Clinical value of early-phase ^{99m}Tc-MIBI SPECT in rapid washout parathyroid adenomas

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Abstract

Objective: Parathyroid adenomas with rapid tracer washout may be missed on delayed-phase technetium-99m-sestamibi (^{99m}Tc-MIBI) imaging, potentially leading to false-negative localization. This retrospective single-center study evaluated the clinical value of early-phase single photon emission computed tomography (SPECT) compared with delayed-phase SPECT in detecting rapid washout parathyroid adenomas, particularly in centers without access to SPECT/computed tomography (CT), and assessed whether this washout pattern could be predicted by biochemical parameters. **Subjects and Methods:** Eighteen patients with surgically and histopathologically confirmed parathyroid adenomas who underwent dual-phase ^{99m}Tc-MIBI SPECT imaging were included. Early-phase and delayed-phase SPECT images were independently reviewed by two experienced nuclear medicine physicians. Lesion detection rates were compared using McNemar's test, interobserver agreement was assessed using Cohen's kappa coefficient, and preoperative biochemical parameters were compared between adenomas detected only on early-phase imaging and those visible on delayed-phase imaging. **Results:** Early-phase SPECT enabled detection of all surgically confirmed adenomas, whereas delayed-phase SPECT failed to identify 8 of 18 lesions (44%) due to rapid tracer washout, with a statistically significant difference between the two phases ($P<0.01$). No significant differences were observed in preoperative biochemical parameters between rapid washout and persistent uptake groups, indicating that early washout could not be reliably predicted clinically. Despite localization being achieved using SPECT without CT correlation, postoperative parathyroid hormone levels normalized in all patients, confirming surgical success. Interobserver agreement was excellent for both imaging phases ($\kappa=1.00$). **Conclusion:** These findings indicate that early-phase ^{99m}Tc-MIBI SPECT significantly improves detection of rapid washout parathyroid adenomas and, as this pattern cannot be anticipated biochemically, its routine inclusion represents a simple and cost-effective strategy with direct relevance for routine clinical practice in centers without SPECT/CT.

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Introduction

Primary hyperparathyroidism is an endocrine disorder that usually develops due to a single parathyroid adenoma and can be cured surgically. Accurate preoperative localization of the lesion is crucial in planning minimally invasive parathyroidectomy. For this purpose, technetium-99m-sestamibi (^{99m}Tc-MIBI) parathyroid scintigraphy is the most commonly used nuclear medicine method [1].

Parathyroid scintigraphy is based on the increased uptake of ^{99m}Tc-MIBI in parathyroid tissues containing oxyphil cells rich in mitochondria. The classical method consists of dual-phase planar imaging (early and delayed phases). However, single-photon emission computed tomography (SPECT) and SPECT/computed tomography (CT) applications, which combine anatomical and functional information, have recently increased sensitivity significantly [2].

The issue of imaging timing remains controversial. Most studies report that delayed-phase SPECT/CT provides higher accuracy [3]. However, in some cases, parathyroid adenomas may rapidly lose ^{99m}Tc-MIBI uptake in the early phase; this early washout pattern leads to reduced visibility on delayed images [4]. In this case, early-phase SPECT is a potential alternative that may improve sensitivity. However, early-phase SPECT is not routinely performed in many centers, mostly due to workflow constraints. This leads to underdiagnosis of early washout adenomas, a clinically relevant but underrecognized subgroup. Also, considering that SPECT/CT is still not feasible for many centers under real-world conditions, this situation becomes an even more significant problem in clinical practice.

The aim of this study is to determine the diagnostic detection rate of parathyroid adenomas demonstrating an early washout pattern with early-phase SPECT images and to

compare the results with those of dual-phase imaging with delayed-phase SPECT. Additionally, we aimed to evaluate whether there were clinical or biochemical differences between the two groups.

Subjects and Methods

Study design and patient selection

This retrospective observational study included 18 patients who presented to our nuclear medicine clinic with suspected primary hyperparathyroidism and underwent parathyroid scintigraphy between January 2025 and October 2025.

Surgical management and postoperative outcome

All patients underwent minimally invasive parathyroidectomy based on preoperative localization findings obtained from ultrasonography and ^{99m}Tc-MIBI SPECT imaging. The surgical approach was tailored according to the exact localization of the adenoma. Surgical success was confirmed biochemically. In all patients, postoperative serum parathormone (PTH) levels returned to the normal range, indicating biochemical cure. No cases of persistent or recurrent hyperparathyroidism were observed during the early postoperative period.

The study was conducted in accordance with the principles of the Helsinki Declaration after approval from the local ethics committee (Ethics Committee No: 454 18/12/2025).

Inclusion criteria

Patients meeting the following criteria were included in the study:

1. Presence of a lesion suggestive of parathyroid adenoma on ultrasonography (US),
2. Undergoing ^{99m}Tc-MIBI parathyroid scintigraphy with available early and delayed SPECT images,
3. Histopathological confirmation of parathyroid adenoma following surgery,
4. Recorded preoperative serum calcium (Ca) and parathormone (PTH) levels.

Exclusion criteria

1. Patients diagnosed with secondary or tertiary hyperparathyroidism,
2. Cases that could not be evaluated due to significant motion artifacts during imaging,
3. Patients with concomitant thyroid nodules or malignancy that could affect ^{99m}Tc-MIBI uptake or washout were excluded.

Imaging protocol

All patients received an intravenous injection of 740 Megabecquerel (MBq) ^{99m}Tc-MIBI.

Planar imaging

Planar images were acquired using a LEHR parallel-hole collimator, 140keV±10% energy window, 256×256 matrix, and 8-10min static acquisition. Early-phase images were obtained at 20 minutes post-injection and delayed-phase images at 120 minutes.

SPECT imaging

Early and delayed phase images were acquired using a dual-detector gamma camera system (Mediso Anyscan S) with a 128×128 matrix, step-and-shoot technique, and 25 seconds per position.

Reconstruction was performed using OSEM (4 iterations, 8 subsets) with a 6–8 mm Gaussian post-filter.

Early-phase SPECT images were acquired at 20 minutes post-injection. The selection of this time point is based on both institutional optimization and physiological considerations. In ^{99m}Tc-MIBI parathyroid imaging, tracer uptake in oxyphil-rich parathyroid tissue typically peaks within the 15-25 minutes, while thyroid background activity begins to decline earlier. Therefore, acquiring the early-phase at 20 minutes maximizes lesion-to-background contrast and improves visualization of subtle early washout patterns. This timing falls within the recommended early-phase window (10-20 minutes) and aligns with our department's standardized protocol.

Image evaluation

All images were independently evaluated by two nuclear medicine specialists with at least 5 years of experience. Interobserver agreement for lesion detection (positive/negative) and washout pattern classification (persistent delayed-phase uptake vs. early washout) was assessed using Cohen's kappa coefficient (κ) to evaluate the degree of concordance between readers.

Lesions were classified as follows:

1. Parathyroid adenomas demonstrating early washout: foci with significant MIBI uptake in early-phase SPECT (20 min) but absent or markedly decreased uptake in delayed images (120min).
2. Parathyroid adenomas detected by dual-phase imaging with delayed-phase SPECT: foci with significant uptake in both early and delayed phases.

Although early-phase SPECT detected all 18 adenomas, we stratified patients into two groups based on imaging characteristics: those showing persistent uptake on delayed-phase SPECT (n=10) and those exhibiting early washout detectable only by early-phase SPECT (n=8). This grouping reflects differences in tracer kinetics rather than absolute detection capability.

Cases without agreement between readers were classified by consensus.

Data collection and statistical analysis

The following parameters were retrospectively recorded for each patient:

1. Age and sex,
2. Preoperative serum Ca (mg/dL) level,
3. Preoperative serum PTH (pg/mL) level,
4. Lesion size (mm) determined by US or surgical measurement,
5. Lesion location determined by US and SPECT imaging,
6. Imaging pattern (Parathyroid adenomas demonstrating early washout and not demonstrating early washout).

Table 1 summarizes the data for patients detected by dual-phase imaging with delayed- phase SPECT, and Table 2 summarizes the data for those with early washout detected only by early-phase SPECT.

Table 1. *Clinical and imaging characteristics of patients detected by delayed- phase SPECT.*

Sex	Age (years)	Calcium (mg/dL)	PTH (pg/mL)	Lesion size (mm)	Lesion location
Female	49	12.55	399	14×15	Left inferior
Female	61	11.37	115	10×8	Mediastinal
Male	41	9.22	764	10×10	Right inferior
Female	72	10.34	104	11×10	Right inferior
Female	33	11.20	158	3×7	Left inferior
Female	50	10.80	202	6×4	Left inferior
Female	58	10.50	59	8×8	Left inferior
Female	53	11.90	262	11×18	Right superior
Female	39	10.80	148	6×7	Right inferior
Female	51	11.00	245	7×8	Left inferior

Table 2. *Clinical and imaging characteristics of patients with early washout detected only by early-phase SPECT.*

Sex	Age (years)	Calcium (mg/dL)	PTH (pg/mL)	Lesion size (mm)	Lesion location
Female	58	10.44	84	10×14	Right superior
Female	39	10.70	93	6×9	Left inferior
Female	72	11.66	189	16×9	Left inferior
Female	45	11.40	132	12×13	Right inferior
Male	47	11.50	126	12×13	Left inferior
Female	49	11.38	190	5×6	Left inferior
Female	62	9.36	99	7×3	Left inferior
Male	71	8.64	296	4×4	Right superior

Results

Our study included 18 retrospectively evaluated cases of primary hyperparathyroidism. Patients were stratified into two groups based on tracer washout patterns: adenomas (persistent uptake on delayed-phase SPECT, n=10) and early washout adenomas (rapid loss of uptake, detectable only by early-phase SPECT, n=8). This grouping reflects differences in tracer kinetics rather than detection capability.

Continuous variables (age, preoperative serum calcium and PTH levels, lesion size) were assessed for normality using the Shapiro–Wilk test. Independent samples t-test was used for normally distributed variables and Mann–Whitney U test for non-normally distributed variables. Fisher's Exact test was used to compare the categorical variable of sex. A P value <0.05 was considered statistically significant. Analyses were performed using SPSS v.28 (IBM Corp., Armonk, NY, USA).

Results are summarized in Table 3. No statistically significant differences were observed between groups in age, preoperative serum calcium and PTH levels, or lesion size (P> 0.05). No significant difference in sex distribution was identified (Fisher's Exact test, P=0.57).

Table 4 presents the detection performance of early-phase SPECT and delayed-phase SPECT for the 18 histopathology-verified parathyroid adenoma cases.

Early-phase SPECT detected all 18 adenomas, demonstrating 100% sensitivity. In contrast, delayed-phase SPECT identified 10/18 cases, yielding a sensitivity of approximately 55.6%. The two readers demonstrated complete concordance in both lesion detection and washout pattern classification across all 18 patients. Cohen's kappa coefficient was $\kappa=1.00$, indicating perfect interobserver agreement. Although SPECT/CT was not available, lesion localization was concordant with surgical findings in all 18 cases.

To evaluate the difference in sensitivity between early-phase and delayed-phase SPECT, the McNemar test was applied. In 8 cases, early-phase SPECT was positive while delayed-phase SPECT was negative; there were no cases showing the opposite pattern (early negative, delayed positive). The McNemar test yielded a χ^2 value of 8.0, which corresponds to P≈0.005, indicating a statistically significant difference. This demonstrates that early-phase SPECT has higher sensitivity than delayed-phase SPECT in detecting parathyroid adenomas.

A power analysis using McNemar's test was performed to assess the statistical reliability of the observed difference. With the current sample size (n=18) and an observed difference of 44.4% in sensitivity, the study has an estimated power of approximately 75%-80% to detect a significant difference at a significance level of 0.05. Power analysis was conducted using G*Power version 3.1.9.7 (Heinrich Heine University Düsseldorf, Germany). This suggests that, despite the small cohort, the observed increase in detection with early-phase SPECT is statistically robust, although larger prospective studies would further strengthen these findings.

All surgically treated patients achieved biochemical cure, as evidenced by normalization of postoperative serum PTH levels.

Figures 1 and 2 show a parathyroid adenoma located in the right superior gland, which was detected only by early-phase SPECT due to early washout, was not visible on delayed SPECT images.

Figures 3 and 4 show a parathyroid adenoma located in the left inferior gland, which was detected only by early-phase SPECT due to early washout, was not visible on delayed planar or SPECT images.

Table 3. *Comparison of clinical and biochemical parameters between groups.*

Parameter	Delayed-phase SPECT (n=10)	Early washout (n=8)	P-value	Test
Age (years)	50.7±11.6	55.3±12.1	0.45	Mann-Whitney U
Calcium (mg/dL)	10.96±1.03	10.40±1.10	0.35	Mann-Whitney U
PTH (pg/mL)	243.2±206.4	155.4±74.2	0.12	Mann-Whitney U
Lesion size (mm)	9.8±4.2	9.4±4.1	0.78	Mann-Whitney U
Sex (male)	1 (10%)	2 (25%)	0.57	Fisher's Exact

Table 4. *Diagnostic performance of early-phase and delayed-phase SPECT.*

SPECT phase	Histopathology (n)	Positive	Negative	Sensitivity (%)
Early-phase	18	18	0	100
Delayed-phase	18	10	8	55.6

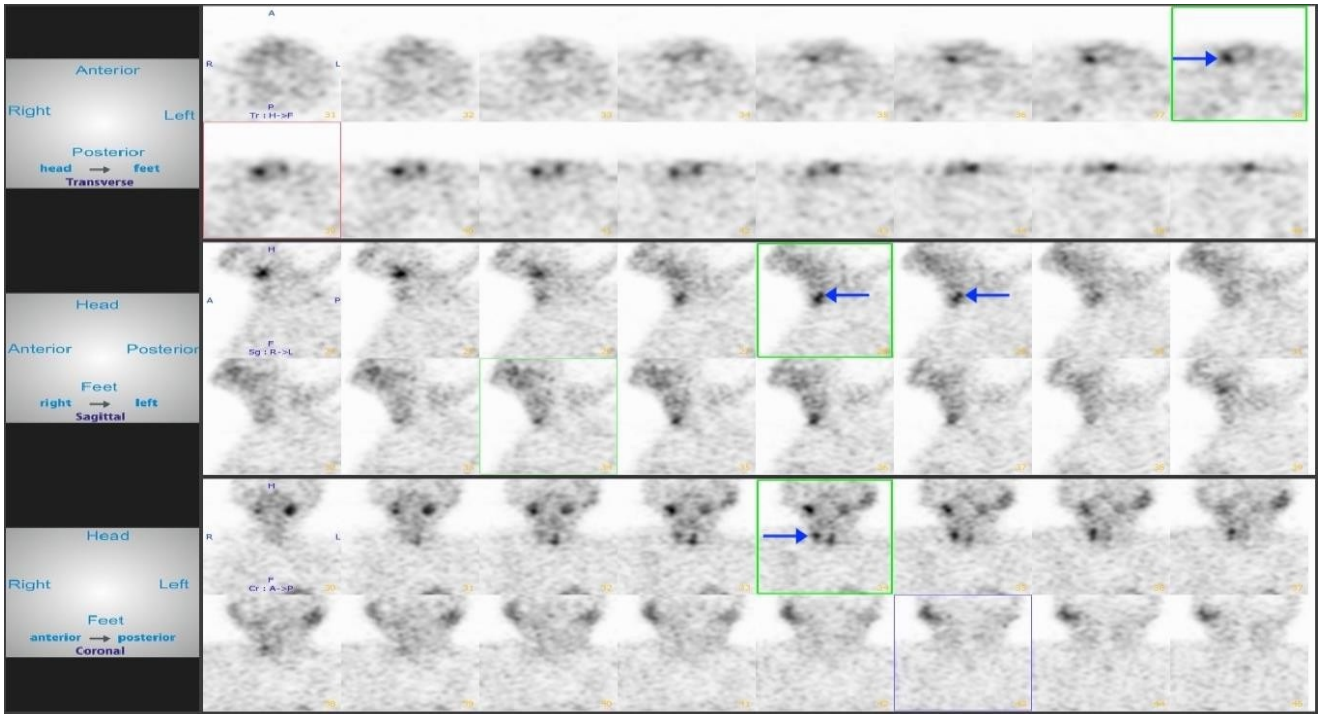

Figure 1. Early-phase SPECT showing focal ^{99m}Tc-MIBI uptake in a right superior parathyroid adenoma (arrow).

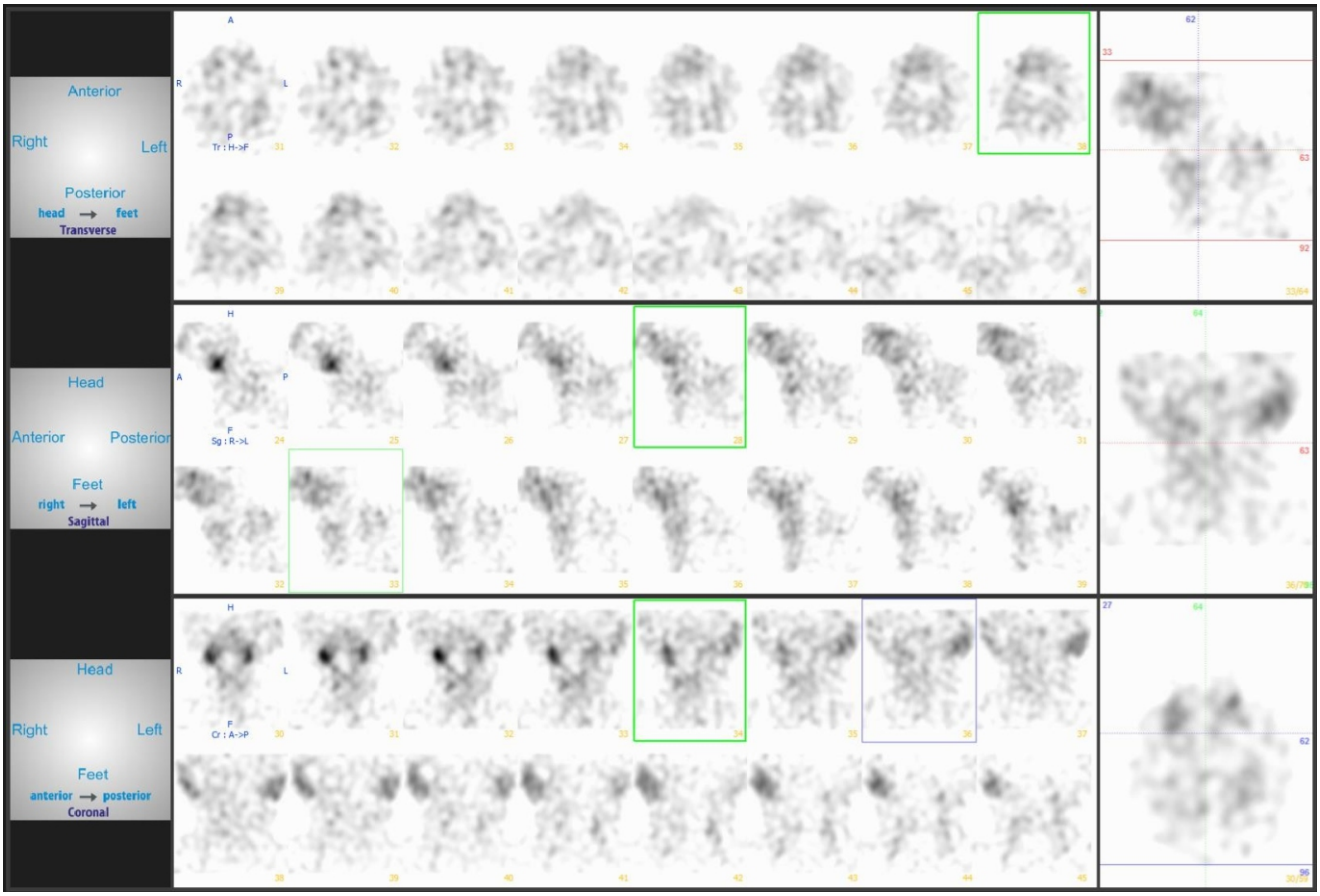

Figure 2. Delayed-phase SPECT of the same patient demonstrating complete washout with no focal uptake.

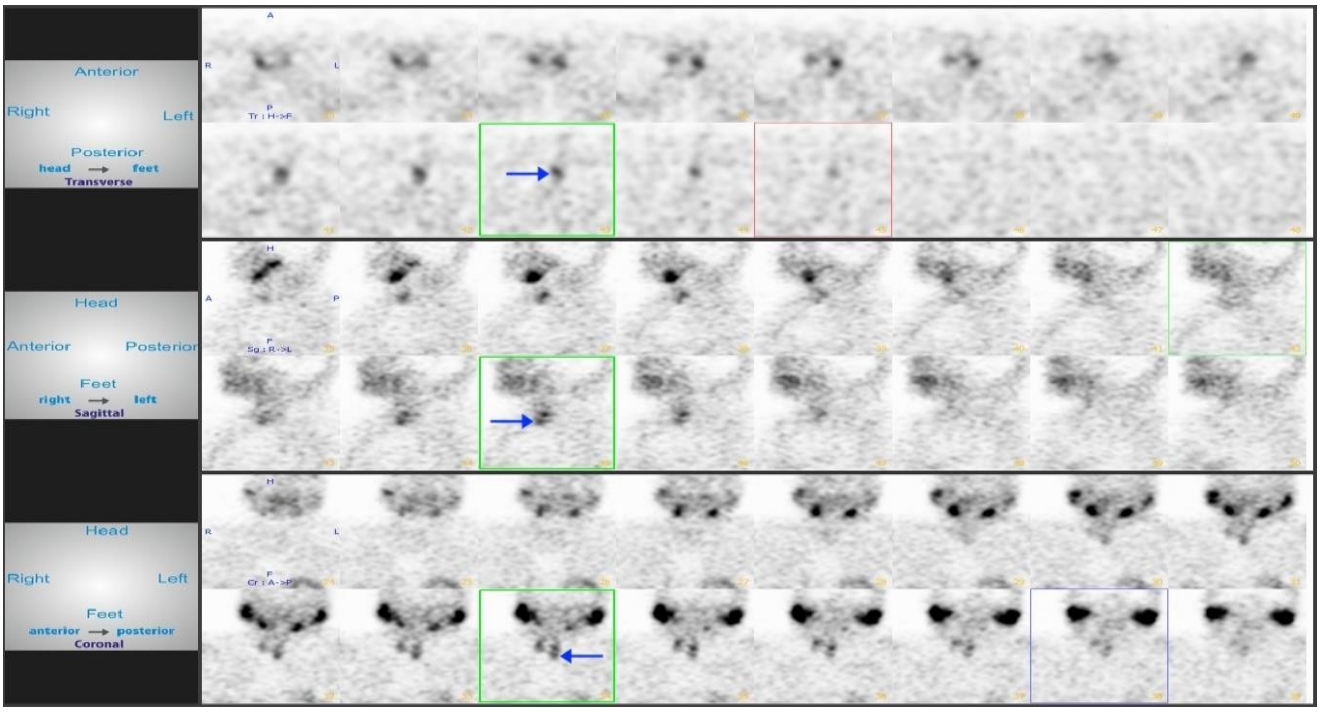

Figure 3. Early-phase SPECT showing focal ^{99m}Tc-MIBI uptake in a left inferior parathyroid adenoma (arrow).

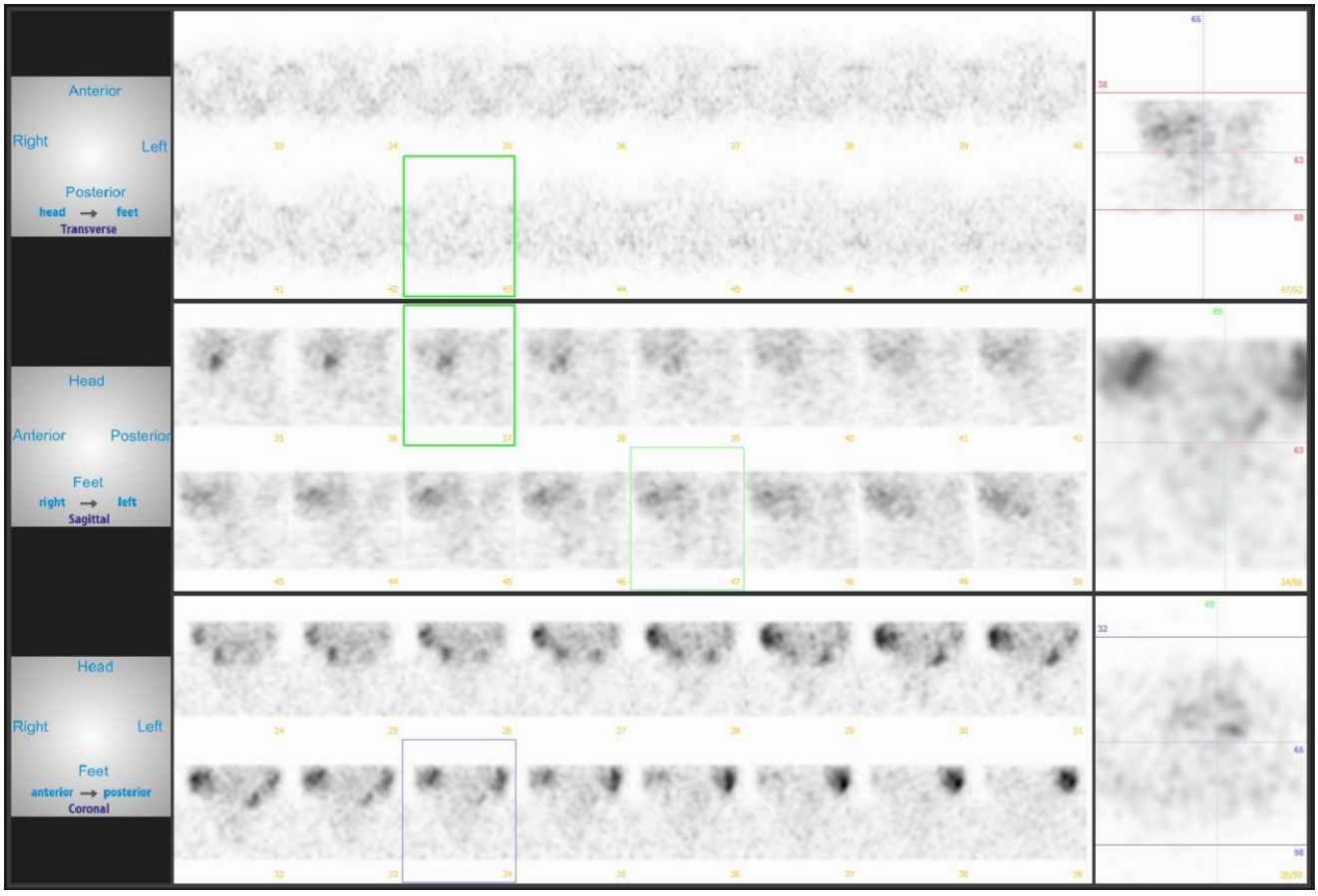

Figure 4. Delayed-phase SPECT of the same patient showing absence of focal uptake consistent with early washout.

Discussion

Although the diagnostic performance of ^{99m}Tc-MIBI parathyroid scintigraphy has been extensively studied, the optimal role of early-phase SPECT in contemporary clinical practice remains debated. While SPECT/CT is increasingly considered the reference standard for preoperative localization, it is not universally available. In this context, our study demonstrates that early-phase SPECT provides clinically meaningful additional information by identifying parathyroid adenomas with rapid tracer washout that would otherwise remain undetected on delayed-phase imaging.

In our study, adenomas detected by dual-phase imaging with delayed-phase SPECT were compared with adenomas demonstrating early washout detectable only by early-phase SPECT (~20 minutes post-injection) and not visible on delayed planar or SPECT images. No significant differences were found between the two groups regarding age, sex, preoperative serum calcium and PTH levels, or lesion size.

There are studies in the literature reporting different findings on this subject. For example, Kushchayeva et al. (2019) detected a positive correlation between lesion size and delayed-phase ^{99m}Tc-MIBI uptake in 135 hyperparathyroidism patients [5]. In the same study, a positive correlation was noted between preoperative serum PTH level and early-phase ^{99m}Tc-MIBI uptake, but no correlation with delayed-phase ^{99m}Tc-MIBI uptake was found; nor was any correlation observed between serum Ca levels and either early or delayed-phase ^{99m}Tc-MIBI uptake. Hung et al (2003). demonstrated a positive correlation between elevated serum PTH levels and the likelihood of detecting parathyroid adenomas on scintigraphy in 24 primary hyperparathyroidism patients [6].

Cermik et al. (2005) found no relationship between preoperative serum PTH levels and ^{99m}Tc-MIBI uptake in 19 primary hyperparathyroidism patients [7]. Arveschoug et al. (2007) reported no association between preoperative PTH levels and early washout in 47 primary hyperparathyroidism patients [8]. Melloul et al. (2001) identified a positive correlation between preoperative serum Ca levels and ^{99m}Tc-MIBI uptake in 31 parathyroid adenoma patients [9]. Dugonjic et al. (2017) found no relationship between preoperative serum Ca levels and ^{99m}Tc-MIBI uptake in 46 parathyroid adenoma cases [10].

One of the notable aspects of our study is the hypothesis that adenomas exhibiting early washout may reflect a biologically distinct phenotype. Some studies have suggested that differences in mitochondrial density, oxyphil cell proportion, p53 expression, or membrane proteins such as P-glycoprotein (PGP), which contribute to multidrug resistance, may cause rapid ^{99m}Tc-MIBI clearance [11]. Additionally, some studies have proposed a positive relationship between ^{99m}Tc-MIBI uptake and increased tissue perfusion in parathyroid adenomas [12].

Although our study lacks immunohistochemical data, the absence of clinical and biochemical differences between the two groups, combined with imaging findings, indirectly supports this hypothesis of biological heterogeneity. Large prospective studies analyzing biomarkers-including P53, PGP, oxyphil cell ratio, and tissue perfusion parameters-are needed to confirm this hypothesis.

Our study also demonstrates that early-phase SPECT has significantly higher sensitivity than delayed-phase SPECT (100% vs. 55.6%). This finding should be interpreted in the context of the limited sample size. Although the limited sample size, the study focuses on a highly selected cohort with histopathological confirmation and paired imaging comparison, which strengthens the internal validity.

There are various studies comparing the sensitivity of early vs. delayed-phase SPECT imaging. Hunter et al. (2022) found that among 21 parathyroid adenomas identified on delayed-phase SPECT, 14 were also positive on early-phase SPECT and concluded that delayed-phase SPECT was superior [3]. Qu and colleagues calculated sensitivity above 70% for delayed-phase SPECT in 244 patients. Civelek et al. (20 02) reported sensitivities of 96% for single adenomas, 83% for double adenomas, and 45% for hyperplastic glands in a cohort of 338 patients using delayed-phase SPECT alone [13].

Perez-Monte et al. (1996) achieved 91% sensitivity using early-phase SPECT, but only 74% sensitivity using delayed-phase SPECT due to rapid tracer washout [4]. Lorberboym et al. (2003) reported that in 52 patients, SPECT increased diagnostic sensitivity from 79% to 96% compared with dual-phase imaging, particularly in cases with multinodular goiter or ectopic adenomas [14]. As shown in our study, adenomas showing early washout may occur in any parathyroid adenoma patient and cannot be predicted using clinical or biochemical parameters. In many centers, only delayed-phase SPECT images are acquired for efficiency reasons; however, as illustrated by our findings, this may be inadequate. Therefore, we emphasize that early-phase SPECT images should be considered an important adjunct to the routine dual-phase protocol. Current European Association of Nuclear Medicine (EANM) guidelines also recommend acquiring both early and delayed-phase SPECT or SPECT/CT images whenever feasible, even in centers that typically obtain only delayed-phase SPECT images [15].

In our cohort of 18 parathyroid adenoma patients, the rate of early washout adenomas detected only by early-phase SPECT was 44%, which is higher than the 8%-40% reported in previous studies [14, 16]. Normal parathyroid tissue is dominated by chief cells; several studies have shown that the transformation of these cells into oxyphil cells influences ^{99m}Tc-MIBI uptake and retention [17]. This transformation is more common in chronic kidney disease [18], and therefore early washout patterns are reportedly less frequent in tertiary hyperparathyroidism [5]. Several factors may explain our higher rate of early washout adenomas, including uniform acquisition parameters, early imaging at 20 minutes post-injection, and strict inclusion criteria requiring histopathological confirmation.

Another methodological strength of our study is the excellent reproducibility of image interpretation. Interobserver agreement between the two nuclear medicine physicians was perfect (κ=1.00), confirming the robustness and consistency of the diagnostic evaluation. This finding is in line with previous studies demonstrating high reliability in the interpretation of ^{99m}Tc-MIBI parathyroid scintigraphy, particularly when evaluating early washout patterns.

Our study has limitations, it is a small-sample, single-center retrospective study. The limited sample size must be considered when interpreting statistical results. Additionally, our gamma camera system lacks SPECT/CT. Hybrid imaging with SPECT/CT provides superior anatomical localization and is widely recommended when available so our findings are not intended to challenge the role of SPECT/CT as the reference technique, but rather to optimize SPECT - only protocols where hybrid imaging is not available. In our study, 18 patients in whom parathyroid adenoma was detected with early-phase SPECT and who underwent minimally invasive surgery had normal postoperative parathormone levels, indicating that in centers without SPECT/CT, early SPECT may allow accurate lesion localization and surgical success. In such settings, optimizing SPECT-only protocols, including the routine acquisition of early-phase images, may substantially improve lesion detection and support surgical outcome in centers without SPECT/CT. Moreover, the strong statistical difference and perfect interobserver agreement suggest that the results are robust. Finally, as noted, immunohistochemical analyses were not available. Larger, multicenter prospective studies incorporating histopathological biomarkers are needed to better characterize clinical, biochemical, and biological features of early washout parathyroid adenomas.

In conclusion, early-phase SPECT constitutes a valuable complementary imaging approach for the detection of parathyroid adenomas with rapid tracer washout. As this kinetic behavior cannot be anticipated based on clinical or biochemical parameters, the inclusion of early-phase SPECT should be considered, particularly in centers without routine access to SPECT/CT, to reduce false-negative findings and support minimally invasive parathyroid surgery in routine clinical practice.

The authors declare that they have no conflicts of interest.

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