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$^{99m}TcO_4^-$/^{99m}Tc-MIBI dual-tracer scintigraphy for preoperative localization of parathyroid adenomas

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Abstract

Objective: To investigate the accuracy of dual-tracer scintigraphy for locating parathyroid adenomas in patients with primary hyperparathyroidism (PHPT).

Methods: We reviewed 268 patients with PHPT. All patients underwent technetium-99m pertechnetate ($^{99m}TcO_4^-$) scintigraphy and technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI) dual-tracer scintigraphy of the thyroid and parathyroid glands, respectively. $^{99m}TcO_4^-$ planar scintigraphy was carried out initially followed by dual-phase ^{99m}Tc-MIBI single-photon emission computed tomography (SPECT)/CT the next day. The findings were combined and interpreted. Individual ^{99m}Tc-MIBI and dual-tracer scintigraphy were both analyzed. The sensitivity, specificity, and accuracy were determined in relation to surgical findings. The average interval between scan and surgery was 13 days.

Results: The positive and negative predictive values of ^{99m}Tc-MIBI SPECT/CT were 92.0% and 71.3%, respectively, and the sensitivity, specificity, and accuracy were 88.3%, 79.2%, and 85.8%, respectively. The positive and negative predictive values of dual-tracer scintigraphy were 96.3% and 82.3%, respectively, and the sensitivity, specificity, and accuracy were 92.9%, 90.3%, and 92.2%, respectively. Youden's index for dual-tracer scintigraphy and ^{99m}Tc-MIBI SPECT/CT were 0.83 and 0.63, respectively.

Conclusions: These finding suggest that $^{99m}TcO_4^-$ and ^{99m}Tc-MIBI dual-tracer scintigraphy is more accurate than other scintigraphy methods for detecting parathyroid adenoma, and may thus be the most suitable imaging technique in patients with PHPT.

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Introduction

Primary hyperparathyroidism (PHPT) can be caused by parathyroid adenoma, hyperplasia, or parathyroid carcinoma, and is characterized by high serum calcium and parathyroid hormone (PTH) levels. It can lead to multisystem diseases, including skeletal, gastrointestinal, cardiovascular, renal, and central nervous system complications. The only curative treatment for symptomatic PHPT is resection of the hyperfunctioning parathyroid glands.[1] However, preoperative localization of the parathyroid adenoma is crucial for planning effective minimally invasive surgery.[2]

Radioisotope scintigraphy of the parathyroid glands can help the endocrine surgeon to locate the abnormal gland before surgery in patients with PHPT. Thallium-201 (^{201}Tl) and technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI) are the most commonly used tracers. The biological features of ^{201}Tl are similar to those of K^+, but its binding affinity to K^+ activation sites is 10 times stronger than that of K^+ during the Na^+-K^+ ATPase activation process. ^{99m}Tc-MIBI is a lipophilic monovalent cation complex that can diffuse passively into the cell membrane and accumulate in the mitochondria. The metabolic product of ^{99m}Tc-MIBI is succinic acid salt, which enhances its ability to combine with mitochondria. Each tracer is taken up simultaneously in both the thyroid and parathyroid glands, but is washed out from the thyroid more rapidly than from a hyperfunctioning parathyroid.[3] However, the adenoma-washout rate is variable and may be rapid,[4–6] and more effective ways of visualizing and locating the hyperfunctioning parathyroid gland are required. ^{99m}Tc-MIBI dual-phase scintigraphy has been used successfully in a number of centers,[7–10] while, dual-tracer scintigraphy has also been useful for differentiating between thyroid tissue and parathyroid adenomas.[11] In dual-tracer scintigraphy, ^{99m}Tc-MIBI displays the thyroid and parathyroid, while $^{99m}TcO_4^-$ delineates the thyroid alone. Subtracting the two resulting sets of images thus reveals the hyperfunctioning parathyroid tissue. ^{18}F-choline positron emission tomography/computed tomography (CT) can also improve the localization of the hyperparathyroid glands, but is not conventionally recommended for PHPT.[12–14]

We have been carrying out dual-tracer scintigraphy at our institute since 2006. In this study, we carried out a retrospective audit to compare the accuracies of $^{99m}TcO_4^-$/^{99m}Tc-MIBI dual-tracer scintigraphy and ^{99m}Tc-MIBI single-photon emission CT (SPECT)/CT alone for identifying parathyroid adenomas in patients with PHPT, and to investigate the use of dual-tracer scintigraphy as a preoperative aid for surgical planning.

Patients and methods

Patients

This study was approved by the ethics committee of Sir Run Run Shaw Hospital

(October 8, 2014). Each patient proved signed informed consent.

A total of 487 patients underwent dual-tracer parathyroid scintigraphy in our center from January 2006 to February 2016, of whom 268 patients diagnosed with PHPT who underwent both dual-tracer parathyroid scintigraphy and surgery were included in the current study.

Dual-phase and dual-tracer scintigraphy

All patients were imaged according to our institution's standard procedures, using a GE Infinia Hawkeye IV SPECT camera (GE Healthcare, Piscataway, NJ, USA) equipped with four-slice CT. $^{99m}TcO_4^-$ planar scintigraphy was carried out first, 20 to 30 minutes after the administration of 185 MBq of $^{99m}TcO_4^-$. Dual-phase ^{99m}Tc-MIBI scintigraphy was performed and interpreted the next day. Planar imaging was performed 10 minutes and 2 hours after administration of 555 MBq of ^{99m}Tc-MIBI, respectively. ^{99m}Tc-MIBI SPECT/CT was carried out 2 hours after administration of the tracer. The average interval between the scan and surgery was 13 days.

Image interpretation

All planar and SPECT/CT images were interpreted by two experienced nuclear medicine physicians with 29 and 26 years' experience of practicing nuclear medicine, respectively. One physician recorded his findings based on ^{99m}Tc-MIBI planar scintigraphy and SPECT/CT, but blinded to the $^{99m}TcO_4^-$ scintigraphy results. The other physician had access to the ^{99m}Tc-MIBI planar scintigraphy and SPECT/CT results, and to the corresponding $^{99m}TcO_4^-$ scintigraphy. They evaluated the presence and number of foci compatible with hyperfunctioning parathyroid glands visually and determined their location. A positive test was defined as focal ^{99m}Tc-MIBI uptake, even if only faint, or no focal ^{99m}Tc-MIBI uptake but a lesion detected by CT.

Performance analysis

The results of each scintigraphy were evaluated for every patient with reference to the surgical and pathological results as the gold standard. The scintigraphy results were classified as true positive when a detected focus corresponded to an abnormal parathyroid gland, false positive if a detected focus did not correspond to an abnormal parathyroid gland, or false negative if an area considered as normal on scintigraphy corresponded to a hyperfunctioning parathyroid gland. We calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of each modality on a per-patient basis.

Statistical analysis

Data were analyzed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA) and 95% confidence intervals (CIs) were calculated. The sensitivity, specificity, PPV, NPV, and Youden's index were calculated statistically for each scintigraphic method, according to the pathological results. Data were analyzed using *t*-tests and χ^2 tests. A value of $P < 0.05$ means indicated a significant difference.

Results

The 268 cases included 81 men and 187 women, aged 32 to 73 years (median age, 49 years), with a mean preoperative serum PTH level of 155.4±58.8 pg/mL (range, 85–368 pg/mL; reference level, 16–65 pg/mL) (Table 1). Among these patients, 168 had parathyroid adenomas, 21 had parathyroid hyperplasia, seven had parathyroid carcinoma, and the others had pathologically normal parathyroid glands. The mean

weight of the lesions was 260.5±76.6 mg. Serum PTH levels decreased in all patients at day 1 postoperatively.

The PPV and NPV of ^{99m}Tc-MIBI SPECT/CT scintigraphy for detecting a hyperfunctioning parathyroid were 92.0% and 71.3%, respectively, and its sensitivity, specificity, and accuracy were 88.3%, 79.2%, and 85.8%, respectively. However, the diagnosis for 35 patients based on these scintigraphy results (35/268, 13.1%) was significantly changed ($P = 0.03$) after accounting for the $^{99m}TcO_4^-$ scintigraphy results; the results for 18 patients changed from negative to positive, while the results for the other 17 changed from positive to negative. The PPV and NPV of dual-tracer scintigraphy were thus 96.3% and 82.3%, respectively, and the sensitivity, specificity, and accuracy were 92.9%, 90.3%, and 92.2%, respectively. The specificity of dual-tracer scintigraphy was significantly higher than that of 99mTc-MIBI SPECT/CT ($P = 0.03$). Youden's index (YI) for dual-tracer scintigraphy was 0.83, compared with 0.63 for ^{99m}Tc-MIBI SPECT/CT (Table 2).

Table 1. Characteristics of patients with PHPT.

Parameter	
Median age (year)	49
Sex (n=268)	
Male	30.2% (n = 81)
Female	69.8% (n = 187)
Course of disease (month)	31.3 ± 27.1
Clinical manifestation	
Stone	45.1% (n = 121)
Gastrointestinal discomfort	34.0% (n = 91)
Bone pain	33.2% (n = 89)
Hematuria	32.5% (n = 87)
Hypertension	20.0% (n = 53)
Height loss	9.7% (n = 26)
Fracture	5.2% (n = 14)
Other	28.4% (n = 76)
Preoperative PTH serum level (ng/L)	155.4 ± 58.8

The addition of $^{99m}TcO_4^-$ imaging could clearly detect hyperparathyroidism in patients with focally increased ^{99m}Tc-MIBI uptake on early-phase scans but no retention on delayed imaging, suggesting a negative result, as shown in Figures 1 and 2. Similarly, cases with distinct early-phase focal ^{99m}Tc-MIBI uptake with early washout, suggestive of thyroid adenomas, were considered to be parathyroid adenomas if clear photopenic areas were detected simultaneously on $^{99m}TcO_4^-$ scans. Furthermore, if ^{99m}Tc-MIBI uptake is focally increased at the periphery of the gland, despite washout or not on delayed imaging, $^{99m}TcO_4^-$ imaging may help to confirm or deny the diagnosis if it lacks a contour or peripheral focus (Figures 3 and 4).

We also calculated the 95% CIs for the sensitivity, specificity, and accuracy of each modality, and showed that dual-tracer scintigraphy was superior to dual-phase

Table 2. Accuracies of ^{99m}Tc-MIBI imaging and dual-tracer imaging.

		Surgical finding					
Technique		+	−	Sensitivity, %	Specificity, %	Accuracy, %	YI
^{99m}Tc-MIBI SPECT/CT	+	173	15	88.3	79.2	85.8	0.68
	−	23	57				
Dual-tracer scintigraphy	+	182	7	92.9	90.3	92.2	0.83
	−	14	65				
P value				0.10	0.03	0.15	

YI: Youden's Index

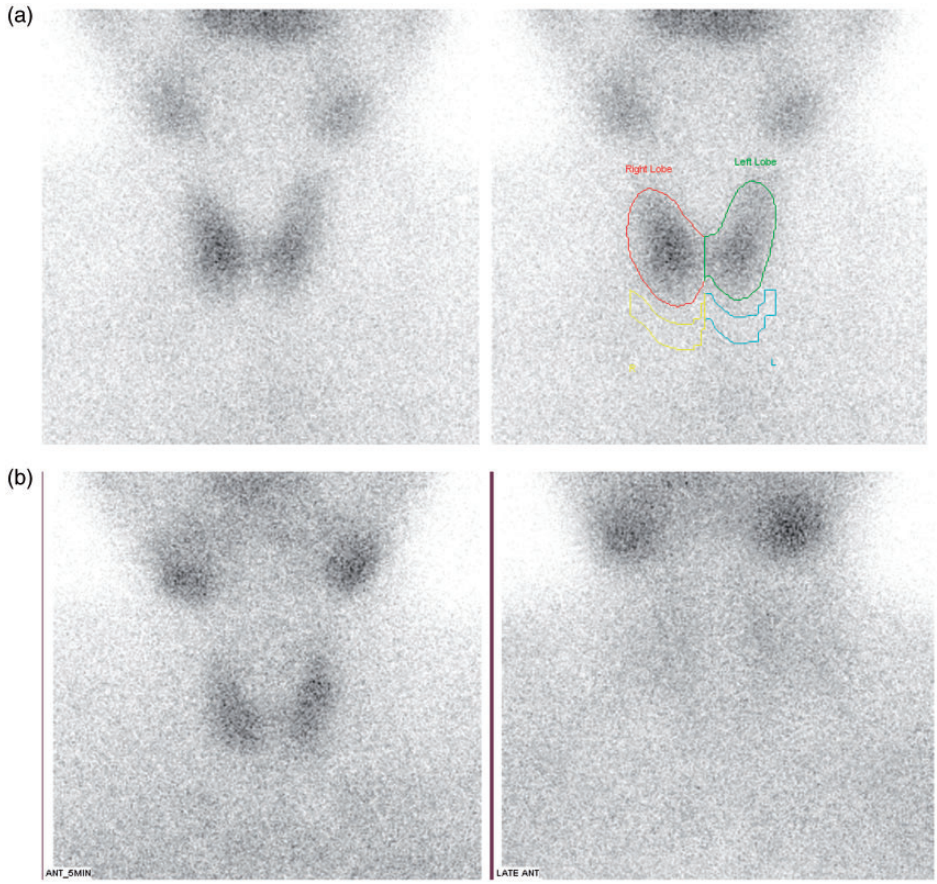

Figure 1. (a) $^{99m}TcO_4^-$ imaging showing focal photopenia on left upper thyroid lobe. (b) Dual-phase ^{99m}Tc-MIBI imaging indicatines increased radioactivity in the left upper lobe on early-phase imaging, retained slightly on delayed imaging. Dual-phase ^{99m}Tc-MIBI imaging alone suggests negative results, but hyperparathyroidism would be considered based on the combined imaging results.

SPECT/CT, as indicated by higher Wilson's 95% CI for sensitivity and accuracy, with little overlap (Table 3). Furthermore, dual-tracer scintigraphy detected ectopic parathyroid tissue in 30 patients without the need for further examination.

Discussion

Previous studies have reported wide variations of 55% to 90% in the sensitivity of ^{99m}Tc-MIBI dual-phase scintigraphy for detecting a hyperfunctioning parathyroid,[3,15–17] while other studies showed that dual-tracer scintigraphy could obviously increase the sensitivity and accuracy. The addition of a second radiopharmaceutical would improve the role of the ^{99m}Tc-MIBI scintigraphy and enhance the information provided by SPECT/CT. Moreover, dual-tracer parathyroid scintigraphy can play a critical role in the detection and localization of parathyroid adenomas, particularly in cases in which ^{99m}Tc-MIBI is washed out of the parathyroid rapidly but remains in thyroid adenomas and lymph nodes.[18]

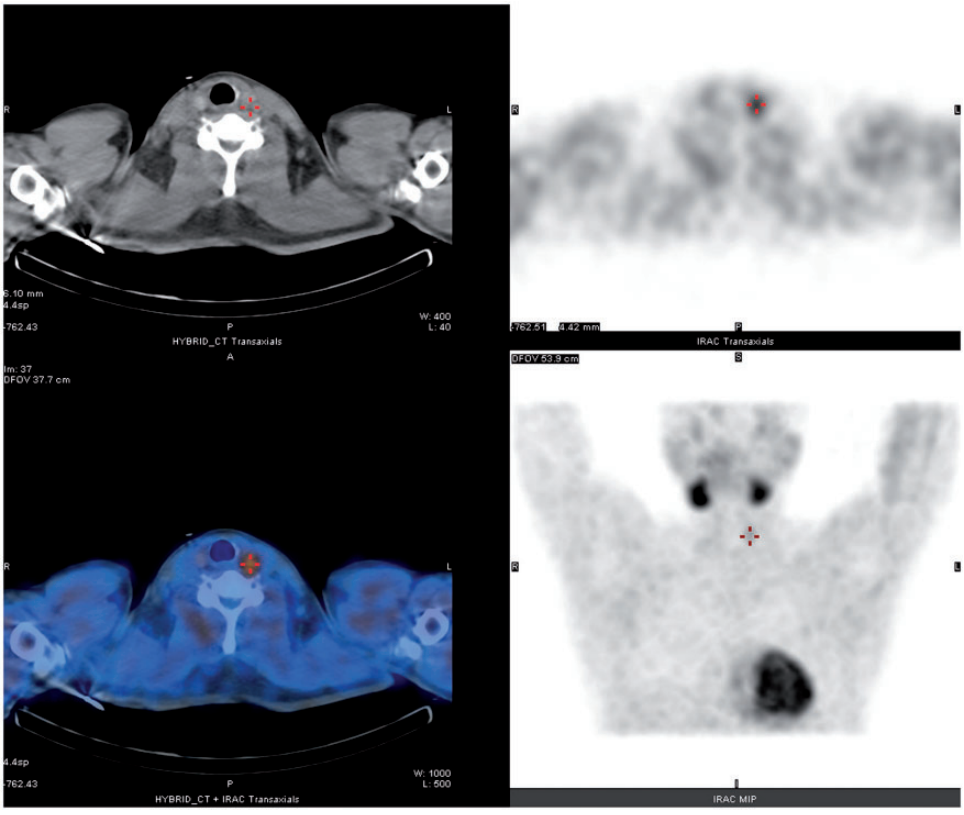

Figure 2. ^{99m}Tc-MIBI SPECT/CT imaging. Radioactivity was slightly increased at the red mark, suggesting a hyperfunctioning parathyroid gland. Postsurgical histology revealed a hyperplastic parathyroid gland (0.15 g) corresponding to the focus. Serum PTH levels decreased from 136 pg/mL preoperatively to 26 pg/mL on the day after surgery.

Furthermore, dual-tracer scintigraphy can also be used to exclude ectopic parathyroid tissue, as well as differentiating between parathyroid adenomas and other neck pathologies by second-radiopharmaceutical scintigraphy.

Although dual-tracer scintigraphy may increase radiation exposure, it may also simplify the preoperative evaluation in many patients with PHPT. Furthermore, dual-tracer scintigraphy may provide a precise preoperative localization, thus greatly increasing the confidence of the interpretation and decreasing operation time. The current study showed that dual-tracer scintigraphy was superior to dual-phase SPECT/CT, and the overall accuracy of dual-tracer scintigraphy in this study was 92.2%. Dual-tracer scintigraphy provided immediate and tangible patient benefits, because the additional $^{99m}TcO_4^-$ scintigraphy allowed the results to be reinterpreted and any additional pathologies requiring workup to be detected. These results thus provide theoretical support for the importance of dual-tracer scintigraphy of the parathyroid in terms of limiting both false-positive and false-negative results, as indicated by the changed diagnoses in 35 patients after taking account of the results of $^{99m}TcO_4^-$ scintigraphy.

From a practical point of view, the fusion of the two radiopharmaceutical-based

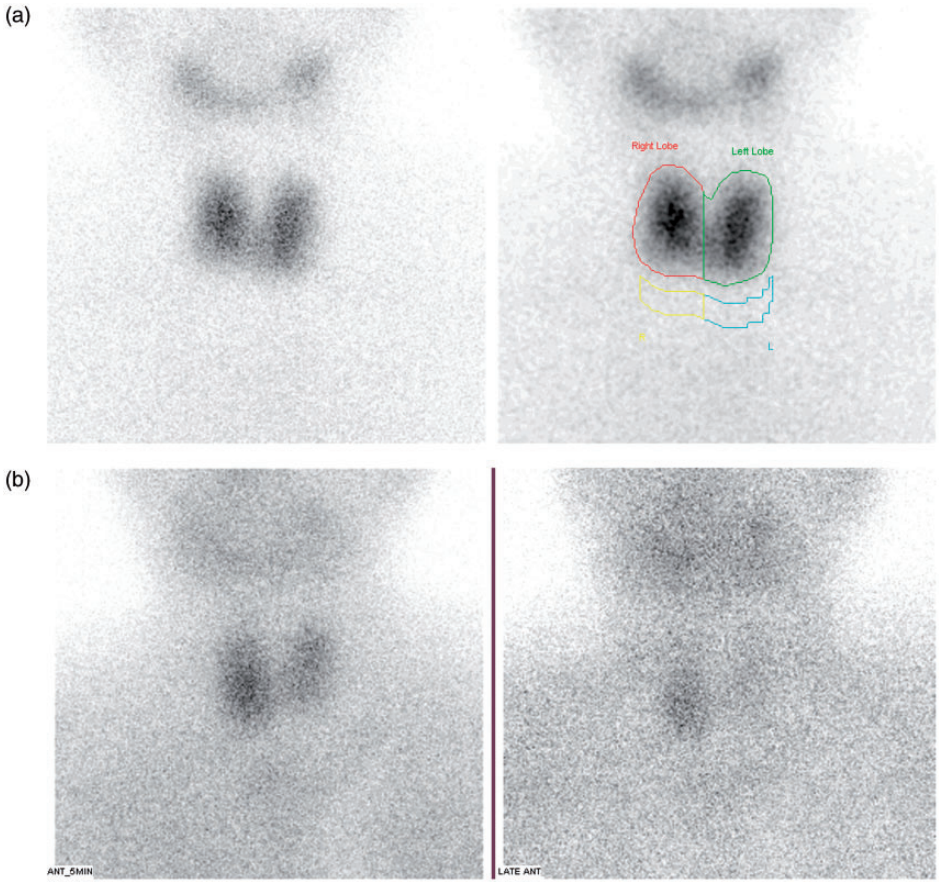

Figure 3. (a) $^{99m}TcO_4^-$ imaging showing normal radioactivity in both thyroid glands. (b) Dual-phase ^{99m}Tc-MIBI imaging showing increased radioactivity in the lower extremity of the right lobe, suggesting hyperthyroidism.

images can be managed easily by surgeons familiar with multimodal image fusion, such as SPECT/CT and diagnostic CT. Furthermore, the improved accuracy of dual-tracer SPECT/CT imaging provides the clinical team with extra confidence in the diagnostic results, and with the detailed anatomical information necessary to carry out minimally invasive surgery. In addition, this technique allows any unusual anatomy or unusual placement of the parathyroid tissue to be visualized.[18]

The use of dual-tracer scintigraphy can improve clinical patient management in several situations,[19–21] including in cases where ^{99m}Tc-MIBI uptake is focally increased on early-phase scans but shows no retention on delayed imaging, cases with distinct early-phase focal ^{99m}Tc-MIBI uptake with early washout, and in the event of focally increased ^{99m}Tc-MIBI uptake at the periphery of the gland, with or without washout on delayed imaging. In these cases, dual-phase ^{99m}Tc-MIBI dual-phase imaging alone may suggest a negative result, while the addition of $^{99m}TcO_4^-$ could clearly identify hyperparathyroidism. Characteristically increased focal ^{99m}Tc-MIBI uptake and

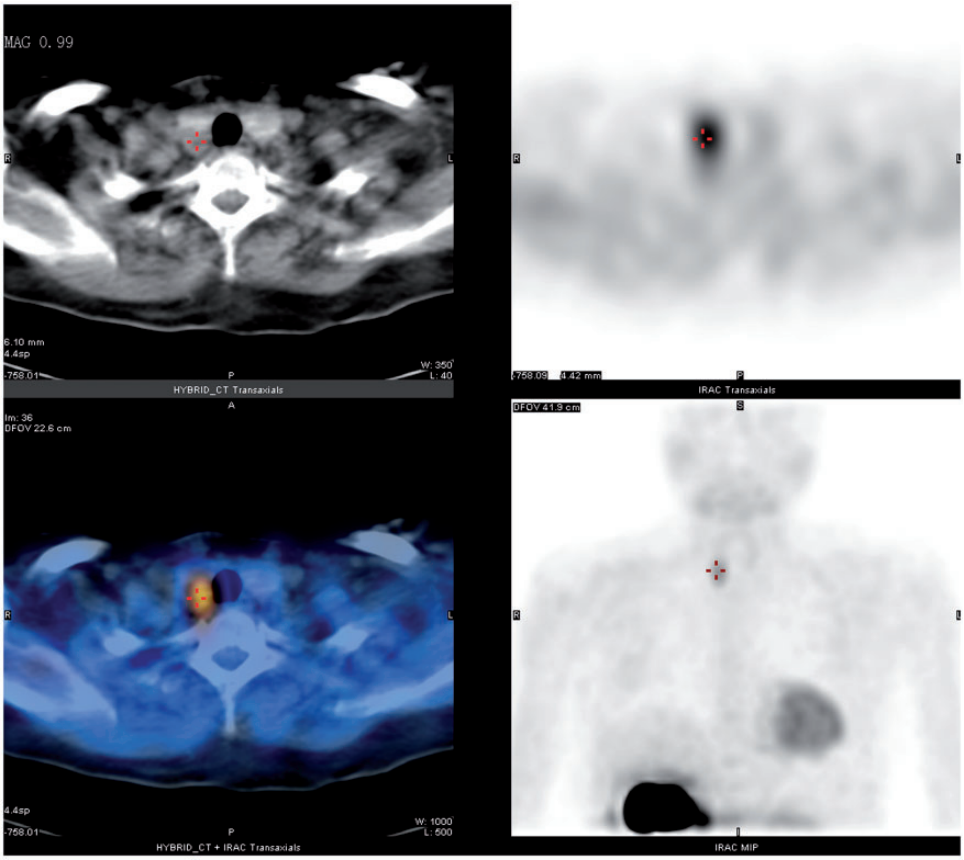

Figure 4. ^{99m}Tc-MIBI SPECT/CT imaging. Uniform density, clear boundary, and increased radioactivity at the red mark suggested a hyperfunctioning parathyroid gland. A parathyroid adenoma (0.34 g) corresponding to the focus was found by pathology. Serum PTH levels decreased from 312 pg/mL preoperatively to 37 pg/mL on the day after surgery.

Table 3. Sensitivity, specificity, PPV, NPV, and accuracy for each modality, with Wilson's 95% confidence intervals.

Parameter	^{99m}Tc-MIBI SPECT/CT	Dual-tracer scintigraphy
Sensitivity	0.883 (0.83–0.92)	0.929 (0.88–0.96)
Specificity	0.792 (0.68–0.87)	0.903 (0.81–0.95)
PPV	0.920 (0.87–0.95)	0.963 (0.93–0.98)
NPV	0.713 (0.61–0.80)	0.823 (0.72–0.89)
Accuracy	0.858 (0.81–0.89)	0.922 (0.88–0.95)

PPV: positive predictive value, NPV: negative predictive value.

delayed retention are generally considered to indicate a typical parathyroid adenoma, but a thyroid lesion, typically a thyroid adenoma, should be considered in the event of corresponding strong $^{99m}TcO_4^-$ uptake. The main factor limiting the specificity of dual-tracer imaging is the presence of an underlying thyroid disease, such as Hashimoto's thyroid disease or multinodular goiter.[22,23] However, some true-positive patients also had evidence of underlying thyroid disease, and both thyroid and parathyroid diseases were found in the pathological assessments

of these cases. Moreover, our study suggested that dual-tracer SPECT/CT imaging could significantly reduce the impact of underlying thyroid disease on the diagnostic performance.

In conclusion, dual-phase ^{99m}Tc-MIBI scintigraphy may produce false-positive results in patients with thyroid disease, while the addition of $^{99m}TcO_4^-$ imaging and CT information can increase awareness of thyroid issues. These findings suggest that $^{99m}TcO_4^-$ and ^{99m}Tc-MIBI dual-tracer scintigraphy is more accurate for detecting parathyroid adenomas than other scintigraphy methods, and may be the most suitable imaging technique in patients with primary hyperparathyroidism.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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