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Original Article

Diagnostic value of ^{99m}Tc-Sestamibi planar imaging and SPECT/CT for secondary hyperparathyroidism

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Abstract: Objectives: To explore the diagnostic value of ^{99m}Tc-Sestamibi multiple-phase static planar imaging and SPECT/CT in secondary hyperparathyroidism. Methods: This was a retrospective analysis of 40 cases of clinically diagnosed secondary hyperparathyroidism with multiple-phase static planar imaging, 15 min SPECT/CT fusion imaging, and ultrasonography. All cases were confirmed by pathological examination. Detection of lesions was compared between dual-phase and multi-temporal planar imaging, the detection rate of lesions using planar imaging, SPECT/CT, and ultrasonography was analyzed, and the characteristics of parathyroid tissue calcification detected by SPECT/CT were summarized. Results: The number of lesions detected was 69 by multi-temporal planar imaging and 57 by dual-phase imaging; scans at both 60 min and 90 min detected 12 lesions. SPECT/CT detected more lesions than planar imaging and ultrasonography; the sensitivities were 93.1%, 47.9%, and 70.1%, the accuracy was 88.7%, 47.6%, and 69.7%, respectively, and the specificity was 100%. Eighteen of 40 patients had parathyroid tissue calcification, 134 lesions in 32 patients exhibited calcification, and 90.6% of the 32 lesions were ^{99m}Tc-Sestamibi positive. Conclusions: Multi-temporal planar imaging detected more lesions than dual-phase imaging. SPECT/CT plays an important role in the qualitative and quantitative evaluation and positioning of secondary hyperparathyroidism lesions.

Keywords: ^{99m}Tc-Sestamibi, parathyroid scintigraphy, SPECT/CT, ultrasonography, secondary hyperparathyroidism, calcification

Introduction

Secondary hyperparathyroidism (SHPT) is a common complication of chronic renal insufficiency. Long-term disturbances of calcium and phosphorus metabolism may lead to hyperparathyroid bone disease, ectopic calcification, and cardiovascular and nervous system dysfunction. Due to ineffective drug and interventional treatment, patients with refractory SHPT often undergo surgery, which can improve quality of life and reduce hospitalization rates and mortality [1-3]. SHPT often involves multiple glands and the location of parathyroid lesions is highly variable (up to the carotid sheath, down as far as the mediastinum) [4]. Thus, imaging is important for planning and guiding surgical treatment in SHPT. Methods used clinically for preoperative localization of parathyroid lesions include ultrasonography, CT, and MRI, but nuclear medicine imaging has advantages in terms of both the qualitative evaluation of such lesions and the detection of their position. ^{99m}Tc-Sestamibi dual-phase imaging has become common in nuclear medicine because of its simplicity, while SPECT/CT has further improved diagnosis of SHPT. This study was designed to investigate the diagnostic value of planar imaging, SPECT/CT, and ultrasonography and the value of determining calcification by SPECT/CT.

Methods

Patients

A retrospective analysis was made of the clinical and imaging data of patients who underwent ^{99m}Tc-Sestamibi parathyroid scintigraphy followed by lesion removal within 2 months of the examination and were diagnosed with SHPT in our hospital between June 2009 and August 2014. Forty patients were included in the study; 14 were male and 26 were female and their mean age was 52 ± 13 years. This study was approved by the Institutional Review Board of

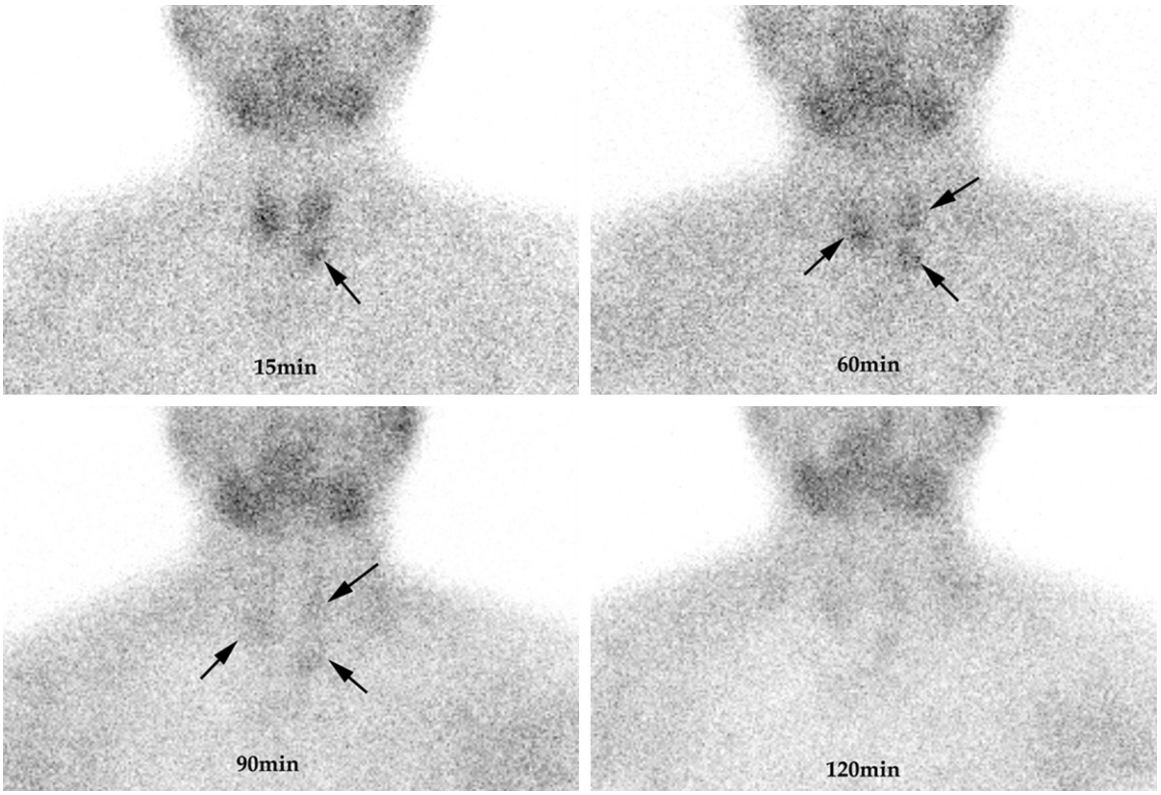

Figure 1. A 36-year-old woman with a history of renal insufficiency and hemodialysis for 9 years underwent parathyroid imaging for elevated parathyroid hormone (2637 pg/ml; normal range 15-65 pg/ml) that had persisted for more than 3 months. On multi-temporal planar imaging, abnormal uptake was observed in the lower pole of the left lobe of the thyroid at 15 min and in the middle of the right lobe of the thyroid and the upper and lower poles of the left lobe at 60 min; the radioactivity of the lesions was gradually reduced at 90 min and 120 min.

Zhongshan Hospital, Fudan University. Informed consent for the possible future elaboration of data was obtained from all subjects included in this study at the time of the initial clinical examination.

Image acquisition

After injection of 555 MBq (15 mCi) of ^{99m}Tc-Sestamibi, an early parathyroid scan of the neck and chest was obtained at 15 min and delayed scans were obtained after 60 min, 90 min, and 120 min (if necessary, scans were delayed for 4-6 hours to allow for the thyroid elution rate). Whole body planar imaging was also performed 60 min and 120 min after the injection. Planar image acquisition conditions were: matrix 256 × 256; zoom 2.19; count 300 K/frame; and use of a low energy, high resolution parallel-hole collimator. SPECT/CT images were obtained 15 min after injection using a 16-slice diagnostic CT system (Philips Precedence; Philips Medical Systems, Bothell, Wisconsin, USA) with the following acquisition conditions: matrix 64 × 64; zoom 1.85; 5.6°/frame; 64 frames; and 20 s/frame. Immediately after SPECT, CT images were obtained under the following conditions: slice thickness 3.0 mm; 120 kV; 315 mA; and interlayer spacing 3.0 mm. The raw data from SPECT were reconstructed into axial, coronal, and sagittal slices with ordered subset expectation maximization (three iterations over eight subsets). SPECT and CT images were fused using the manufacturer's software (Syntegra v2.3; Philips Medical Systems). For patients who had undergone parathyroid resection with autologous transplantation, the transplanted area was included in planar and SPECT/CT images by the above methods.

Image interpretation

Two experienced nuclear medicine physicians interpreted the images. Scintigraphy was considered positive when focal tracer retention in the neck or mediastinum was clearly evident on static planar and/or SPECT/CT images. Sc-

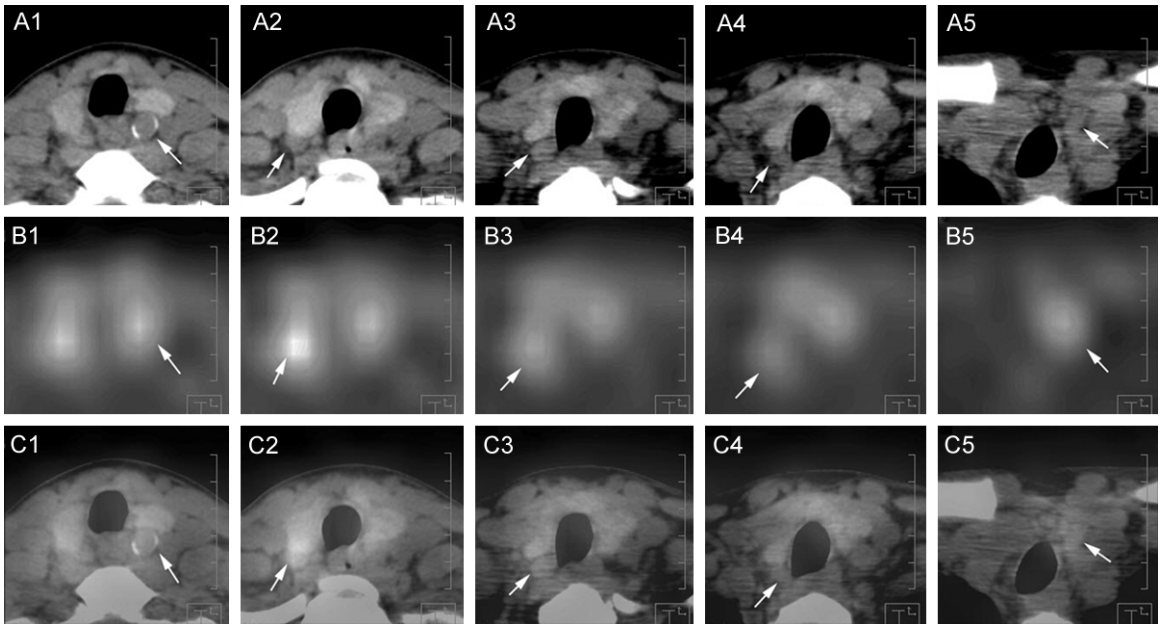

Figure 2. SPECT/CT shows three lesions in the middle and lower part of the right lobe of the thyroid and two lesions in the upper and lower part of the left lobe. These were low density nodules with abnormal uptake and annular calcification surrounding the upper part of the left lobe (A1-A5: CT images; B1-B5: SPECT images; C1-C5: SPECT/CT images). Pathologic examination after surgery confirmed the presence of parathyroid adenoma.

intigraphy was negative when focal uptake in the neck and mediastinum was absent on both static planar and SPECT/CT studies.

Statistical analysis

Statistical analysis was performed using SPSS 20 (IBM, Armonk, New York, USA), with two-tailed $P < 0.05$ considered significant. Continuous variables were expressed as the mean ± standard deviation, while categorical variables were expressed as a frequency or percentage. Taking the pathological results as gold standard, diagnostic sensitivities, specificities, and accuracies of planar imaging, SPECT/CT imaging, and ultrasonography were calculated. Lesion number and size detected by the three methods were compared by the chi-square (χ^2) test and one-way ANOVA analysis, respectively.

Results

Operative results

In our series, 144 parathyroid glands (PTGs) in 40 patients were identified and surgically resected. On pathologic examination, 95 PTGs exhibited hyperplasia, 28 showed hyperplasia with neoplasia, and 21 were adenomas. Twenty-five patients had four PTGs, eight patients had three, five patients had two, and two patients had five (**Figures 1** and **2**). Six patients underwent preoperative and postoperative imaging and resection. Three patients underwent parathyroidectomy with autotransplantation (PTx + AT); two suffered local recurrence and one developed foreign body granulation tissue. Two patients with in situ residual recurrence underwent subtotal PTx. In one patient who underwent PTx + AT, local recurrence was detected on the first scan, recurrence in the graft on the second scan, and an ectopic mediastinal parathyroid on the third scan.

Multi-temporal planar imaging results

Parathyroid scans of the neck and chest were obtained at 15 min, 60 min, 90 min, and 120 min except in six patients in whom imaging was delayed for 5 h, five who were delayed for 4 h, and one who was delayed for 6 h. Imaging detected 22 lesions at 15 min, 54 lesions at 60 min, 56 lesions at 90 min, and 51 lesions at 120 min. Multi-temporal planar imaging detected 69 lesions and dual-phase imaging detected 57 lesions. Imaging at 60 min and at 90 min detected 12 lesions.

Planar imaging, SPECT/CT imaging, and ultrasonography results

Based on the pathologic findings, the sensitivities of SPECT/CT, planar imaging, and ultraso-

Table 1. Comparisons of detectabilities in identifying parathyroid lesions among ultrasonography, planar imaging and SPECT/CT based on pathological findings

Imaging modality		Pathology		Sensitivity	Specificity	Accuracy
		Positive	Negative			
Ultrasonography	Positive	101	1	70.1%	100%	69.7%
	Negative	43	0			
Planar imaging	Positive	69	1	47.9%	100%	47.6%
	Negative	75	0			
SPECT/CT	Positive	134	7	93.1%	100%	88.7%
	Negative	10	0			

Table 2. Comparisons between SPECT/CT, ultrasound and planar imaging in detecting parathyroid lesions

Imaging modalities		SPECT/CT		χ^2	*P*-value
		Positive	Negative		
Ultrasonography	Positive	101	0	21.771	< 0.001
	Negative	33	10		
Planar imaging	Positive	68	0	7.687	0.006
	Negative	66	10		

Table 3. Comparisons of lesion size detected on planar imaging, SPECT/CT, and ultrasonography through one-way ANOVA analysis

Imaging modalities	Diameter (mm)	*F*-value	*P*-value
Ultrasonography	11.2 ± 4.5	4.069	0.018
Planar imaging	11.6 ± 3.7		
SPECT/CT	10.2 ± 3.7		

Multiple comparisons (LSD) show that lesions detected on SPECT/CT and ultrasonography were significantly smaller than those detected on planar imaging (P = 0.044 and 0.009, respectively), while no significant difference of lesion size was identified between ultrasonography and planar imaging (P = 0.437).

nography were 93.1%, 47.9%, and 70.1%, the specificity was 100%, and the accuracy was 88.7%, 47.6%, and 69.7%, respectively (**Table 1**). As shown in **Table 2**, the efficacy of SPECT/CT for the detection of lesions was superior to that of ultrasonography (χ^2 = 21.771, P < 0.001) and planar imaging (χ^2 = 7.687, P = 0.006).

Lesion size on planar imaging, SPECT/CT, and ultrasonography

The abilities of the three methods to determine lesion size differed significantly on ANOVA (F = 4.069, P = 0.018). Pairwise comparisons by the least significant difference method showed that the lesion diameter determined by SPECT/CT was less than that on ultrasonography (P = 0.044) and planar imaging (P = 0.009). There was no significant difference between ultrasonography and planar imaging (P = 0.437) (**Table 3**).

Calcification of parathyroid lesions detected by SPECT/CT

Based on the number of patients, the calcification rate was 45.0% (18/40); based on the number of lesions, the calcification rate was 23.9% (32/134). Of the 32 parathyroid lesions, 90.6% were ^{99m}Tc-Sestamibi positive. On pathologic examination, 18 PTGs exhibited hyperplasia, nine showed hyperplasia with neoplasia, and five were adenomas. On morphologic examination, 25 lesions showed annular calcification (**Figure 2**) and seven showed punctate calcification. The diameter of calcified lesions was 11.7 ± 4.00 mm (P = 0.014 compared with non-calcified lesions), parathyroid hormone (PTH) was 2446.1 ± 922.22 pg/ml (P = 0.003) and the ^{99m}Tc-Sestamibi positive rate was 90.6% (P = 0.001); these were statistically significant, but differences in pathologic type and location were not statistically significant (**Table 4**). On ultrasonography, the calcification rate was 20.0% based on the number of patients (8/40) and 12.9% based on the number of lesions (13/101).

Discussion

SHPT occurs in patients with chronic renal insufficiency, intestinal malabsorption syndrome, Fanconi syndrome and renal tubular acidosis, or vitamin D deficiency or resistance. It may also occur during pregnancy or breast-feeding, in patients with excessive secretion of PTH leading to long term low calcium levels, and in those with low magnesium levels or chronic hyperphosphatemia. Long term parathyroid hyperplasia can lead to the development of a functional autonomous adenoma. SHPT is a common complication of end-stage renal disease, characterized by excessive secretion of PTH resulting in parathyroid hyperplasia and disturbances of calcium and phosphorus me-

Table 4. Comparisons of features between calcified and non-calcified lesions detected by SPECT/CT

Lesion	Calcification (n = 32)	Non-calcification (n = 10)	Statistics	*P*-value
Diameter (mm)	11.72	9.902	2.501	0.014[a]
Serological PTH (pg/ml)	2446.1	1924.6	3.062	0.003[a]
Positive in ^{99m}Tc-MIBI uptake	29 (90.6%)	59 (57.8%)	11.261	0.001[b]
Pathology			1.418	0.492[b]
Hyperplasia	18 (56.2%)	69 (67.6%)		
Adenoma	5 (15.6%)	11 (10.8%)		
Hyperplasia with neoplasia	9 (28.1%)	22 (21.6%)		

[a]*t*-test; [b]chi-square test; PTH, parathyroid hormone.

tabolism. It can lead to bone pain, itching, multiple fractures, metastatic calcification, and renal anemia, seriously affecting the patient's quality of life and survival [5]. Currently, common treatments include medication and interventional and surgical treatment. Due to ineffective drugs and interventional treatment, severe SHPT often requires surgery. Accurate preoperative localization can improve the success rate, reduce operative time, avoid the missing of lesions, and reduce complications and relapse rate.

Pathologically, parathyroid hyperplasia generally refers to diffuse or nodular hyperplasia throughout the entire gland, generally involving multiple glands. Adenoma refers to tumor cells arranged in nests, cysts, or sheets; nuclei are usually larger than in the surrounding normal parathyroid cells and 70% of cells are seen to be in mitosis, though the mitosis is not pathologic. Nuclear atypia may occur in adenoma but is rare in hyperplasia. Hyperplasia with neoplasia refers to local adenomatous hyperplasia following proliferation. In the surgical treatment of 144 lesions in the present study, 95 PTGs exhibited hyperplasia, 28 hyperplasia showed neoplasia, and 21 were adenomas. This means that, in cases of long term high PTH, hyperplasia can convert to adenoma. SHPT parathyroid tissue lesions mostly showed hyperplasia, which differs from the situation in primary hyperparathyroidism. Nuclear medicine imaging cannot distinguish hyperplasia from adenoma, but their clinical outcomes are the same and therefore this does not affect subsequent treatment decisions.

Compared with primary hyperparathyroidism, SHPT usually involves multiple glands and exhibits greater variability in location. Common sites are the carotid sheath, tracheoesophageal groove, or mediastinum [6]; thus, accurate positioning before surgery is important. Ultrasonography has become the most commonly used method in the clinic because it has high penetration, is simple to use, provides real-time images, and does not involve radiation. Its disadvantages are that it is operator dependent and ectopic, and cannot detect lesions of size less than 1 cm. The diagnostic sensitivity is 50-80% [7]. MRI has high soft tissue resolution, can be multiplanar, and allows multisequential imaging, and its sensitivity for the diagnosis of ectopic parathyroid gland is superior to that of CT; its disadvantages are that it is relatively expensive and time-consuming. CT is also commonly used in preoperative localization because of its high imaging speed, high density resolution, accurate positioning, and high penetration; however, it requires the use of contrast agents, which may be toxic in patients with uremia and thus limit its clinical application.

Scintigraphy is a noninvasive method for the diagnosis of hyperparathyroidism that is increasingly attracting clinicians' attention. Parathyroid scintigraphy includes ^{201}Tl (or ^{99m}Tc-Sestamibi)/$^{99m}TcO4^-$ (or ^{123}I) subtraction methods and the ^{99m}Tc-Sestamibi dual-phase method. The sensitivity of subtraction methods is 66-99% [8], but because of their complexity and the possibility of interference from many factors, they are rarely used clinically. In the ^{99m}Tc-Sestamibi dual-phase method, an early parathyroid scan of the neck and chest is obtained 15 min after injection of 740 MBq (20 mCi) of ^{99m}Tc-Sestamibi and a delayed parathyroid scan is obtained after 120 min. Because of its relatively simple procedure and high accuracy, this is becoming the most commonly used imaging method.

The mechanism of ^{99m}Tc-Sestamibi capture by the parathyroid involves active transport and passive diffusion. These processes are increased in overactive cells and the presence of greater numbers of mitochondria can favor ^{99m}Tc-Sestamibi binding. Therefore, lesions in hyperthyroid patients take up greater amounts of ^{99m}Tc-Sestamibi and both thyroid and parathyroid tissue exhibit radioactivity on imaging. Because normal thyroid tissue removes ^{99m}Tc-Sestamibi faster than that in hyperparathyroidism, the parathyroids in hyperthyroid patients continue to exhibit radioactivity in the late imaging phase. ^{99m}Tc-Sestamibi dual-phase imaging is a functional imaging method; hyperparathyroidism is detected but normal parathyroid is often not imaged due to small size, poor blood flow, or low cell activity. The dual-phase method is appropriate for the elution rate of lesions, which is slower than that of normal thyroid tissue, but normal or faster eluting lesions are easily missed. In addition, in SHPT patients with chronic renal failure, renal insufficiency in itself leads to slow excretion of radiopharmaceuticals; the blood background radioactivity is therefore relatively high, leading to reduced lesion contrast. Over time, this background level is reduced and the display of lesions improves; thus, we chose the multi-temporal ^{99m}Tc-Sestamibi scintigraphy method for our study.

Studies have shown that the 15 min scan detects the lowest number of lesions, which may be because the lesions are covered by normal thyroid tissue. The 90 min scan finds the largest number of lesions; this may be because both fast and slow eluting lesions can be captured in this time window. Uptake of ^{99m}Tc-Sestamibi by lesions is greatest at 15 min but is influenced by that of normal thyroid tissue; 60 min and 90 min scans can capture relatively fast eluting lesions and scans at 120 min or later can capture slower eluting lesions. Our data suggest that, compared with the dual-phase method, the multi-temporal method can find more lesions, thus avoiding the missing of lesions due to variation in elution rate.

^{99m}Tc-Sestamibi is better for the diagnosis of primary hyperparathyroidism than for the diagnosis of SHPT. This is because primary hyperparathyroidism often involves only a single gland and pathologically is usually an adenoma [9]; in the present study, SHPT was found to often involve multiple glands and pathologic examination showed hyperplasia. The sensitivity of detection of hyperplasia by ^{99m}Tc-Sestamibi is lower than that of adenoma, which may be related to the presence of fewer eosinophils and mitochondria, resulting in glands with low ^{99m}Tc-Sestamibi uptake and rapid clearance [10]. We found the sensitivity of planar imaging to be 47.9%, which is consistent with the 34-66% reported in the literature [11]. The limitations of planar imaging are that it is difficult to find small and occult lesions and lesions cannot be accurately positioned. In this study, the use of a parallel-hole collimator also reduced the resolution of this method; a pinhole collimator provides higher sensitivity by expanding the field of view. The value of SPECT/CT in nuclear medicine imaging has been confirmed in the literature [12-14]. The present study showed that SPECT/CT had a sensitivity of 93.1%, an accuracy of 88.7%, and a specificity of 100%. Zhen [15] and others have found the sensitivity and accuracy of SPECT/CT to be 78.9% and the specificity 100%; in the same study, ultrasonography had a sensitivity of 70.1%, an accuracy of 69.7%, and a specificity of 100%. SPECT/CT can find more and smaller lesions than planar imaging, and ultrasonography and can accurately position lesions on cross-sections and coronal and sagittal planes.

The early failure rate of parathyroid resection in SHPT patients is reported to be 5-10% [16, 17], with a recurrence rate within 5 years of as high as 20-30% [17]. The main reason for failure is the presence of ectopic parathyroid and the missing of parathyroid lesions intraoperatively. In the present study, of six patients who underwent preoperative and postoperative and resection, four suffered local recurrence. The main reason was the missing of lesions during surgery due to deep location, small size, or similarity in appearance to normal thyroid tissue or lymph nodes. One patient who underwent PTx + AT was suffered relapse in the transplanted area. The first image showed local recurrence, the second image showed relapse in the transplanted area, indicating that the concentration of radioactivity in lesions in the transplanted area was higher than in the previous scan, and the third image indicated an ectopic mediastinal parathyroid; no further surgery was undertaken. On retrospective analysis of the case, the ectopic mediastinal parathyroid was seen to have taken up some radioactivity but was missed on the first two images, which may have been due to the high uptake in situ and in the

transplanted lesions. One patient was false positive in the transplanted area because of positive lesions in situ and in the transplanted area. It is important to be aware of the possibility of false positive findings, especially when the time to surgery is short and images are positive both in situ and in the transplanted area.

We used diagnostic CT in our study, not only to position lesions but also to determine their anatomic details. We found that parathyroid lesions are prone to calcification; the calcification rate was 45.0% based on the number of patients and 23.9% based on the number of lesions. Morphologically, the calcification was mostly annular, and 90.6% of calcified parathyroids absorbed ^{99m}Tc-Sestamibi. Ultrasonography is more sensitive for the detection of calcification; on ultrasonography in the present study, the calcification rate was 20.0% based on the number of patients and 12.9% based on the number of lesions. This difference is probably related to the small size of lesions, their deep location, and operator factors.

The pathogenesis of calcification involves renal insufficiency in hemodialysis patients with severe SHPT increasing secretion of PTH; this stimulates the dissolving of bone salt and its release into the blood, causing high calcium and phosphorus levels and soft tissue (including parathyroid tissue in hyperthyroidism) and vascular wall calcification [18]. In the present study, calcified lesions were relatively large compared with non-calcified lesions and their PTH levels and ^{99m}Tc-Sestamibi positive rate were higher (**Table 4**). Absorption of ^{99m}Tc-Sestamibi by calcified lesions is related to high intact PTH (iPTH) levels. Fuster [19] found that ^{99m}Tc-Sestamibi uptake was significantly correlated with iPTH level but not with other indicators such as calcium, phosphorus, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D.

In summary, multiple-phase static imaging can detect more lesions than dual-phase imaging. SPECT/CT is better in detecting overactive parathyroid tissue than simple planar imaging and ultrasonography, and can position lesions accurately on cross-sections and coronal and sagittal planes. Parathyroid lesions are prone to calcification. In postoperative follow-up, SPECT/CT can detect in situ residual or occult lesions, transplanted area relapse, and ectopic parathyroid tissue and provides accurate positioning. The limitation of this study is that the use of multiple-phase static imaging increased the examination time.

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Disclosure of conflict of interest

None.

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