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Incremental Value of Multimodality Imaging for Preoperative Localization in Primary Hyperparathyroidism: A Stepwise Strategy for Focused Parathyroidectomy

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Abstract

Objective: Accurate preoperative localization of the affected parathyroid gland is important for focused parathyroidectomy in primary hyperparathyroidism, yet no single imaging modality is uniformly reliable. This study evaluated the incremental localization benefit of combining ultrasonography (US), ^{99m}Tc-sestamibi scintigraphy (MIBI), and four-dimensional computed tomography (4D-CT) and assessed agreement between imaging-measured and histopathological adenoma size.

Methods: This retrospective, single-center study included 118 patients with histopathologically confirmed parathyroid adenoma who underwent parathyroidectomy between 2015 and 2025. Imaging-based localization was compared with the surgically confirmed location of the adenoma. Sensitivity, positive predictive value, and incremental localization accuracy were calculated. Size agreement was assessed using Bland-Altman analysis, and US sensitivity was examined according to gland location.

Results: Site-level sensitivity was 71.8% for US, 72.8% for MIBI, 66.7% for CT, and 60.0% for 4D-CT, with no significant pairwise differences (all p>0.05). Adding MIBI to US significantly increased localization accuracy from 71.7% to 84.1% (n=113, McNemar p<0.001); adding 4D-CT to US+MIBI further raised accuracy from 73.5% to 79.4% in a smaller cohort (n=34), though this increment was not statistically significant (p=0.50). US sensitivity fell sharply with anatomical difficulty, from 80.9% for inferior glands to 61.1% for superior and 16.7% for ectopic glands. US also systematically underestimated adenoma size, particularly for larger lesions (bias -10.8 mm; 95% limits of agreement -50.1 to 28.5 mm).

Conclusion: Combining US with MIBI improved localization accuracy. The addition of 4D-CT yielded a further, statistically non-significant increase in the smaller cohort studied. These findings support a stepwise approach to preoperative imaging for focused parathyroidectomy.

Keywords: Hyperparathyroidism, parathyroid neoplasms, ultrasonography, technetium tc 99m sestamibi, four-dimensional computed tomography, parathyroidectomy

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Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder caused, in the great majority of cases, by a single hyperfunctioning parathyroid adenoma (1,2). Surgery remains the only curative treatment, and the shift from bilateral neck exploration toward minimally invasive parathyroidectomy (MIP) has made accurate preoperative localization a prerequisite for successful, low-morbidity surgery rather than an optional adjunct (3,4). When localization fails or is discordant, surgeons are left to choose between an unguided bilateral exploration and a targeted approach built on imperfect information, and either choice carries real consequences for operative time, gland preservation, and complication risk, particularly in patients with ectopic glands, coexisting thyroid pathology, or prior neck surgery.

PHPT is now most often diagnosed incidentally on routine biochemical screening rather than through overt symptoms of hypercalcemia, and this shift has increased the proportion of patients presenting with smaller, more subtle adenomas that are inherently harder to localize (1). As MIP has become the default surgical approach for these patients, the practical burden of imaging has shifted from simply confirming the diagnosis to reliably guiding a focused operative plan, so that any gain in localization accuracy translates directly into fewer converted or extended explorations. The purpose of preoperative imaging in this setting is therefore not to diagnose PHPT, which is already established biochemically before any scan is ordered, but to facilitate focused, minimally invasive surgery by telling the surgeon precisely where to look.

Ultrasonography (US) and ^{99m}Tc-sestamibi scintigraphy (MIBI) are the two most widely used first-line modalities, and four-dimensional computed tomography (4D-CT) has increasingly been adopted as a problem-solving tool when first-line imaging is negative or inconclusive. Reported diagnostic performance, however, varies markedly between series, and much of this variability appears to reflect differences in operator experience, patient selection, and how "correct localization" is defined rather than a genuine, reproducible superiority of one modality. Individual series and meta-analyses disagree on which modality performs better, with reported US sensitivities ranging as low as 76% (5-7). This inconsistency suggests that the clinically relevant question may not be which single modality is superior, but whether combining modalities changes management-relevant accuracy in a way that individual head-to-head comparisons cannot capture.

4D-CT, introduced in 2006 (8), has been proposed as an alternative to routine scintigraphy (9), with pooled per-patient sensitivity of 75-81% (10). Because 4D-CT is typically reserved for cases with negative or discordant first-line imaging, however, its reported performance is difficult to interpret in isolation and is likely affected by the selection of an inherently harder subgroup of patients; its added radiation exposure and cost further argue for a selective rather than routine role. Evidence on agreement between imaging-measured and true histopathological adenoma size is similarly limited and conflicting, ranging from strong correlation (11) to essentially none (12), raising the question of whether imaging-based size estimates can be trusted for surgical planning.

Our own center previously reported clinical and surgical outcomes in a related cohort of 112 patients, including single-modality sensitivities for US, MIBI, and computed tomography (CT), but did not evaluate 4D-CT, combined-modality performance, or size agreement (13). We hypothesized that the sequential addition of imaging modalities would improve localization accuracy beyond what any single test could achieve, and that this incremental benefit, rather than head-to-head superiority of one modality, is the more clinically actionable question for surgical planning. The present study was designed to determine whether integrating commonly used imaging modalities provides incremental localization benefit over single-modality imaging in patients undergoing surgery for PHPT, and to characterize the agreement between imaging-based and histopathological adenoma size measurements.

Methods

Study Design and Setting

This retrospective single-center study was conducted at the Department of Otorhinolaryngology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye. All patients who underwent parathyroidectomy for PHPT between January 1, 2015 and December 31, 2025 were identified through the institutional electronic medical record system. Although our institution has previously reported the clinical outcomes of parathyroid surgery in a broader PHPT cohort (13), the present study was designed to address a distinct research question focusing on the incremental value of multimodality imaging for preoperative localization and included only patients with histopathologically confirmed parathyroid adenoma. The study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval date: June 1, 2026; decision no. 2026/20-46). Given the retrospective study design, the requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki.

Patients and Eligibility

Inclusion criteria were: (i) parathyroidectomy for PHPT performed at the study center within the defined period; (ii) at least one preoperative localization study (US, MIBI,

and/or 4D-CT); and (iii) histopathological confirmation of parathyroid adenoma. Patients with a final histopathological diagnosis other than adenoma (hyperplasia, carcinoma, atypical neoplasia, reactive lymph node) or with missing pathology data were excluded, since the study question specifically concerns localization of solitary adenomas rather than multigland or malignant disease, which follow different surgical algorithms. Of 132 patients initially identified, 14 were excluded (9 hyperplasia, 2 carcinoma, 1 atypical parathyroid neoplasia, 1 reactive lymph node, 1 indeterminate pathology), leaving 118 patients with histopathologically confirmed adenoma for analysis. The patient selection process is summarized in Figure 1.

Data Collection

Demographic data (age, sex, and year of surgery), preoperative biochemical parameters [serum parathyroid hormone (PTH) and calcium levels], imaging findings for each modality, intraoperative findings (location of the excised gland and whether autotransplantation was performed), and histopathological findings (diagnosis, maximum specimen dimension, and weight) were obtained from the electronic medical records through a review of surgical, radiology, and pathology reports.

Imaging Classification

Because imaging reports were recorded as free text rather than structured fields, each modality (US, MIBI, CT, 4D-CT) was coded into one of three categories: not performed (excluded from that modality's denominator), negative (no lesion identified, considered a localization failure), or positive (a lesion described). Positive findings were compared against the surgically confirmed gland at two levels of agreement: site-level (concordance of both side and quadrant/pole, the stricter and clinically more relevant definition for focused surgical planning) and side-level (concordance of side only, a more lenient definition comparable to some prior reports). Reported dimensions, expressed in mixed units and decimal notations, were converted to a single maximal diameter in millimeters for each lesion; when more than one dimension or lesion was recorded, the largest reported value was used.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median [interquartile range (IQR)], as appropriate; categorical variables as number (%). For each modality, sensitivity, positive predictive value (PPV), and accuracy were calculated among patients who underwent that test, with Wilson 95% confidence intervals (CIs) calculated for the anatomical subgroup sensitivities of US. Pairwise and incremental comparisons between modalities used McNemar's test rather than unpaired methods, because the same patients typically underwent more than one imaging study and outcomes were therefore correlated within individual; each comparison was restricted to the paired subcohort in which both compared modalities (or modality combinations) had actually been performed, so that denominators varied across comparisons. Incremental (stepwise) accuracy was defined as the proportion of patients correctly localized by at least one modality when a second or third modality was added sequentially (US alone, then US+MIBI, then US+MIBI+4D-CT), with each increment tested against the preceding step using McNemar's test within the relevant paired subcohort. Agreement between imaging-measured and histopathological maximal diameter was assessed with Pearson and Spearman correlation coefficients and with Bland-Altman analysis (mean bias and 95% limits of agreement). A two-sided $p<0.05$ was considered statistically significant throughout, and no correction for multiple comparisons was applied given the hypothesis-generating nature of the secondary analyses. All analyses were performed in Python (pandas, SciPy, statsmodels). Given the exploratory nature of several secondary analyses and the modest size of certain subgroups, particularly the 4D-CT cohort, results are reported with exact sample sizes throughout so that readers can independently gauge the precision underlying each estimate.

Results

Patient Characteristics

Of 132 patients screened, 118 (89.4%) had histopathologically confirmed parathyroid adenoma and were included in the analysis (Figure 1). Mean age was 56.2±13.5 years, and 96 patients (81.4%) were female. Mean preoperative PTH was 232.4±233.9 pg/mL, and median excised adenoma weight was 1.2 g (IQR 0.6-2.2 g; n=102 with recorded weight). Mean histopathological maximal adenoma diameter was 27.6±19.1 mm (Table 1). Surgery dates spanned the full 2015-2025 study period.

Single-Modality Localization Performance

US was performed in 117 patients (site-level sensitivity 71.8%, PPV 78.5%), MIBI in 114 patients (sensitivity 72.8%, PPV 82.2%), CT in 63 patients (sensitivity 66.7%, PPV 79.2%), and 4D-CT in 35 patients (sensitivity 60.0%, PPV 70.0%) (Table 2). Side-level sensitivities, a more lenient definition, were correspondingly higher for all modalities (82.9-83.3% for US and MIBI). Pairwise McNemar comparisons showed no statistically significant difference between any two modalities (all $p>0.05$), with the US-versus-CT comparison approaching but not reaching significance ($p=0.077$).

Incremental Localization Accuracy

In the subcohort of 113 patients who underwent both US and MIBI, US alone correctly localized the adenoma in 71.7% of cases; adding MIBI increased accuracy to 84.1%, a statistically significant improvement (exact McNemar

p<0.001) driven by 14 patients in whom MIBI succeeded where US had failed. In the smaller subcohort of 34 patients who underwent all three modalities, accuracy rose stepwise from 58.8% with US alone to 73.5% with US+MIBI (5 net gains, exact McNemar p=0.063) and to 79.4% with US+MIBI+4D-CT (exact McNemar p=0.50 for this final increment); neither step reached statistical significance in this smaller subgroup, in contrast to the larger 113-patient cohort, reflecting both the reduced sample size available for these comparisons and the selective use of 4D-CT in more difficult cases (Table 3, Figure 2).

Agreement Between Imaging and Histopathological Size

Among 105 patients with paired US and histopathological measurements, US correlated weakly with histopathological size (Spearman rho=0.233, p=0.017; Pearson r=0.194, p=0.047). US systematically underestimated adenoma size, with a mean bias of -10.8 mm (95% limits of agreement -50.1 to 28.5 mm; paired t-test and Wilcoxon test both p<0.0001); US underestimated size in 70.5% of cases and overestimated it in 23.8%. This underestimation was most pronounced for larger adenomas: mean bias was +1.4 mm in the smallest size tertile, -7.4 mm in the middle tertile, and -31.3 mm in the largest tertile, indicating that US-based size estimates become progressively less reliable as adenomas grow larger. Agreement within a clinically tolerable margin was limited: only 45.7% of US measurements fell within ±5 mm of the histopathological value, and 65.7% fell within ±10 mm. CT (n=52) showed a similarly weak, non-significant correlation (Spearman rho=0.230, p=0.101; bias -12.0 mm), while 4D-CT

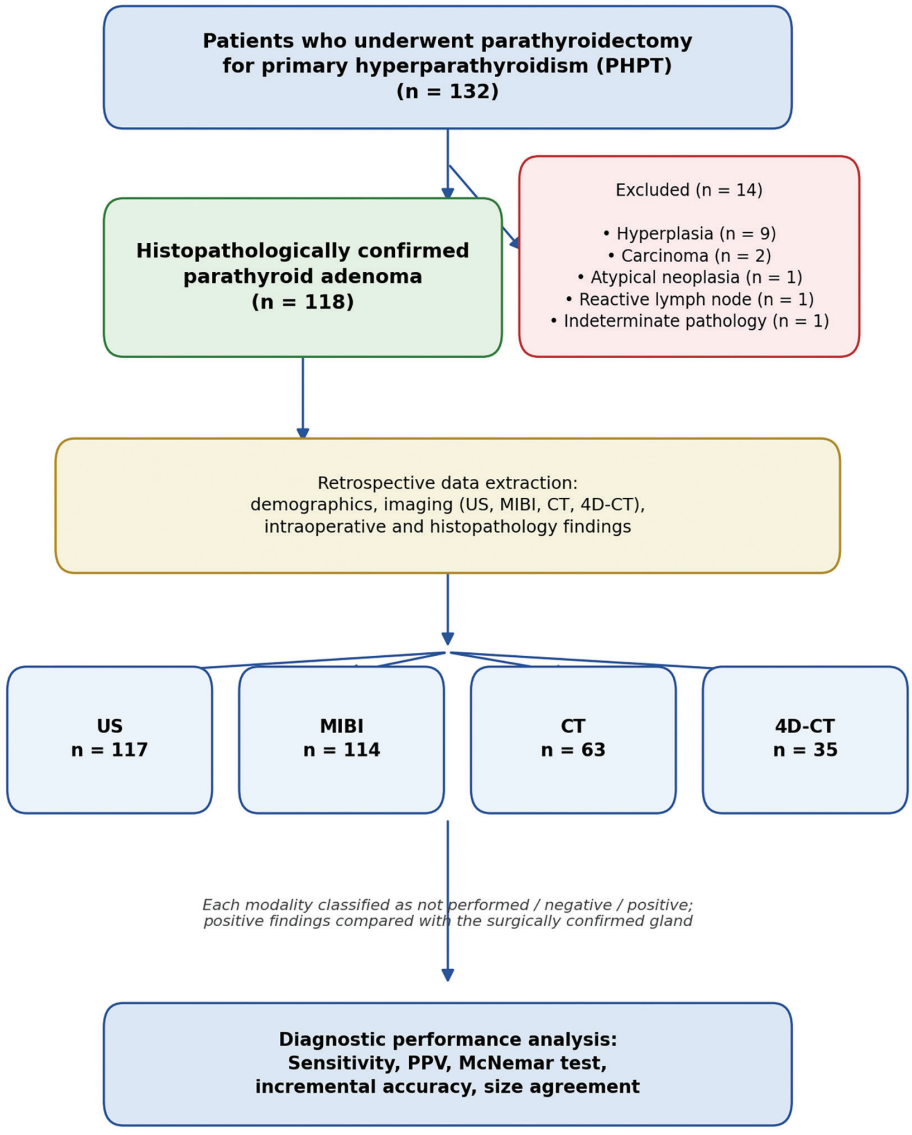

Figure 1. Patient selection flow diagram
US: Ultrasonography, MIBI: ^{99m}Tc-sestamibi scintigraphy, CT: Computed tomography, 4D-CT: Four-dimensional computed tomography, PPV: Positive predictive value

(n=31) showed a stronger correlation than either US or CT (Spearman rho=0.474, p=0.007; Pearson r=0.551, p=0.001; bias -7.2 mm), although this finding should be interpreted cautiously given the smaller, non-randomly selected 4D-CT subgroup (Table 4, Figure 3).

Modality Concordance and Anatomical Subgroup Performance

Among the 113 patients who underwent both US and MIBI, both modalities were positive in 90 (79.6%), US alone was positive in 13 (11.5%), MIBI alone was positive in 10 (8.8%),

Table 1. Patient demographic, biochemical, and histopathological characteristics (n=118)

Variable	Value
Age, years (mean ± SD)	56.2±13.5
Sex, female / male, n (%)	96 (81.4)/22 (18.6)
Preoperative PTH, pg/mL (mean ± SD)	232.4±233.9
Excised adenoma weight, g, median (IQR), (n=102)	1.2 (0.6-2.2)
Histopathological maximal diameter, mm (mean ± SD)	27.6±19.1

SD: Standard deviation, PTH: Parathyroid hormone, IQR: Interquartile range

Table 2. Single-modality diagnostic performance for adenoma localization

Modality	N tested	Negative	Positive	Correct (site-level)	Sensitivity % (site-level)	Sensitivity % (side-level)	PPV % (site-level)	PPV % (side-level)
US	117	10	107	84	71.8	82.9	78.5	90.7
MIBI	114	13	101	83	72.8	83.3	82.2	94.1
CT	63	10	53	42	66.7	79.4	79.2	94.3
4D-CT	35	5	30	21	60.0	77.1	70.0	90.0

No pairwise McNemar comparison between modalities reached statistical significance (all p>0.05); US vs. CT was closest to significance (p=0.077). US: Ultrasonography, MIBI: ^{99m}Tc-sestamibi scintigraphy, CT: Computed tomography, 4D-CT: Four-dimensional computed tomography, PPV: Positive predictive value, N: Number of patients

Table 3. Incremental (stepwise) localization accuracy

Cohort	Step	N	Accuracy %	McNemar p (vs. previous step)
A: US+MIBI performed	US alone	113	71.7	—
A: US+MIBI performed	+ MIBI	113	84.1	<0.001
B: US+MIBI+4D-CT performed	US alone	34	58.8	—
B: US+MIBI+4D-CT performed	+ MIBI	34	73.5	0.063
B: US+MIBI+4D-CT performed	+ 4D-CT	34	79.4	0.50

US: Ultrasonography, MIBI: ^{99m}Tc-sestamibi scintigraphy, 4D-CT: Four-dimensional computed tomography

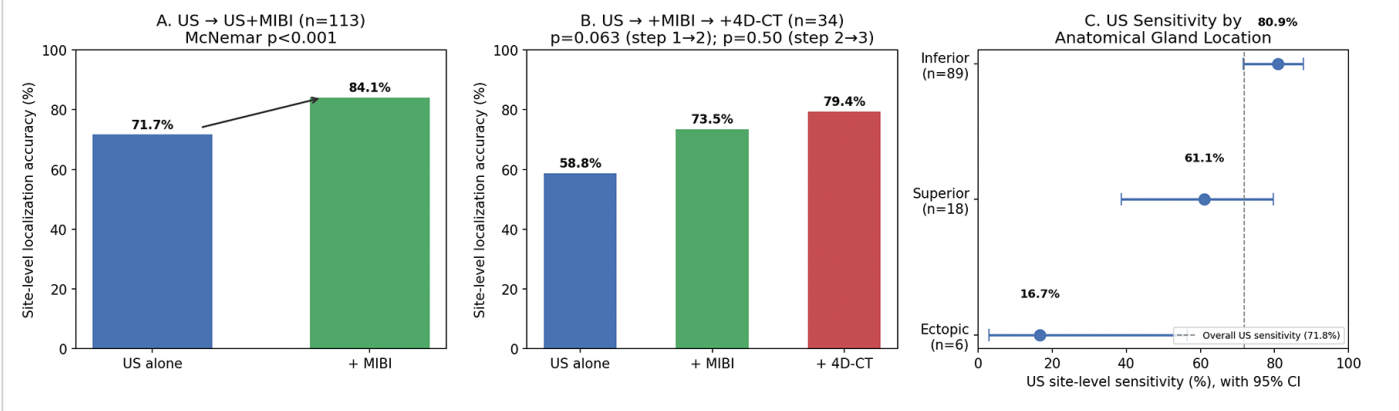

Figure 2. Incremental (stepwise) localization accuracy and anatomical determinants of US performance. (A) Addition of MIBI to US in patients who underwent both tests. (B) Sequential addition of MIBI and 4D-CT in patients who underwent all three modalities. (C) Forest plot of US site-level sensitivity by anatomical gland location, with 95% Wilson CIs; dashed line indicates overall US sensitivity
US: Ultrasonography, MIBI: ^{99m}Tc-sestamibi scintigraphy, 4D-CT: Four-dimensional computed tomography, CI: Confidence interval

Table 4. Agreement between imaging-measured and histopathological adenoma size

Modality	N	Pearson r (p)	Spearman rho (p)	Mean bias, mm	95% limits of agreement, mm
US	105	0.194 (0.047)	0.233 (0.017)	-10.8	-50.1 to 28.5
CT	52	0.161 (0.255)	0.230 (0.101)	-12.0	-53.9 to 29.9
4D-CT	31	0.551 (0.001)	0.474 (0.007)	-7.2	-32.6 to 18.3

US: Ultrasonography, CT: Computed tomography, 4D-CT: Four-dimensional computed tomography, r: Pearson correlation coefficient, rho: Spearman rank correlation coefficient

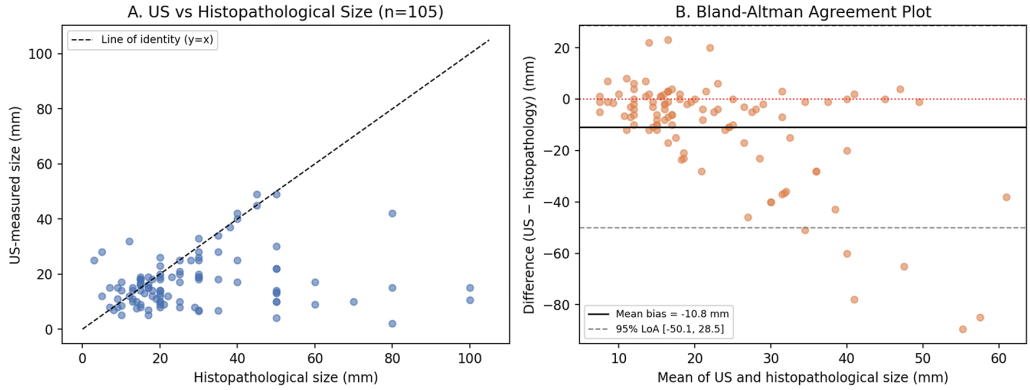

Figure 3. Agreement between US-measured and histopathological adenoma size. (A) Scatter plot with line of identity. (B) Bland-Altman plot showing mean bias and 95% limits of agreement
US: Ultrasonography, LoA: Limits of agreement

and both were negative in none, indicating that discordant single-positive findings occurred in roughly one in five patients and that a purely single-modality strategy would have missed a positive finding altogether in 8.8-11.5% of cases depending on which test was omitted. US sensitivity varied markedly by anatomical location of the pathological gland: 80.9% for inferior glands (n=89, 95% CI 71.5-87.7%), 61.1% for superior glands (n=18, 95% CI 38.6-79.7%), and only 16.7% for ectopic glands (n=6, 95% CI 3.0-56.4%) (Figure 2C). This location-based gradient was steeper than the difference between any two imaging modalities reported above, indicating that anatomical location, rather than choice of first-line test, was the strongest single determinant of US localization success in this cohort. The wide CI around the ectopic-gland estimate reflects the small number of such cases, but the point estimate and its direction were consistent with the well-established difficulty of sonographically visualizing deep, mediastinal, or retroesophageal glands.

Combined-Modality Strategies

When any two or three modalities were considered jointly (localization considered successful if at least one modality was concordant), US+MIBI achieved 83.9% accuracy (n=118), and the three-modality combination of US+MIBI+4D-CT achieved the highest overall accuracy at 85.6% (n=118), compared with 71.8-72.8% for the best-performing single modality. These combined-modality accuracies consistently exceeded single-modality sensitivities, reinforcing that sequential, rather than single, imaging is associated with materially higher localization accuracy in this cohort. Taken together, the site-level, side-level, incremental, and anatomical-subgroup analyses converge on a consistent picture: individual modalities perform comparably but incompletely, and their combination, rather than substitution of one for another, accounts for most of the achievable gain in localization accuracy.

Discussion

The principal finding of this study is that no single imaging modality was clearly superior, whereas sequential multimodality imaging provided clinically meaningful incremental localization benefit. Specifically, adding MIBI to US increased localization accuracy from 71.7% to 84.1% ($p<0.001$). In a smaller subgroup, the subsequent addition of 4D-CT increased accuracy to 79.4%, although this improvement did not reach statistical significance. The combined use of all three modalities yielded the highest overall localization accuracy (85.6%). The purpose of preoperative imaging in PHPT is not to establish the diagnosis, but to facilitate focused minimally invasive surgery. Our findings suggest that this aim may be achieved more effectively through a stepwise imaging approach rather than reliance on a single preferred modality. The combined

use of imaging modalities produced incremental gains in localization success and supports the adoption of a stepwise preoperative imaging strategy before MIP.

The sensitivities observed for the individual modalities in our cohort—71.8% for US, 72.8% for MIBI, and 66.7% for CT—were within the broad range reported in the literature, although closer to the lower limits. Meta-analyses have likewise failed to demonstrate a consistent superiority of US over MIBI or vice versa (6,7). Interestingly, the direction of superiority between these modalities has also been inconsistent across individual studies. In a series of 104 patients, US was markedly more sensitive than MIBI with single-photon emission computed tomography (SPECT), at 75% vs. 57% (14), and a separate series of 156 patients likewise found ultrasound superior to scintigraphy for predicting adenoma location (15), whereas other series have reported the opposite (5). This inconsistency indicates that there is insufficient evidence to support an institutional or individual preference for a single "best" imaging modality. From a surgical planning perspective, the more relevant question is how much additional confidence is gained by adding a second modality after the first examination. Rather than debating which single modality should be preferred, it may therefore be more useful to standardize the circumstances in which a second imaging test should be introduced.

In our cohort, that second modality was almost always MIBI. MIBI correctly localized the pathological gland in 14 patients in whom US had failed. Thus, MIBI did not merely confirm the US finding; it identified a true pathological focus that had not been demonstrated by US. This finding is consistent with the substantial increase in sensitivity reported when the two modalities are used together (11). Accordingly, when US is non-localizing, proceeding to MIBI may be more appropriate than repeating or overinterpreting the ultrasound examination.

The increase in localization success obtained by adding 4D-CT to the US and MIBI combination, from 73.5% to 79.4%, did not reach statistical significance. Moreover, the finding that 4D-CT had the lowest standalone sensitivity in our cohort (60.0%) appears at first to conflict with the 75-88% sensitivities reported in the literature (10,16). Indeed, in a recent larger meta-analysis including 23 studies and 5,845 patients, 4D-CT had a sensitivity of 81% and a specificity of 89%, with sensitivity substantially exceeding the 65% reported for sestamibi SPECT/CT (17). Nevertheless, we believe that the lower rate observed in our series reflects selection bias rather than inadequate performance of the modality itself. Only 35 of 118 patients (30%) underwent 4D-CT, most likely because the examination was reserved for more challenging cases with negative or discordant first-line imaging. In addition to selection bias, reader dependence may also explain differences in reported 4D-CT performance. In a series of 95 patients, the sensitivity of surgeon-interpreted 4D-CT was 71%, increasing to 76% when combined with radiology interpretation (18). Thus, the "true" performance of 4D-CT may depend not only on the patient population in which it is used, but also on who interprets the examination and how it is reviewed. Therefore, 4D-CT should be assessed within its role as a problem-solving modality and interpreted by experienced readers rather than being benchmarked as a routine first-line examination. Considering radiation exposure and cost, our findings support selective use of 4D-CT in patients with negative or discordant US and MIBI findings rather than its routine application (9).

The anatomical subgroup analysis revealed what we consider the most surgically applicable finding of the study. The sensitivity of US was not a fixed characteristic of the modality, but decreased progressively as the anatomical difficulty of the target gland increased: 80.9% for inferior glands, 61.1% for superior glands, and only 16.7% for ectopic glands (Figure 2C). This finding indicates that the overall sensitivity commonly reported for US is essentially a population-weighted average and may misrepresent performance at both ends of the anatomical spectrum. It may overestimate the expected success for superior or ectopic glands while underestimating the degree of confidence that may be reasonable when a typical inferior gland is clearly identified. A similar gradient of difficulty also appears to apply to adenoma size. In one study, 4D-CT achieved 100% sensitivity for adenomas smaller than 2 cm, whereas US reached only 76.2% in the same subgroup (16). This suggests that small size and atypical localization represent separate but related dimensions of difficulty that challenge the limits of US. In clinical practice, these findings imply that the need for additional imaging should not be determined solely by an institution's overall sensitivity rate, but should also take into account the suspected anatomical location and size of the adenoma. An equivocal or suspicious US finding in a superior or paratracheal location should lower the threshold for adding MIBI or 4D-CT more than a similarly uncertain finding in a typical inferior location. The near-complete failure of US in ectopic disease, with correct localization in only 1 of 6 patients, further emphasizes the importance of cross-sectional imaging in the group in whom unguided bilateral exploration may also be most challenging.

Adenoma sizes measured by both US and CT showed poor agreement with histopathological measurements, and this disagreement was not random. US systematically underestimated size, particularly in larger adenomas. Whereas no meaningful bias was observed in the smallest tertile, the mean bias reached -31.3 mm in the largest tertile. Strong correlations between US and histopathological size have been reported, but primarily in series in which US

was performed by highly experienced endocrinologists (11). In contrast, a study using contrast-enhanced US found no correlation at all (12). It has also been reported that correctly lateralized adenomas are significantly larger than those not detected by US or scintigraphy (14). This finding further highlights that larger adenomas may be easier to detect, while accurate measurement of their size remains a separate challenge. Surgeons should therefore not expect US to provide an accurate estimate of true adenoma size, particularly for larger lesions, and should instead anticipate a tendency toward underestimation.

The gap between quadrant-level (site-level) and side-level accuracy observed in our cohort has also been described at other institutions. In a series of 437 patients comparing US and 4D-CT against surgical outcome, US sensitivity for correct quadrant fell to 37.7%, well below its 55.7% sensitivity for correct side alone; 4D-CT showed the same pattern, 52.2% by quadrant versus 69.2% by side (19). Our own results move in the same direction—US site-level sensitivity of 71.8% against a side-level 82.9%—at a higher absolute level and with a smaller but directionally consistent gap. This suggests that the quadrant-versus-side distinction is not an artifact of our dataset but a structural feature of how these tests are validated, and reinforces that future studies should state explicitly which definition of "correct localization" they are reporting rather than leaving readers to assume comparability across series.

Study Limitations

This study has limitations. These include its retrospective, single-center design; the possibility of misclassification of rare anatomical descriptions because free-text imaging reports required rule-based standardization; and the relatively small, non-random subgroup of patients who underwent 4D-CT, which limited both the precision of its standalone performance estimate and the statistical power of the sequential imaging analyses. Nevertheless, the study also has important strengths. These include a 10-year cohort treated by a single surgical team, histopathological confirmation in all cases, and simultaneous evaluation of four imaging modalities within the same patient population. Unlike previous comparative studies, the present analysis did not merely compare the isolated performance of individual modalities, but quantitatively assessed the additional contribution of a sequential imaging strategy. It therefore addressed a question that is more directly relevant to surgical decision-making. Because our findings reflect the experience of a single tertiary referral center, they may not be directly generalizable to institutions with different imaging technology, operator expertise, or case mix. Prospective multicenter validation of the proposed stepwise imaging algorithm is therefore warranted.

Conclusion

Based on our findings, we propose the stepwise preoperative imaging algorithm shown in Figure 4. US should be used as the first-line modality. MIBI should be added when US is negative, discordant, or anatomically uncertain. When both first-line modalities remain negative or discordant, particularly in patients with suspected superior or ectopic glands, 4D-CT should be used selectively as a problem-solving examination. In conclusion, no single imaging modality can reliably localize all parathyroid adenomas. However, the stepwise and complementary use of US, MIBI, and selectively applied 4D-CT provides a practical framework for preoperative planning before MIP.

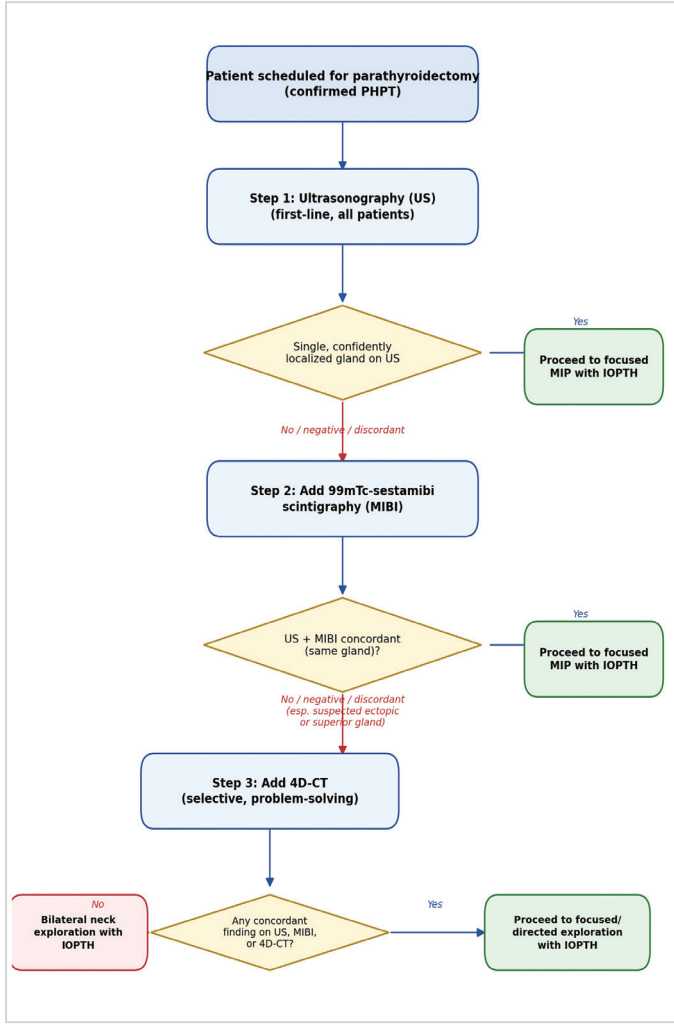

Figure 4. Proposed stepwise preoperative imaging algorithm for primary hyperparathyroidism
IOPTH: Intraoperative parathyroid hormone monitoring, MIP: Minimally invasive parathyroidectomy, PHPT: Primary hyperparathyroidism, 4D-CT: Four-dimensional computed tomography

Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval date: June 1, 2026; decision no. 2026/20-46).

Informed Consent: Given the retrospective study design, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Ö., Ö.S., A.F.B., Concept: E.Ö., N.K., Design: E.Ö., N.K., Data Collection and/or Processing: E.Ö., Ö.S., A.F.B., G.Ç.K., Ç.A., Ö.Ö.B., N.K., Analysis or Interpretation: E.Ö., Ç.A., Literature Search: E.Ö., G.Ç.K., N.K., Writing: E.Ö., Ö.S.

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Main Points

- No single imaging modality—ultrasonography, sestamibi scintigraphy, or 4D-CT—reliably localizes all parathyroid adenomas in primary hyperparathyroidism.
- Adding sestamibi scintigraphy to ultrasonography significantly increases localization accuracy (71.7% to 84.1%, $p<0.001$), demonstrating a genuine incremental rather than merely confirmatory benefit.
- Ultrasonography sensitivity is strongly dependent on anatomical gland location, ranging from 80.9% for inferior glands to only 16.7% for ectopic glands.
- Ultrasonography systematically underestimates adenoma size, particularly for larger lesions, and should not be relied upon alone for surgical planning.
- A stepwise multimodal imaging strategy—adding sestamibi scintigraphy and, selectively, 4D-CT when first-line imaging is negative or discordant—is recommended before minimally invasive parathyroidectomy.

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