Original Article

DOI: 10.14235/bas.galenos.2025.49092
Bezmialem Science 2025;13(2):139-47

The Role of 4D-CT in Hyperparathyroidism with Negative Scintigraphy: Identifying Causes of Diagnostic Challenges

Negatif Sintigrafi Hiperparatiroidizmde 4D-BT'nin Rolü: Tanısal Zorlukların Nedenlerinin Belirlenmesi

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ABSTRACT

Objective: The objective of this study is to evaluate the efficacy of four-dimensional computed tomography (4D-CT) in detecting parathyroid lesions not detected by scintigraphy, based on surgical findings, determine the frequency of lesions that go unnoticed or are evaluated as false positives (FP) and identify the causes thereof.

Methods: The population of this retrospective study consisted of 44 patients diagnosed as having hyperparathyroidism in our tertiary university hospital between August 2022 and January 2024, underwent scintigraphy, and had a 4D-CT scan upon negative scintigraphy results. A number of preoperative parameters, including demographic, laboratory, and clinical characteristics and imaging results of 38 patients included in the study sample, were analyzed. The patients' preoperative 4D-CT and surgical findings were compared in terms of abnormal parathyroid lesions.

Results: The mean age of the sample was 54.8±13.1 years. Twenty (52.6%) patients were asymptomatic, and 18 (47.4%) were symptomatic. 4D-CT imaging results revealed that the diagnoses of 36 (76.6%) patients were true positive (TP), 5 (10.6%) were FP, and 6 (12.8%) were false negative (FN). There were significant differences between the TP, FP, and FN groups in age, preoperative calcium levels, maximum lesion diameter, and short-to-long axis ratio of the lesion.

Conclusion: The 4D-CT demonstrates high accuracy in detecting parathyroid lesions in patients with scintigraphy-negative hyperparathyroidism. Factors such as preoperative calcium levels, age, and lesion size significantly influence diagnostic outcomes. The integration of 4D-CT into preoperative evaluation can enhance

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Amaç: Bu çalışmanın amacı, sintigrafi ile tespit edilemeyen paratiroid lezyonlarının tespit edilmesinde dört boyutlu bilgisayarlı tomografinin (4D-CT) etkinliğini değerlendirmek, cerrahi bulgulara dayanarak gözden kaçan veya yanlış pozitif (FP) olarak değerlendirilen lezyonların sıklığını belirlemek ve bunların nedenlerini tanımlamaktır.

Yöntemler: Bu retrospektif çalışmanın popülasyonu, Ağustos 2022 ile Ocak 2024 arasında üniversitemizin hastanesinde hiperparatiroidizm teşhisi konan, sintigrafiye tabi tutulan ve negatif sintigrafi sonuçları üzerine 4D-CT taraması yapılan 44 hastadan oluşuyordu. Çalışma örneğine dahil edilen 38 hastanın demografik, laboratuvar ve klinik özellikleri ile görüntüleme sonuçları dahil olmak üzere bir dizi parametre analiz edildi. Hastaların 4D-CT ve cerrahi bulguları anormal paratiroid lezyonları açısından karşılaştırıldı.

Bulgular: Örneklemin ortalama yaşı 54,8±13,1 yıldı. Yirmi (%52,6) hasta asemptomatik, 18 (%47,4) hasta semptomatikti. 4D-CT görüntüleme sonuçları, 36 (%76,6) hastanın tanısının gerçek pozitif (TP), 5 (%10,6) hastanın false positives (FP) ve 6 (%12,8) hastanın yanlış negatif (FN) olduğunu gösterdi. true positive (TP), FP ve FN grupları arasında yaş, preoperatif kalsiyum seviyeleri, maksimum lezyon çapı ve lezyonun kısa-uzun eksen oranı açısından anlamlı farklılıklar vardı. Daha küçük lezyon boyutu, daha düşük preoperatif kalsiyum seviyeleri ve ileri yaş, daha yüksek FP ve FN sonuçları ile ilişkiliydi.

Sonuç: Sintigrafi negatif hiperparatiroidizmi olan hastalarda paratiroid lezyonlarını tespit etmede 4D-CT yüksek doğruluk

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Received: 26.09.2024
Accepted: 11.01.2025
Published date: 24.04.2025

Cite this article as: Keven A, Gürbüz AF, Arslan G. The role of 4D-CT in hyperparathyroidism with negative scintigraphy: Identifying causes of diagnostic challenges. Bezmialem Science. 2025;13(2):139-47

ABSTRACT

lesion localization, improving surgical planning and management.

Keywords: Four-dimensional computed tomography, primary hyperparathyroidism, parathyroid adenoma, parathyroid hyperplasia

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göstermektedir. Preoperatif kalsiyum seviyeleri, yaş ve lezyon büyüklüğü gibi faktörler, tanısal sonuçları önemli ölçüde etkiler. Preoperatif değerlendirmeye 4D-CT'nin entegrasyonu, lezyon lokalizasyonunu geliştirerek cerrahi planlama ve yönetimi iyileştirebilir.

Anahtar Kelimeler: Dört boyutlu bilgisayarlı tomografi, primer hiperparatiroidizm, paratiroid adenomu, paratiroid hiperplazisi

Introduction

Primary hyperparathyroidism (pHPT) is a common endocrinological disorder that is often detected within the scope of routine biochemical screening (1). Women are affected two to three times more often than men, especially after menopause. The diagnosis of pHPT is made based on high serum calcium and parathyroid hormone (PTH) levels as part of routine biochemical tests in asymptomatic cases or after presenting with symptoms such as kidney stones, stomach ulcers, bone cysts, and depression (2). In approximately 85% of patients, pHPT is caused by a solitary parathyroid adenoma (2). On the other hand, the incidence of pHPT cases featuring multiglandular involvement due to multiple adenomas (4%) or diffuse hyperplasia (10%) (2) is much less, reported in the literature between 8% and 33% (3).

Parathyroidectomy (PTx) is the only curative treatment method for pHPT (1). Before surgical intervention, technetium-99m sesta-methoxy isobutylisonitrile (Tc-99m sestamibi) scintigraphy is usually performed first, followed by ultrasonography (USG) to confirm the diagnosis (4,5). The parathyroid glands are generally localized at the four ends of the thyroid gland and less frequently in the superior mediastinum. However, it may be difficult to localize the parathyroid glands, which may also be localized elsewhere. The positive predictive value (PPV) for the accurate lateral localization of a parathyroid adenoma can be as high as 97% in cases where scintigraphy and ultrasound results are compatible (6). Cervical USG performed by an experienced parathyroid sonographer is the least costly imaging modality and is the most cost-effective strategy when combined with sestamibi or four-dimensional computed tomography (4D-CT) (7).

Multiglandular diseases (MGDs) of the parathyroid are caused by hyperplasia of all parathyroid glands or sometimes by double adenomas (8). Solitary adenomas can be treated with unilateral neck exploration and excision of the adenoma. Nevertheless, bilateral neck exploration may be required in patients suspected of having MGD and in patients in whom the localization of the lesion cannot be determined on preoperative imaging since the sensitivity of imaging in detecting MGD is lower in these patients.

CT is one of the most widely used modalities, and its usefulness has been demonstrated in several recently published studies (9,10). CT provides high-quality anatomic detail regarding the localization and ectopic localizations of the parathyroid glands in the neck. 4D-CT, first introduced by Rodgers et al. (11) in 2006, has been studied extensively since then. 4D-CT has emerged as a promising method for preoperative localization and consists of multiphase CT acquired at non-contrast, contrast agent-enhanced, arterial, and delayed phases. 4D-CT refers to the addition of time as the fourth dimension to the traditional three spatial dimensions (length, width, and height) used in imaging. In the context of parathyroid adenomas, this means that 4D-CT captures images of the neck at multiple time points during the administration of contrast material. The fact that the hypervascularity of parathyroid lesions leads to rapid enhancement (detectable in the arterial phase) and contrast washout (detectable in the venous and late phases) compared to lymph nodes constitutes the primary basis for the use of 4D-CT in the detection of parathyroid lesions.

Several recent studies recommend 4D-CT for preoperative assessment of parathyroid gland localization, particularly in patients with negative or inconclusive USG and Tc-99m sestamibi results, patients undergoing reoperation for parathyroid disease, and patients with pHPT with mild hypercalcemia and MGD (12-14). 4D-CT disadvantages include exposure to radiation, cost, and need for iodinated contrast. The volume CT dose index ($CTDI_{vol}$) typically ranges between 19 and 24 mGy (32-cm phantom), and the dose length product typically ranges between 400 and 600 mGy cm per CT phase (15).

Although previous studies reported that 4D-CT has higher sensitivity than USG and scintigraphy, the reasons why 4D-CT misses some lesions are not fully clear (16-18). In this context, this study was carried out to evaluate the efficacy of 4D-CT in detecting parathyroid lesions not detected by scintigraphy based on surgical findings, determine the frequency of lesions that go unnoticed or are evaluated as false positives (FP), and identify the causes thereof.

Methods

Study Design and Setting

This study was designed as a retrospective study. The protocol of this study was approved by the Akdeniz University ethics committee (approval number: 328, date: 06.06.2024). The study was carried out in accordance with the ethical principles outlined in the revised Declaration of Helsinki adopted by the World Medical Association General Assembly in Edinburgh in 2000. Informed consent was obtained from the patients before the conduct of the study.

Population and Sample

The study population consisted of 44 patients diagnosed as having hyperparathyroidism in our tertiary university hospital between August 2022 and January 2024, underwent scintigraphy, and had a 4D-CT scan upon negative scintigraphy results. Of these patients, six patients whose surgical outcomes were not available were excluded from the study. Of the remaining 38 patients included in the study sample, 35 were followed with a diagnosis of pHPT and 3 with a diagnosis of secondary hyperparathyroidism. One of the patients with pHPT had comorbid multiple endocrine neoplasia type 1 syndrome. Nine patients had MGD.

Patients' age, gender, serum calcium and PTH levels, presence of multinodular goiter, PTx history, and histopathological findings were obtained from the hospital's archive system (MIA MED, 1.0.1.3295) (Figure 1).

Imaging Protocol

The 4D-CT examinations were performed by obtaining precontrast, postcontrast arterial and venous phase images with a 2 x 64-slice dual-energy CT scanner (Siemens Somatom Definition Edge, Erlangen, Germany). Using the bolus tracking method, the "region of interest" was placed on the single-slice reference image in the descending aorta, and the threshold contrast value was set to 180 hounsfield units (HU) to begin imaging. Then, 80-100 mL of non-ionic iodinated low osmolarity contrast medium was injected via an antecubital vein with an automatic pump at a rate of 4-5 mL/sec. Following the injection, 40 mL of physiological serum solution was administered to ensure the homogeneous distribution of the contrast medium. The timing of the imaging was adjusted using the automatic bolus tracking method.

CT angiography scan parameters were set as follows: tube voltage: 120 kV; tube current: 300-640 mA; collimation: 128×0.5 mm; pitch value: 0.5 mm; gantry rotation time: 400 msec; slice thickness: 1 mm; and reconstruction interval: 1 mm. Per our imaging protocol, the arterial phase was used with a 25-second delay, and the venous phase was used with a 60-second delay.

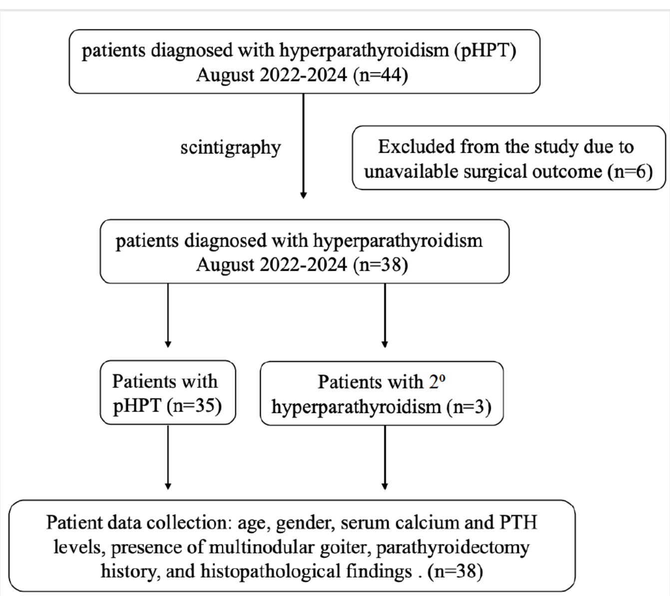

Figure 1. Flowchart

Analysis of Imaging Findings

The imaging findings of the patients available in the image archive system (Sectra Workstation IDS7; Sectra AB**,** Linköping, Sweden) were evaluated by a head and neck radiologist (A.G.A) who had 35 years of CT experience and was blinded to the clinical and pathological characteristics of the patients. The long axis of each parotid lesion was measured in millimeters using 4D-CT. The localization of the lesions, whether they were single, multiple, or ectopic, whether they had a polar vessel sign, their shape, their homogeneity, and whether they were calcified were evaluated. The densities of each parotid lesion in the precontrast, arterial, and venous phases were calculated in terms of HU (Figure 2).

The locations of all parathyroid lesions obtained with 4D-CT were classified as accurate or inaccurate by a radiologist (A.K.) with 19 years of experience by comparing the surgery notes with the radiological assessment reports. The compatibility of surgical findings with imaging findings and radiology reports in terms of exact anatomical quadrant localization of the parathyroid lesion, depth in the neck, and approximate size of the adenoma was deemed to indicate accurate localization (Figure 3). Missed-out lesions were evaluated retrospectively to identify factors limiting the initial interpretations, such as surgical extent, ectopic localization of multinodular goiter and parathyroid lesions, and multi-glandular disease. Patients with double adenomas or parathyroid hyperplasia were deemed to have MGD.

Statistical Analysis

The results of the statistical analyses were expressed using descriptive statistics, i.e., mean ± standard deviation values in the case of continuous (numerical) variables determined to conform to the normal distribution, median with minimum and maximum values in the case of continuous variables determined not to conform to the normal distribution, and numbers and percentage values in the case of categorical variables. The normal distribution characteristics of the numerical variables were analyzed using appropriate tests and visual tools such as histograms and quantile-quantile plots depending on the sample size and the characteristics of the data. Accordingly, while the Shapiro-Wilk test was preferred for small-size comparisons ($n<50$), the Kolmogorov-Smirnov and Anderson-Darling tests were used for large-size comparisons ($n\geq50$).

Kruskal-Wallis H and Mann-Whitney U tests were used to compare age, preoperative calcium and PTH levels, maximum lesion diameter, short-to-long axis ratio of the lesion, attenuation values in non-contrast CT, contrast enhancement in arterial and venous phases, and washout value between the groups.

Additionally, Pearson's chi-square test or Fisher-Freeman-Halton test were used to compare the groups in terms of variables such as gender, symptom status, specific symptoms, presence of multinodular goiter, PTx history, number of

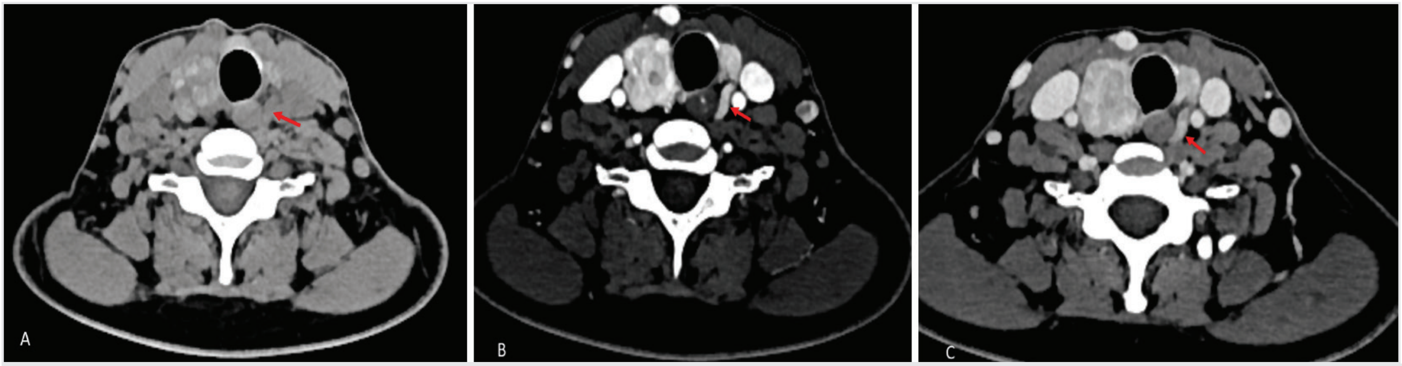

Figure 2. In a 48-year-old female patient followed up for recurrent multinodular goiter after total thyroidectomy, a 4D CT image shows a lesion located along the inferior part of the left lobe, between the ICA and the esophagus. The lesion is **A)** hypodense relative to thyroid parenchyma on pre-contrast sections, **B)** homogeneously enhances in the arterial phase, and **C)** shows washout in the venous phase, consistent with a parotid adenoma (red arrow)

ICA: Internal carotid artery, CT: Computed tomography

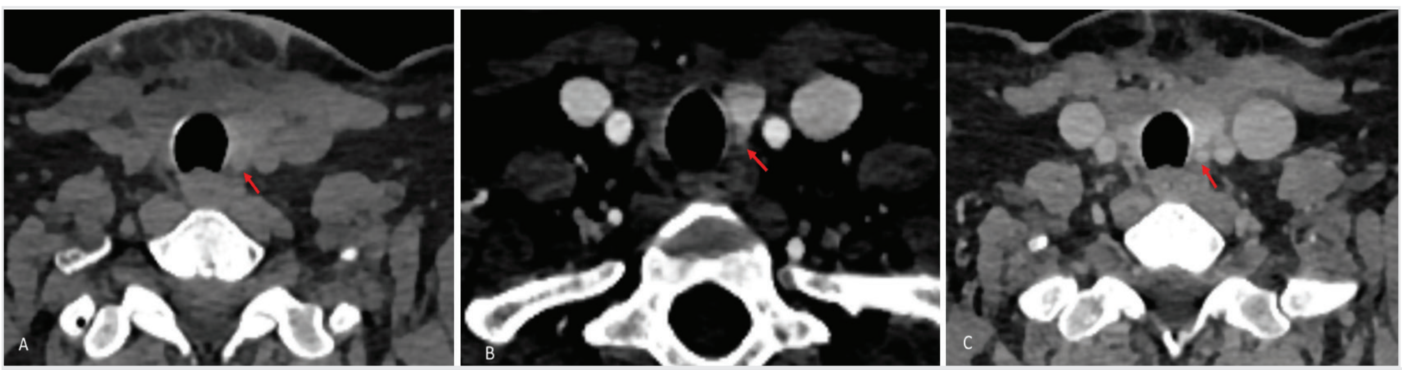

Figure 3. In a 46-year-old female patient, 4D-CT images reveal: the right lobe of the thyroid is surgically removed, and in the inferior part of the left lobe, **A)** a hypodense nodule compared to thyroid parenchyma on pre-contrast sequences, **B)** a nodule enhancing with contrast in the arterial phase, and **C)** a 6 mm nodule showing washout in the late phase (red arrow). Histopathological examination confirmed the lesion as a thyroid nodule

CT: Computed tomography

parathyroidectomies, pathology findings, localization of the lesion, presence of polar vessel sign, lesion shape, presence of calcification, and homogeneity.

Results

Patients' Characteristics

The mean age of the sample, which included 38 participants, 31 (81.6%) females and 7 (18.4%) males, was 54.8±13.1 years. Twenty (52.6%) patients were asymptomatic, and 18 (47.4%) were symptomatic. Among specific symptoms, nephrolithiasis was detected in 8 (44.4%) patients, osteoporosis/osteopenia in 6 (33.3%), chronic kidney disease in 2 (11.1%), and bone pain in 2 (11.1%). The mean preoperative calcium level of the patients was 11.0±0.6 mg/dL. The median preoperative PTH level of the patients was 91.0 pg/mL. Thirteen (34.2%) of the patients had goiter, and 4 (10.5%) had a history of PTx. Of the four patients with a history of PTx, two (50.0%) had undergone PTx once, and two (50.0%) had undergone PTx twice.

Pathology results based on 4D-CT classification indicated that three (60%) out of five FP patients had thyroid nodules, one (20%) had carotid bodies, and one (20%) had lymph nodes. On the other hand, three (50%) out of 6 false negative (FN) patients had parathyroid tissue, and the other three (50%) had parathyroid hyperplasia (Table 1).

Diagnostic Accuracy of 4D-CT

There were significant differences between the TP, FP, and FN groups in age, preoperative calcium levels, maximum lesion diameter, and short-to-long axis ratio of the lesion ($p<0.05$ for each case). On the other hand, there was a significant difference between the groups in terms of the presence of multinodular goiter ($p=0.032$).

The mean age was significantly lower in the TP group than in the FP+FN group (borderline significant, $p=0.053$). Preoperative calcium level and maximum lesion diameter were significantly higher in the TP group than in the FP + FN group ($p=0.016$ and $p=0.007$, respectively). The lesion's median short-to-long axis

Table 1. Distribution of demographic, clinical and imaging characteristics of patients who underwent parathyroid surgery by diagnostic accuracy groups

	Diagnostic accuracy groups based on 4D-CT imaging results			p-value
	TP (n=36)	FP (n=5)	FN (n=6)	
Age§	54.5 (15.0-78.0)	57.0 (45.0-70.0)	67.0 (60.0-78.0)	**0.027***
Gender‡				
Female	27 (75.0)	4 (80.0)	6 (100.0)	0.481**
Male	9 (25.0)	1 (20.0)	0 (0.0)	
Symptom status‡				
Asymptomatic	19 (52.8)	2 (40.0)	3 (50.0)	0.895**
Symptomatic	17 (47.2)	3 (60.0)	3 (50.0)	
Specific symptoms‡				
Nephrolithiasis	8 (47.1)	1 (33.3)	1 (33.3)	0.191**
Osteoporosis/osteopenia	6 (35.3)	0 (0.0)	1 (33.3)	
Chronic kidney disease	1 (5.9)	2 (66.7)	0 (0.0)	
Bone pain	2 (11.8)	0 (0.0)	1 (33.3)	
Preoperative calcium level (mg/dL §	11.1 (10.0-12.0)	10.5 (9.0-10.7)	10.9 (10.7-11.5)	**0.006***
Preoperative PTH level (pg/mL)§	95.5 (32.0-2933.0)	84.0 (62.0-2933.0)	69.0 (32.0-98.0)	0.101*
Presence of multinodular goiter, yes‡	11 (30.6)[a]	1 (20.0)[a]	5 (83.3)[b]	**0.032****
History of parathyroidectomy, yes‡	3 (8.3)	2 (40.0)	0 (0.0)	0.131**
Number of parathyroidectomies (%)‡				
1	1 (33.3)	1 (50.0)	0 (0.0)	0.999**
2	2 (66.7)	1 (50.0)	0 (0.0)	
Pathology findings‡				
Parathyroid tissue	12 (33.3)[a]	0 (0.0)[a]	3 (50.0)[a]	
Adenoma	18 (50.0)[a]	0 (0.0)[b]	0 (0.0)[a]	
Parathyroid hyperplasia	6 (16.7)[a]	0 (0.0)[a]	3 (50.0)[a]	
Thyroid nodule	0 (0.0)[a]	3 (60.0)[b]	0 (0.0)[a]	
Lymph node	0 (0.0)[a]	1 (20.0)[b]	0 (0.0)[a,b]	
Carotid body	0 (0.0)[a]	1 (20.0)[b]	0 (0.0)[a,b]	
Maximum lesion diameter (mm)§	11.8 (4.6-24.0)	4.9 (3.0-24.0)	6.5 (4.3-12.0)	**0.022***
Localization of the lesion‡				
Right upper	2 (5.6)	0 (0.0)	1 (20.0)	0.070**
Right lower	17 (47.2)	1 (20.0)	1 (20.0)	
Left upper	1 (2.8)	1 (20.0)	2 (40.0)	
Left lower	14 (38.9)	2 (40.0)	1 (20.0)	
Ectopic	2 (5.6)	1 (20.0)	0 (0.0)	
Presence of polar vessel sign, yes‡	14 (38.9)	3 (60.0)	2 (33.3)	0.769**
Lesion shape‡				
Oval	31 (86.1)[a]	2 (40.0)[b]	6 (100.0)[a]	**0.045****
Round	5 (13.9)[a]	3 (60.0)[b]	0 (0.0)[a]	
Short-to-long axis ratio of the lesion§	0.4 (0.1-0.9)	0.7 (0.4-0.7)	0.4 (0.4-0.6)	**0.050***
Presence of calcification, yes‡	2 (5.6)	0 (0.0)	0 (0.0)	0.999**
Homogeneity‡				
Homogeneous	23 (63.9)	5 (100.0)	3 (75.0)	0.303**
Heterogeneous	13 (36.1)	0 (0.0)	1 (25.0)	
Non-contrast CT attenuation values (HU)§	52.5 (25.0-138.0)	62.0 (31.0-76.0)	48.0 (42.0-58.0)	0.910*
Attenuation values in the arterial phase (HU)§	236.5 (70.0-649.0)	236.0 (112.0-599.0)	199.0 (116.0-484.0)	0.793*
Attenuation values in the venous phase (HU)§	121.0 (10.0-258.0)	136.0 (109.0-151.0)	136.5 (111.0-242.0)	0.666*
Washout value§	44.0 (-25.0-85.0)	40.0 (-21.0-74.0)	39.5 (-25.0- 50.0)	0.557*

‡: n (%), §: Median (minimum-maximum), *: Kruskal-Wallis H test, **: Pearson's chi-square test or Fisher-Freeman-Halton test, FP: False positives, TP: True positive, FN: False negative, CT: Computed tomography, HU: Hounsfield units

ratio was significantly lower in the TP group than in the FP + FN group (p=0.044).

There was no significant difference between the groups in terms of gender, symptom status, specific symptoms (nephrolithiasis, osteoporosis/osteopenia, chronic kidney disease, bone pain), preoperative PTH level, presence of multinodular goiter, PTx history, number of parathyroidectomies, pathology findings, localization of the lesion, presence of polar vessel sign, lesion shape, presence of calcification, homogeneity, non-contrast CT attenuation values, attenuation values in the arterial and venous phases and washout value (p>0.05 for each case) (Table 2).

Discussion

We conducted this study to evaluate the efficacy of 4D-CT in localizing parathyroid lesions that went unnoticed by scintigraphy in patients with pHPT. Our findings showed that 4D-CT was highly accurate in detecting lesions not detected by scintigraphy and revealed the impact of specific clinical parameters on diagnostic accuracy.

In a meta-analysis of the diagnostic accuracy of 4D-CT in localizing pathological parathyroid glands in patients with hyperparathyroidism, Kluijfhout et al. (16) reported that CT accurately determined the quadrant in which the pathological parathyroid gland was localized with an overall pooled sensitivity of 73%, which increased to 81% with lateralization, and a PPV of 81%. Along these lines, Kairemo et al. (19) reported that 4D-CT had higher sensitivity than USG and parathyroid dual-phase scintigraphy in patients with pHPT. On the other hand, Siraj et al. (20) emphasized that thallium-201 parathyroid scintigraphy might play an additional diagnostic role in patients with negative scintigraphy results. We also found the TP rate of 4D-CT (76.6%) to be high, which was in line with the literature findings (16,19).

The 4D-CT is becoming increasingly popular due to its fast acquisition time, anatomical detail, and sensitivity compared to scintigraphy and/or USG. As demonstrated by the findings of our study, the performance of 4D-CT is even more evident in complex cases where conventional imaging yields negative or inconclusive results or cases requiring reoperation. In a study evaluating the efficacy of 4D-CT in patients in whom one or both single photon emission CT (SPECT)/CT and USG gave negative results, Yanar et al. (21) reported a pathological gland localization rate of 73.7%, sensitivity of 82.4% [95% confidence interval (CI): 60.4-95.3%], PPV of 93.3% (95% CI: 73.8-99.6%), and accuracy of 78.9%. In a study conducted with 100 patients over 50 years of age who underwent PTx for pHPT and whose sestamibi SPECT scintigraphy and USG results were incompatible, Tian et al. (22) found that the sensitivity of 4D-CT (72.9%) was higher than that of sestamibi SPECT scintigraphy (48.3%) and USG (52.3%).

In parallel, our findings revealed the efficacy of 4D-CT in the localization of parathyroid lesions and its capacity to accurately detect lesions that went unnoticed by scintigraphy and thus demonstrated that it could play an important role in surgical planning and management. The findings of our study also showed that factors such as preoperative calcium levels, age, and lesion size significantly affected the risk of misdiagnosis and, therefore 4D-CT might result in higher FP and FN rates in normocalcemic hyperparathyroid cases or patients with low baseline PTH levels. Lower baseline PTH levels and higher rates of MGD are associated with lower localization rates on preoperative imaging and increased rates of failed minimally invasive PTx (23). In another study, Al-Difaie et al. (24) found that 4D-CT had high lesion-based sensitivity in patients with pHPT and low baseline PTH levels but that the success rate of image-guided resection was relatively low in patients with low baseline PTH levels. Low baseline PTH levels have also been associated with lower diagnostic accuracy of methods such as scintigraphy and USG (25,26). In this context, in addition to demonstrating the efficacy of 4D-CT in the scintigraphy-negative patient population, our study demonstrates the importance of increased attention during 4D-CT examination and surgical planning in patients with low baseline PTH levels. The fact that low PTH values are associated with the presence of MGD and the small size of parotid lesions in the literature reveals the importance of considering these factors in the radiological evaluation of cases with low PTH values.

Although it is known that the presence of thyroid nodules limits the efficacy of USG, it did not affect the localization of parathyroid adenoma by 4D-CT in our study. However, when FP patients were evaluated retrospectively, thyroid nodules were the leading cause of incompatibility between 4D-CT and surgical findings, even though our sample size was small. As a matter of fact, in a study including 411 patients in which the diagnostic efficacy of 4D-CT was evaluated, Sho et al. (27) found discordance between 4D-CT results and surgical findings in 123 (29.9%) patients and found that the presence of multinodular goiter/thyroid nodules was associated with discordance between 4D-CT results and pathology findings. They also found that MGD, a parathyroid lesion size of 10 mm or less, and an inferiorly positioned parathyroid lesion were associated with discordance between preoperative parathyroid 4D-CT results and intraoperative findings.

MGDs was the most common source of error in 4D-CT localization studies overall, suggesting that the reported relative superiority of 4D-CT over USG and sestamibi SPECT in detecting the MGD is only modest. Although 4D-CT is the least operator-dependent modality compared to USG or sestamibi SPECT, detecting MGD with 4D-CT remains a significant challenge, as with other localization techniques. In this regard, considering that the surgeons must be aware of the significant limitations of 4D-CT in surgical planning concerning patients with MGD, routine use of a risk-scoring system based on biochemical factors for detecting MGD may improve preoperative identification of these patients.

Both morphologically and on pre-contrast images, lymph nodes can mimic parathyroid lesions due to their similar hypodense appearance relative to the thyroid gland. However, on contrast-enhanced images, lymph nodes exhibit a progressive increase in

Table 2. Pairwise comparisons of demographic, clinical and imaging characteristics of patients who underwent parathyroid surgery between true and false diagnosis groups

	True and false diagnosis groups based on 4D-CT imaging results		p-value
	TP (n=36)	FP + FN (n=11)	
Age[§]	54.5 (15.0-78.0)	60.0 (45.0-78.0)	0.053*
Gender[‡]			
Female	27 (75.0)	10 (90.9)	0.413**
Male	9 (25.0)	1 (9.1)	
Symptom status[‡]			
Asymptomatic	19 (52.8)	5 (45.5)	0.936**
Symptomatic	17 (47.2)	6 (54.5)	
Specific symptoms[‡]			
Nephrolithiasis	8 (47.1)	2 (33.3)	0.399**
Osteoporosis/osteopenia	6 (35.3)	1 (16.7)	
Chronic kidney disease	1 (5.9)	2 (33.3)	
Bone pain	2 (11.8)	1 (16.7)	
Preoperative calcium level (mg/dL)[§]	11.1 (10.0-12.0)	10.7 (9.0-11.5)	**0.016***
Preoperative PTH level (pg/mL)[§]	95.5 (32.0-2933.0)	76.0 (32.0-2933.0)	0.175*
Presence of multinodular goiter, yes[‡]	11 (30.6)	6 (54.5)	0.171**
History of parathyroidectomy, yes[‡]	3 (8.3)	2 (18.2)	0.578**
Number of parathyroidectomies[‡]			
1	1 (33.3)	1 (50.0)	0.999**
2	2 (66.7)	1 (50.0)	
Pathology findings[‡]			
Parathyroid tissue	12 (33.3)[a]	3 (27.3)[a]	
Adenoma	18 (50.0)[a]	0 (0.0)[b]	
Parathyroid hyperplasia	6 (16.7)[a]	3 (27.3)[a]	
Thyroid nodule	0 (0.0)[a]	3 (27.3)[b]	
Lymph node	0 (0.0)[a]	1 (9.1)[a]	
Carotid body	0 (0.0)[a]	1 (9.1)[a]	
Maximum lesion diameter (mm)[§]	11.8 (4.6-24.0)	5.7 (3.0-24.0)	**0.007***
Localization of the lesion[‡]			
Right Upper	2 (5.6)	1 (10.0)	0.053**
Right Lower	17 (47.2)	2 (20.0)	
Left Upper	1 (2.8)	3 (30.0)	
Left Lower	14 (38.9)	3 (30.0)	
Ectopic	2 (5.6)	1 (10.0)	
Presence of polar vessel sign, yes[‡]	14 (38.9)	5 (45.5)	0.737**
Lesion shape[‡]			
Oval	31 (86.1)	8 (72.7)	0.367**
Round	5 (13.9)	3 (27.3)	
Short-to-long axis ratio of the lesion[§]	0.4 (0.1-0.9)	0.5 (0.4-0.7)	**0.044***
Presence of calcification, yes[‡]	2 (5.6)	0 (0.0)	0.999**
Homogeneity[‡]			
Homogeneous	23 (63.9)	8 (88.9)	0.236**
Heterogeneous	13 (36.1)	1 (11.1)	
Non-contrast CT attenuation values (HU)[§]	52.5 (25.0-138.0)	49.0 (31.0-76.0)	0.921*
Attenuation values in the arterial phase (HU)[§]	236.5 (70.0-649.0)	221.0 (112.0-599.0)	0.523*
Attenuation values in the venous phase (HU)[§]	121.0 (10.0-258.0)	136.0 (109.0-242.0)	0.460*
Washout value[§]	44.0 (-25.0-85.0)	40.0 (-25.0-74.0)	0.364*

‡: n (%), §: Median (minimum-maximum), *: Mann-Whitney U test, **: Pearson's chi-square test or Fisher-Freeman-Halton test, a,b: Different superscripts indicate statistical differences between groups in each row. There is no statistical difference between groups with the same superscripts, HU: Hounsfield units

enhancement, particularly in the venous phase, which is atypical for parathyroid lesions. Our study, along with the literature, suggests that millimeter-sized carotid body tumors and lymph nodes with atypical enhancement patterns can be misdiagnosed as parathyroid glands. Nonetheless, there is a paucity of literature specifically examining the FP rate of 4D CT for these two lesions.

The findings of this study, together with the relevant findings in the literature, suggest that future research should focus on technical and methodological improvements to increase the efficacy of 4D-CT. In this context, combining new-generation imaging methods, especially fluorocholine positron emission tomography-CT (FCH-PET/CT) with 4D-CT, can potentially increase diagnostic accuracy and reduce FP and FN rates (28). In fact, the study by Stanciu et al. (29) showed that SPECT/CT was superior to scintigraphy and could accurately localize parathyroid adenoma, indicating the future potential of combined imaging methods.

Study Limitations

This study has several important limitations. First, its retrospective design might have introduced certain biases compared to prospective studies, which might limit the validity of the data obtained. Additionally, our small sample size might have negatively affected the accuracy and reliability of our findings compared to studies with larger sample groups.

Secondly, given that it is a costly imaging modality and exposes patients to radiation, 4D-CT may not be routinely used in every patient, which may limit its widespread clinical use. The literature has raised valid concerns regarding patient radiation exposure with a three-phase protocol. However, the small attributable risk in the typical middle-aged patient with PHPT is outweighed by the benefits of increased diagnostic accuracy.

Thirdly, the fact that 4D-CT yields FN or FP results in some patients has led us to question its reliability. FN results may lead to difficulties in detecting small or ectopic lesions in particular, whereas FP results may lead to unnecessary surgical interventions. Therefore, using 4D-CT in combination with other imaging modalities should be considered, as it may help increase diagnostic accuracy.

Conclusion

In conclusion, our study revealed that 4D-CT had high diagnostic accuracy in diagnosing scintigraphy-negative hyperparathyroidism and could effectively detect lesions that could not be detected by scintigraphy. Our findings indicated that 4D-CT had a high TP rate and low FP and FN rates. In addition, factors such as preoperative calcium levels, age, and small lesion size were found to significantly affect the risk of misdiagnosis.

Ethics

Ethics Committee Approval: This study was designed as a retrospective study. The protocol of this study was approved by the Akdeniz University ethics committee (approval number: 328, date: 06.06.2024).

Informed Consent: Informed consent was obtained from the patients before the conduct of the study.

Footnotes

Authorship Contributions

Concept: A.K., G.A., Design: A.K., A.F.G., Data Collection or Processing: A.K., A.F.G., G.A., Analysis or Interpretation: A.K., A.F.G., G.A., Literature Search: A.K., A.F.G., G.A., Writing: A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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