0.4–5.6)	1.74 (0.2–8)	0.968	1.85 (0.2–8)	1.6 (0.51–5.4)	0.698	1.52 (0.66–4.08)	2.98 (1.5–5.4)	0.089
Alb-sCa (mg/dl)	11 (9.3–14)	11.1 (9.6–13.8)	0.258	11 (9.3–14)	11.1 (9.5–13.8)	0.180	11 (9.6–13.4)	11.2 (9.5–13.8	0.077	11.5 (9.6–13.8)	10.9 (10.9–12.2)	0.278
P (mg/dl)	2.7 (1–4.34)	2.57 (1.2–4.4)	0.268	2.65 (1–4.4)	2.77 (1.47–4.34)	0.612	2.77 (1.2–4.4)	2.53 (1.47–3.4)	0.104	2.53 (1.6–4.4)	2.8 (2.56–3.21)	0.193
CaxP (mg^2/dl^2)	29.76 (12.8–46.33)	29.44 (14.04–42.24)	0.443	29.37 (12.8–45.36)	30.24 (17.05–46.33)	0.397	30.24 (14.04–46.33)	29.44 (17.05–39.98)	0.139	29.85 (19.6–42.2)	33.02 (28–34.99)	0.282
iPTH (ng/L)	133 (25–531)	108 (70.2–431)	0.024*	135 (25–531)	117 (59.9–431)	0.049*	126 (59.9–453)	108 (70.2–331)	0.154	94 (73–331)	80 (70.2–385)	0.865

eGFR=estimated glomerular filtration rate. Alb-sCa=albumin-corrected serum calcium. P=phosphorus. Ca×P=calcium–phosphorus product. iPTH=intact parathyroid hormone. PHPT=primary hyperparathyroidism. TSH=thyroid-stimulating hormone. USG=ultrasonography. 4D-CT=4-dimensional computed tomography. ^{18}F-fluorocholine PET/CT=fluorine-18 fluorocholine positron emission tomography/computed tomography. A p value <0.05 was considered statistically significant and is indicated by an asterisk (*).

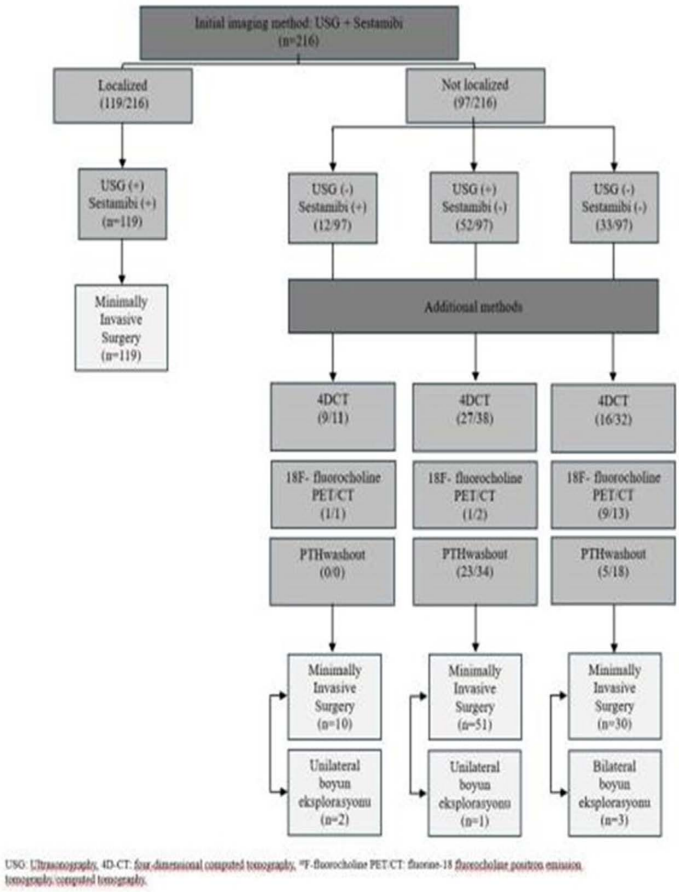

Figure 1. Localization of lesions not identified by initial preoperative imaging with neck ultrasonography and Tc-99m sestamibi scintigraphy in patients with primary hyperparathyroidism using additional imaging modalities

differences were observed between the two groups in terms of symptom presence (p=0.042), GFR (p=0.032), iPTH levels (p=0.049), and parathyroid gland size (p<0.001). Patients in whom parathyroid adenomas were successfully localized using combined USG and sestamibi scintigraphy were more likely to be symptomatic, had higher iPTH levels, and had larger gland sizes.

Univariate and Multivariate Analyses

For combined USG and sestamibi imaging , univariate analyses were initially performed to identify independent variables significantly associated with successful lesion localization. Variables not directly associated with localization were subsequently excluded, and multivariable logistic regression analyses were conducted to establish independent predictors of successful lesion localization (Table 5). For univariate logistic regression analysis, age (p=0.142), hypercalcemic PHPT or NPHPT status (p=0.072), autoimmune thyroid disease (p=0.065), parathyroid gland size (p=0.001), and iPTH level (p=0.005) met the predefined p<0.20 threshold and were therefore considered for inclusion in the multivariable model. Although symptom presence and estimated GFR also met the p<0.20 criterion in univariate analysis, these variables were not included in the multivariable model due to the lack of clinically meaningful association with parathyroid gland localization success.

For multivariable logistic regression analysis, parathyroid gland size (>1 cm), iPTH level (>134 ng/L), and NPHPT were identified as independent predictors of successful lesion localization with the combined use of USG and sestamibi. Among these, parathyroid gland size emerged as the strongest predictor; a gland diameter greater than 1 cm increased the likelihood of successful localization approximately 2.5-fold (odds ratio [OR]=2.521, p=0.002). Similarly, an iPTH level greater than 134 ng/L was independently associated with higher localization success (OR=2.270, p=0.007). NPHPT was borderline significant in univariate analysis (p=0.072) but became an independent predictor in the multivariable model (OR=2.546, p=0.023), suggesting that when evaluated alongside other covariates, the presence of normocalcemia could additionally contribute to localization success.

DISCUSSION

Accurate localization of the pathological parathyroid lesion is essential for the surgical management of PHPT (1). Neck USG and Tc-99m sestamibi scintigraphy are the commonest first-line localization modalities for PHPT (5). When USG and sestamibi imaging are concordant, the success rate of MIP increases significantly (3). Although some studies suggest that performing both imaging modalities can be unnecessary and not cost-effective when sestamibi and USG localize the lesion to the same region, lesion localization with at least two imaging modalities remains important for MIP (6). To date, there is no clear consensus regarding the optimal imaging modality for parathyroid adenoma localization (3). Localization of a parathyroid lesion by a single imaging modality or discordant localization findings between two imaging studies can create diagnostic and surgical challenges (2). Comparing the relative effectiveness of different imaging modalities is difficult, and no single technique or imaging algorithm has been definitively proven to be superior for parathyroid lesion localization (4). In a study evaluating preoperative imaging results in 220 patients with PHPT who underwent parathyroidectomy, USG identified hormonally active lesions in approximately 75% of patients and with an accuracy of 82% (5). Nasiri et al., in their study of 80 patients with PHPT, detected enlarged parathyroid glands in 76.3% of cases and reported sensitivity and PPV values of 83.5% for USG. In the same study, sestamibi scintigraphy localized adenomas in 78.8% of patients, with sensitivity at 85% and PPV value at 91.3% (11). In our study, lesion localization was achieved by USG in 79.2% of patients with a PPV of 95.9%, while sestamibi scintigraphy achieved localization in 60.9% of patients with a PPV of 96.9%. Although older reports in the literature suggest that combining USG and sestamibi imaging

could achieve localization sensitivities exceeding 90%, subsequent studies have shown substantially lower sensitivity rates ranging 33–92% (6). In our cohort, combined localization with both USG and sestamibi scintigraphy was observed in 55.1% of patients, with a PPV of 96.3%. Although the sensitivity of the combined approach was moderate (55.1%), the high PPV (96.3%) indicates strong reliability when localization is positive. For the surgical management of PHPT, high PPV is clinically valuable because positive localization supports MIP, whereas negative or non-localizing results do not exclude disease, rather, they indicate the need for additional imaging or bilateral exploration. When initial localization methods, such as USG and sestamibi scintigraphy, fail to provide definitive results, 4D-CT can be used as a complementary imaging modality for parathyroid gland localization (8). Day et al. reported a sensitivity of 89% and a PPV of 74% for 4D-CT in 872 patients with PHPT who had unsuccessful lesion localization using USG and sestamibi scintigraphy, and they suggested that 4D-CT could be considered a first-line imaging modality (12). In our study, 4D-CT successfully localized parathyroid lesions in 16 of 33 patients who could not be localized by USG and sestamibi scintigraphy. In patients with PHPT, 18F-fluorocholine PET/CT is recommended as a highly sensitive imaging modality when localization cannot be achieved using conventional methods; however, limitations related to accessibility and cost restrict its widespread use in clinical practice (13). In our study, only 16 of 97 patients whose lesions could not be localized by neck USG and sestamibi scintigraphy underwent 18F-fluorocholine PET/CT. Hyperfunctioning lesions were successfully identified in 68.7% of this subgroup of patients, with a PPV of 100%. Another approach contributing to preoperative localization was PTH washout from suspicious lesions. PTH washout was performed in 18 lesions that were not detected by initial imaging modalities but were considered suspicious based on advanced imaging, leading to successful identification of a hyperfunctioning gland in five patients.

Several studies in the literature have evaluated potential clinical, biochemical, and lesion-related factors that could influence the accuracy of preoperative lesion localization in PHPT. Previous studies have shown that larger parathyroid glands are more readily detected by USG. It has been suggested that an increased number of mitochondria in larger glands leads to higher metabolic activity, thereby facilitating improved visualization on sestamibi scintigraphy. In a study of 100 patients with PHPT, adenoma size was the only significant determinant of accurate localization using USG and sestamibi scintigraphy, whereas age, sex, lesion location (right vs left or superior vs inferior), serum calcium concentration, iPTH level, and urinary calcium excretion were not associated with imaging success (14). Similarly, in a large study by Berber et al. involving 1845 patients with PHPT, gland size was an independent predictor of accurate lesion localization with both USG and sestamibi scintigraphy (15). Consistent with these findings, our study showed that a parathyroid gland size greater than 1 cm significantly increased the likelihood of successful localization using both USG and sestamibi scintigraphy. Small parathyroid adenomas or hyperplasia can yield false-negative results on conventional preoperative imaging. Importantly, discordant or negative imaging findings do not necessarily indicate multiglandular disease; it has been suggested that approximately 70% of such patients can still have single-gland disease amenable to minimally invasive surgery. 4D-CT could be a valuable preoperative imaging modality, particularly in cases with small adenomas or mild hypercalcemia (16). In general, higher serum calcium and iPTH levels are associated with larger parathyroid adenomas, which are more easily localized using USG and sestamibi scintigraphy. This relationship could explain the observed linear correlation between increasing serum calcium and iPTH levels and improved localization sensitivity and PPV when USG and sestamibi scintigraphy are used in combination. Previous studies have also shown that preoperative serum calcium and iPTH levels, which correlate with disease severity, are associated with localization sensitivity on USG and sestamibi scintigraphy (17). Although higher serum calcium and iPTH levels are generally associated with larger adenomas and improved localization sensitivity, our finding that lesion localization success with combined USG and sestamibi was higher in NPHPT than in hypercalcemic PHPT appears, at first glance, to diverge from the existing literature. This unexpected observation could be explained by referral patterns inherent to tertiary referral centers. A substantial proportion of patients with hypercalcemic PHPT referred to our institution represent selected, complex cases, including those with prior unsuccessful localization attempts, ectopic gland locations, or multiglandular disease. Notably, all ectopic cases in our cohort were included in the non-localized lesion group, and these were more frequently observed among patients who were hypercalcemic. This finding suggests that referral bias might have enriched the hypercalcemic subgroup with technically challenging cases, thereby reducing overall localization success in the group. In contrast, patients with NPHPT were more often evaluated at our center as first-line cases without prior failed localization attempts. Therefore, our findings should not be interpreted to be indicating intrinsically easier localization in NPHPT, rather, as reflecting the case-mix and referral patterns characteristic of a tertiary care center.

In our study, when serum calcium levels exceeded 11.4 mg/dL, the PPV reached 100% across all four imaging modalities. Additionally, an iPTH level greater than 134 ng/L was identified as a predictive factor for increased lesion localization success using USG and/or sestamibi scintigraphy. Low serum 25-hydroxyvitamin D (25OHD) levels are commonly observed in PHPT and have been associated with a more severe biochemical phenotype, including higher iPTH levels and larger adenoma size (18). However, in our study, serum 25OHD levels were not significantly associated with preoperative lesion localization success. This finding is consistent with previous reports, including the study by Tassone et al., which showed that vitamin D deficiency did not influence the likelihood of positive imaging localization in patients with PHPT (19). Taken together, these data suggest that although vitamin D status can reflect disease severity, it does not appear to independently

affect the performance of preoperative imaging modalities.

The diagnostic performance of USG is highly dependent on the operator's experience. Detection of small adenomas, retropharyngeal or retroesophageal glands, and ectopic mediastinal parathyroid glands can be particularly challenging with USG (20). In a study by Balci et al., the sensitivity of USG for detecting a single adenoma was 89.7%, whereas the PPV for right and left lateralization and quadrant localization was 83.6% and 80.9%, respectively (13). Compared with USG, scintigraphy is less operator-dependent and is more useful for lateralization than for precise quadrant localization (20). For the localization of hyperfunctioning parathyroid glands, 4D-CT has shown higher sensitivity, specificity, and accuracy for lateralization compared with quadrant localization (12). In a study of 44 patients with PHPT evaluating the role of 4D-CT in lesion localization, sensitivity was as 93%, and 4D-CT was particularly useful in detecting ectopic lesions. In that study, 52.1% of parathyroid lesions were located on the left, 35.4% on the right, and 12.5% were bilateral, while 76% were inferiorly located and 24% superiorly located (8). In our cohort, lesion location influenced imaging success only for USG, whereas no such association was observed for scintigraphy, 4D-CT, or PET/CT. This finding might reflect the intrinsic characteristics of USG, which is highly dependent on anatomical accessibility, cervical compartment depth, and operator expertise. Glands located in deeper or anatomically complex regions could therefore be more challenging to detect with USG. In contrast, functional and cross-sectional imaging modalities provide broader anatomical coverage and are less constrained by superficial anatomical windows, potentially reducing the effects of precise gland location on localization performance.

The coexistence of PHPT and thyroid disease has been reported in 17–84% of cases (21–26). Ryan et al. identified multinodular goiter in 50% and Hashimoto's thyroiditis in 17% of patients with PHPT (23). Thyroid nodules and lymph nodes can mimic parathyroid adenomas and reduce the sensitivity of imaging studies (4). In addition, the presence of autoimmune thyroid disease can influence scintigraphy imaging results (27). In our study, the autoimmune thyroid disease and the thyroid nodules were not associated with an increased likelihood of parathyroid lesion localization by imaging modalities. This finding might indicate that, in our cohort, coexisting thyroid disease did not substantially impair imaging performance.

Study Limitations

Our study has several limitations. First, its retrospective design might have introduced selection bias. Second, the study was conducted in a single tertiary referral center, which could limit the generalizability of the findings. Third, not all patients underwent the same advanced imaging modalities and the number of patients evaluated with 18F-fluorocholine PET/CT was relatively small. Lastly, imaging results were based on clinical reports rather than centralized image re-evaluation. Despite these limitations, the relatively large patient cohort and comprehensive evaluation of multiple imaging modalities represent strengths of our study.

CONCLUSION

Our study showed that the combined use of neck USG and Tc-99m sestamibi scintigraphy was associated with a higher likelihood of successful lesion localization in patients with hyperfunctioning parathyroid glands larger than 1 cm, serum iPTH levels exceeding 134 ng/dL, and NPHPT. In these patient subgroups, adequate lesion localization with initial imaging modalities could reduce the need for advanced imaging techniques.

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