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Combined application of ultrasound and SPECT/CT has incremental value in detecting parathyroid tissue in SHPT patients

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Abstract
Purpose: The goal of this study is to investigate whether combined application of ultrasound and 99mTc-sestamibi SPECT/CT had the incremental value in accurately detecting parathyroid tissue in patients with SHPT over either method alone.
Patients and methods: Sixty patients with SHPT on hemodialysis were evaluated preoperatively with parathyroid 99mTc-sestamibi SPECT/CT scintigraphy and ultrasound prior to parathyroidectomy. The sensitivity, specificity and accuracy of 99mTc-sestamibi SPECT/CT scintigraphy, ultrasound and combined application were determined respectively.
Results: The sensitivity, specificity and accuracy of ultrasound were 81% (155/192), 47% (17/36) and 82% (172/228), respectively. The sensitivity, specificity and accuracy of 99mTc-sestamibi SPECT/CT were 85% (163/192), 58% (21/36) and 89% (184/228) respectively. The accuracy of 99mTc-sestamibi SPECT/CT in the diagnosis of parathyroid tissue in patients with SHPT is significantly higher than that of ultrasound. The sensitivity, specificity and accuracy of combined application of ultrasound and 99mTc-sestamibi SPECT/CT were 93% (178/192), 61% (22/36) and 97% (200/228). The sensitivity, specificity and accuracy of combined application of ultrasound and 99mTc-sestamibi SPECT/CT were higher than those of either ultrasound or 99mTc-sestamibi SPECT/CT.

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Conclusions: The combined application of ultrasound and 99mTc-sestamibi SPECT/CT had incremental value in accurately detecting parathyroid tissue in patients with SHPT over either method alone.

Secondary hyperparathyroidism (SHPT) is a common and major complication of patients with end stage renal disease (ESRD) [1]. Current medicine interventions in treating SHPT have the potential to improve biochemical profiles and other surrogate markers [2]. However, some patients would present resistance to these medicines. Uncontrolled SHPT is associated with an increased risk of fractures and mortality. Parathyroidectomy (PTX) is reserved for medically refractory and severe SHPT. PTX increases long-term survival in ESRD patients, decreases the risk of fracture [3]. However, the rate of persistent and recurrent disease after parathyroidectomy is ranged between 10% and 30% [4]. The principal cause of surgical failure still remains the incomplete intraoperative identification and excision of all hyperplasic parathyroid glands [5]. Therefore, it is very important to correctly locate all parathyroid tissues preoperatively.

Different imaging methods have been used in the preoperative localization of parathyroid tissue. However, it is still an argument of which diagnostic method is the best to preoperatively localize parathyroid tissue in patients with SHPT, including ultrasound, 99mTc-sestamibi scintigraphy, intraoperative quick intact parathyroid hormone (iPTH) assay [6]. Accurate localization of abnormal parathyroid gland, especially ectopic parathyroid, may be very useful to guide the surgery, especially in high-risk patients. Previous studies have investigated the role of ultrasound and 99mTc-sestamibi parathyroid scan in the diagnosis of hyperparathyroidism [7,8]. However, these studies investigated the role of planar image, or dual phase planar scintigraphy, or dual tracer planar parathyroid scintigraphy combined with ultrasound, did not investigate the role of parathyroid SPECT/CT tomographic scintigraphy combined with ultrasound in SHPT. The goal of this study is to investigate whether combined application of ultrasound and 99mTc-sestamibi SPECT/CT had the incremental value in accurately detecting parathyroid tissue in patients with SHPT over either method alone.

Materials and methods

Patients

The study population included 60 consecutive ESRD patients between January 2011 and December 2014 on hemodialysis who underwent preoperative evaluation with 99mTc-sestamibi SPECT/CT scintigraphy and ultrasound prior to parathyroidectomy for SHPT at our hospital. Thirty-nine patients were female, 21 patients were male. The average age was $68.1 \pm 8.$ years old. The mean PTH concentration was greater than 600 pg/mL and calcium concentration was greater than 10.4 mg/dL. Preoperatively, all patients underwent dual phase 99mTc-sestamibi SPECT/CT scintigraphy and ultrasound. Our institutional review board provided approval for the procedures of this study.

Dual phase 99mTc-sestamibi scintigraphy with SPECT/CT

Patients were injected intravenously with 740 MBq (range, 718—763 MBq) of 99mTc-sestamibi. The image acquisitions were performed on a dual head gamma camera equipped with 5/8 inch NaI crystals and multidetector (4 row) spiral CT (Symbia T2; Siemens Medical Solutions). Early phase SPECT/CT and delayed phase SPECT images of the neck were obtained at 15 and 120 minutes after injection, respectively. The image acquisition method is same with the previous studies [9,10]. At delayed SPECT/CT phase, only SPECT data was acquired for SPECT/CT. CT acquisition data of early phase can be used for delayed phase SPECT/CT.

The interpretation of 99mTc-sestamibi scintigraphy was performed in consensus by 2 experienced nuclear medicine physicians. The image findings were classified as positive or negative. If the images showed persistent high tracer thyroid uptake at delayed phase, the physician would attach more attention to the CT images. A scintigraphy was recognized as positive if there was a definite focus of increased or separate 99mTc-sestamibi uptake relative to the uptake in the thyroid tissue of neck or mediastinum on either early or delayed SPECT/CT images. Precise location of each focus was also reported. Scintigraphy was negative when focal uptake in the neck or mediastinum was absent on both early and delayed phase SPECT/CT studies. Agreement between the two physicians was achieved in all patients [11].

Ultrasound

The patient was examined in a supine position with the neck hyperextended. Ultrasound was performed using linear transducers (7 to 12 MHz) for cervical examination in a field extending from the angles of the mandible to the sternum notch. Transversal and longitudinal views were obtained. Images of regions of interest were recorded on film reproducing video images. The radiologist interpreted each study together with the surgeon, because some patients had previous operations, such as parathyroid radiofrequency ablation, thyroidectomy, which may influence the result of these scans

due to distortion and scarring. Both were unaware of results of 99mTc-sestamibi scintigraphy. The radiologist was asked to score the presence of a hyperplastic parathyroid gland for each possible location (superior and inferior glands, on the right and left sides). The size of each gland (largest measurement) was measured. Equivocal images were considered negative.

Combined application of 99mTc-sestamibi and ultrasound

True positive of combined application of 99mTc-sestamibi and ultrasound was defined as positive result by 99mTc-sestamibi or ultrasound. True negative of combined application of 99mTc-sestamibi and ultrasound was defined as negative result by 99mTc-sestamibi and ultrasound.

Surgical procedures

Subtotal parathyroidectomy (sPTX) and/or total parathyroidectomy (tPTX) with implant were performed in young patients or candidates for kidney transplantation [12]. tPTX was performed in elder patients without autotransplant. The surgeon referred to the 99mTc-sestamibi scintigraphy and ultrasound results during preoperative planning. The sPTX included the ablation of 3 glands and half of the fourth gland. Half of the gland with most normal appearance was left in situ. The choice of the half gland with the lowest chance of recurrence was based on size criteria, vascularization, appearance, and when possible, absent 99mTc-sestamibi uptake. The excised glands were sent for frozen sections. The parathyroid gland hyperplasia was classified as either diffuse hyperplasia or nodular hyperplasia and based on the histology.

Statistical analysis

All statistical tests were performed by using SPSS 20.0 software (SPSS. Inc., Chicago, IL, USA). Comparisons of ultrasound and pathology, 99mTc-sestamibi SPECT/CT scintigraphy and pathology in the detection of parathyroid were performed using the McNemar's test, a nonparametric method for comparing paired dichotomous data. A two-tailed *P* value of 0.05 was considered to indicate statistical significance.

Results

Operation results

Assuming four parathyroid glands (PTGs) per patient, there should have been a total of 236 PTGs in 60 patients. In our series, 228 PTGs were identified and surgically resected in the 60 patients. Thirteen patients of sixty patients had 5 PTGs. Twelve ectopic PTGs were found in these patients (7 ectopic PTGs located in mediastinum, 3 located intra-thyroid, 2 located in supernumerary retro-esophageal ectopic glands). Thirty-two patients had 4 PTGs, eight patients had 3 PTGs, four patients had 2 PTGs, three patients had one PTG. In all the 60 patients, 9 patients (16 PTGs) previously underwent parathyroid radiofrequency ablation, 2 patients previously undergone hemi-thyroidectomy and hemi-parathyroidectomy. At pathological examinations, 36 PTGs (15.8%) showed normal parathyroid tissue, while 192 PTGs (84.2%) showed abnormal parathyroid tissue, including 49 PTGs (25.5%) with diffuse hyperplasia and 143 PTGs (74.5%) with nodular hyperplasia.

Ultrasound and 99mTc-sestamibi SPECT/CT scintigraphy results

The true positive, false positive, negative, true negative cases of ultrasound, 99mTc-sestamibi SPECT/CT, and combined application of ultrasound and 99mTc-sestamibi SPECT/CT were shown in Table 1. The sensitivity, specificity and accuracy of ultrasound were determined to be 81% (155/192), 47% (17/36) and 82% (172/228) respectively. At the same time, ultrasound showed thyroid disease (including goiter, adenoma, carcinoma) in 57% (34/60) patients. Based on the pathological result, 15 parathyroid glands were false positive results, which were caused by thyroid diseases, including 6 thyroid nodule, 3 thyroid carcinoma, 2 parathyroid carcinoma, 2 inflammatory lymph nodes, 2 skeletal brown tumor. These false positive results of 99mTc-sestamibi SPECT/CT may cause the failure of this operation. We would follow-up these patients in the future. Concomitant thyroid nodularity may influence the diagnostic role of these imaging methods. In the present study, concomitant thyroid disease was found in 57% (34/60) patients, which was similar to previous study [13]. In all 163 parathyroid glands of 99mTc-MIBI SPECT/CT scan, 136 parathyroid glands were positive in early phase, while 142 parathyroid glands were positive in delayed phase. The sensitivity, specificity and accuracy of 99mTc-sestamibi SPECT/CT were 85% (163/192), 58% (21/36) and 89% (184/228), respectively. The sensitivity, specificity and accuracy of combined application of ultrasound and 99mTc-sestamibi SPECT/CT were 93% (178/192), 61% (22/36) and 97% (200/228), respectively (Table 2). In our study population, thirteen patients of sixty patients had 5 PTGs. Twelve ectopic PTGs were found in these patients (7 ectopic PTGs located in mediastinum, 3 located intra-thyroid, 2 located in supernumerary retro-esophageal ectopic glands). 99mTc-sestamibi parathyroid SPECT/CT scan demonstrated 12 ectopic PTGs (Fig. 1), while ultrasound demonstrated only 2 intra-thyroid ectopic PTGs. The other ectopic PTGs were not demonstrated on ultrasound images.

Table 1 TP, FP, FN, TN of ultrasound, 99mTc-sestamibi SPECT/CT, and combined ultrasound and 99mTc-sestamibi SPECT/CT.

	TP	FP	FN	TN
Ultrasound	155	19	37	17
SPECT/CT	163	15	29	21
Combination application	178	14	14	22

TP: true positive; FP: false positive; FN: false negative patients; TN: true negative.

Table 2 Sensitivity, specificity, accuracy of ultrasound, 99mTc-sestamibi SPECT/CT, and combined ultrasound and 99mTc-sestamibi SPECT/CT.

	Sensitivity	Specificity	Accuracy
Ultrasound	0.81	0.47	0.82
SPECT/CT	0.85	0.58	0.89
Combination application	0.93	0.61	0.97

Discussion

SHPT is a frequent major complication for patients with ESRD on long-term dialysis. Patients with severe SHPT and patients with SHPT that is resistant to medical treatment should undergo PTX [14]. In the present study, all patients performed sPTX and/or tPTX, which may relate with the true negative of ultrasound, 99mTc-sestamibi SPECT/CT, and combined application of ultrasound and 99mTc-sestamibi SPECT/CT. PTX usually improves biological parameters as well as clinical signs and symptoms [15]. However, surgical results for uremic SHPT are less satisfactory than those in primary hyperparathyroidism with the rates of persistent and recurrent disease being higher (10%—30%) [16]. The main cause of surgical failure is missed orthotopic or ectopic glands, too large remnant/grafts, or supernumerary macroscopic parathyroid glands [17]. CT, magnetic resonance imaging (MRI), arteriography, and high-resolution ultrasound have all been used in the diagnosis of SHPT [17]. However, the performance of single anatomical technique is not very satisfactory in SHPT.

The present study showed that the combined application of ultrasound and 99mTc-sestamibi parathyroid SPECT/CT scintigraphy for the preoperative localization of parathyroid glands in SHPT had a higher sensitivity, specificity, and accuracy than those of ultrasound or 99mTc-sestamibi parathyroid SPECT/CT scintigraphy alone. The sensitivity, specificity and accuracy of combined application of ultrasound and 99mTc-sestamibi SPECT/CT was 93%, 61% and 97%. Furthermore, the combined application of these imaging techniques is particularly useful and complementary in the planning of the surgical strategy of uremic SHPT. The sensitivity, specificity and accuracy of ultrasound in this study were determined to be 81%, 47% and 82%, respectively. Ultrasound is largely used in clinical practice as it is non-invasive, easily repeatable and has acceptable sensitivity and specificity (45%—80% in SHPT) [18]. Anari et al. demonstrated the sensitivity, specificity, positive predictive value, and negative predictive value of ultrasound for diagnosis of enlarged parathyroid gland was 62.5%, 85.7%, 87.5%, 58.8% [19]. Vulpio et al. also reported that ultrasound parameters (such as maximum longitudinal diameter, structural and vascular echo-pattern scores) of PTGs, correlated to the degree of SHPT and type of hyperplasia, could be used to predict responsiveness to medical therapy [18]. The sensitivity, specificity and accuracy of 99mTc-sestamibi SPECT/CT of this study were determined to be 85%, 58% and 89%, respectively. The present study also demonstrated a discrepancy between ultrasound and 99mTc-sestamibi SPECT/CT. The accuracy of 99mTc-sestamibi SPECT/CT of this study is significantly higher than that of ultrasound ($P < 0.05$).

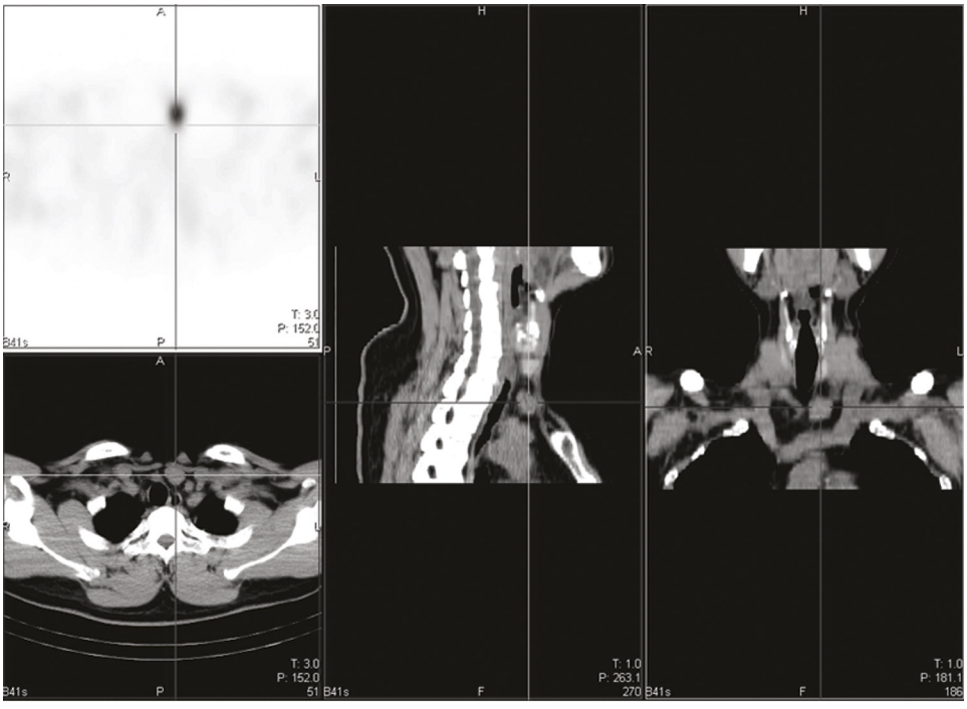

Figure 1. A 62-year-old woman with history of chronic kidney disease treated with hemodialysis. Laboratory tests showed increased serum calcium (21.3 mg/dL) and parathyroid hormone (712 pg/mL) concentrations. Delayed phase of transaxial SPECT (left upper), transaxial CT (left lower), sagittal CT (middle), coronal CT (right) images from 99mTc-sestamibi scan showed abnormal radioactive accumulation in the left upper superior mediastinum. Surgical pathologic result was diffuse parathyroid hyperplasia tissue.

Previous study reported the possible reason for the lower sensitivity of ultrasound was a relatively large number of different operators/reporters (invariably with different levels of experience) involved in parathyroid ultrasound, which would result in greater interobserver variability [20]. On the other hand, Vulpio et al. reported that the percentage of PTGs visualized by ultrasound was higher for superior than that for inferior PTG. The possible cause may be that the superior PTGs are usually localized at the level of the thyrolaryngeal groove, which can be explored easily by ultrasound [6]. Some authors pointed out that the PTG site (superior or inferior, typical or ectopic), the diameter, and the type of hyperplasia are the main factors determining the ultrasound patterns [6]. The other possible reason of lower sensitivity was the overall risk that at least one gland be ectopic in patients with SHPT was 4 times higher [21]. The sensitivity of detecting ectopic PTGs by ultrasound is relative low [22].

Previous studies investigated the role of ultrasound and 99mTc-sestamibi parathyroid scan in the diagnosis of SHPT. Vulpio et al. reported the usefulness of the combined ultrasound and 99mTc-sestamibi scintigraphy in the preoperative evaluation of uremic SHPT. This study reported that the sensitivity of 99mTc-sestamibi scintigraphy was 62% [6]. However, the sensitivity of 99mTc-sestamibi parathyroid SPECT/CT scan of the present study was 85%, which was significantly higher than previous study. The main cause was that the 99mTc-sestamibi parathyroid scan is planar scan in previous study [6], not the SPECT/CT tomographic scan as the present study. The other cause included that the mean PTH concentration was greater than 600 pg/mL and calcium concentration was greater than 10.4 mg/dL. Mshelia et al. reported that 99mTc-MIBI parathyroid scintigraphy was most likely to yield identification and localization of a parathyroid adenoma when both parathyroid hormone (PTH) concentration and calcium are elevated [23]. In the present study, 29 PTGs showed false negative result in 99mTc-sestamibi SPECT/CT scan. Patients with negative ultrasound and scintigraphy results had smaller parathyroid lesions [24]. The specificity of 99mTc-sestamibi SPECT/CT scan in the diagnosis PTG in patients with SHPT is 58%. Previous study reported that differentiating thyroid nodules from parathyroid lesions in parathyroid scintigraphy was often difficult because of the potential for abnormal tracer retention in thyroid nodules. The most common cause of false positive results is the presence of thyroid nodules [25]. Subtraction method, late 99mTc-MIBI delayed acquisitions (2—3 h), and SPECT/CT images can all improve specificity. Thymoma, metastatic or inflammatory lymph nodes, and skeletal brown tumors may also represent rare potential false positive lesions [26]. In the present study, 15 parathyroid glands were false positive results in the 99mTc-sestamibi SPECT/CT, including thyroid nodule, thyroid carcinoma, parathyroid carcinoma, inflammatory lymph nodes, skeletal brown tumor. These false positive results of 99mTc-sestamibi SPECT/CT may cause the failure of this operation. SPECT may also reclassify apparently inferior adenomas (on planar images) to superior, fourth pharyngeal pouch-derived adenomas prolapsed behind the lower pole of the thyroid gland. These adenomas can be located very deeply in the neck, in paraesophageal or retroesophageal locations, and may be missed by neck ultrasound [27].

At the present study, all patients performed the dual phase 99mTc-sestamibi parathyroid SPECT/CT scan. The dual phase planar scintigraphy method utilizing 99mTc-sestamibi has been widely employed in parathyroid scintigraphy. The dual phase planar scintigraphy technique is easy to perform, easy to interpret, economical and has been shown to provide high sensitivity and specificity in patients with primary hyperparathyroidism [28]. Previous studies reported that the sensitivity of 99mTc-sestamibi is low in patients with SHPT, ranging from 34% to 66% [29]. The present study demonstrated the sensitivity, specificity and accuracy of 99mTc-sestamibi SPECT/CT was 85%, 58% and 89%, respectively. Zhen et al. have reported that the sensitivity of 99mTc-sestamibi SPECT/CT was significantly higher than that of planar parathyroid scintigraphy, due to its superior resolution compared to static planar scintigraphy [10]. On the other hand, previous study suggested that both early and delayed phase 99mTc-sestamibi SPECT/CT should be performed in the preoperative evaluation of hemodialysis patients with SHPT, without increasing the radiation dose compared with the use of only the early or the delayed phase [9]. In the present study, 136/163 parathyroid glands were positive in early phase of 99mTc-MIBI SPECT/CT scan, while 142/163 parathyroid glands were positive in delayed phase.

Another finding of the present study is that 12 ectopic parathyroid were demonstrated by 99mTc-sestamibi parathyroid SPECT/CT scintigraphy. However, ultrasound demonstrated only 2 intra-thyroid ectopic PTGs. The other ectopic PTGs was not demonstrated on ultrasound images. It means that ultrasound failed to detect PTG localized in atypical sites, such as anterior or middle mediastinum, retro-esophageal region. Vulpio et al. also reported that ultrasound globally detected 57/99 PTGs in patients with SHPT. However, only one of 15 ectopic PTGs was detected by ultrasound. It means that the sensitivity of ultrasound in detecting the ectopic PTGs was low [18]. On the other hand, the overall risk that at least one gland be ectopic in patients with SHPT is 4 times higher, although the risk of major ectopy is about 2%—3% in primary HPT [21]. Ishibashi et al. also reported that the 99mTc-sestamibi scintigraphy is the only diagnostic method that can identify ectopic glands in patients with SHPT [22]. The scan range of SPECT in the present study included the neck and thorax with an axial field of view of 53.3×38.7 cm because ectopic glands may be widely distributed along the parathyroid cell migration routes [30]. Detection of ectopic parathyroid glands is probably the most important value of preoperative imaging in patients with SHPT. Previous study reported that the high sensitivity to visualize ectopic parathyroid glands was considered the main advantage of scintigraphy compared with ultrasound [6].

Another advantage of SPECT/CT is the accurate and anatomic depiction of the PTG location, size, and adjacent tissues or structure, which facilitates the operative planning. Hybrid SPECT/CT systems that combine conventional CT with SPECT have been available for clinical application in recent years. SPECT/CT has shown to be more specific and sensitive in detecting and interpreting small PTGs. This is due to the combination of precise anatomical detail available with high spatial resolution CT and metabolism or functional information through SPECT [31,32]. In the present study, SPECT/CT was able to accurately localize

and characterize the 12 ectopic parathyroid. Therefore, we suggested the combined application of ultrasound and 99mTc-SPECT/CT was performed for the preoperative location of parathyroid tissue in patients with SHPT.

Limitation

The first limitation is that the dual phase 99mTc-MIBI parathyroid SPECT/CT scintigraphy was used in this study. Previous studies reported that simultaneous dual-isotope imaging, with 99mTc-MIBI + ^{123}I, was superior to that of single tracer technique in primary hyperparathyroidism [33,34]. The second limitation is that the diagnostic indexes of 99mTc-sestamibi parathyroid SPECT/CT were not compared with the PTH levels. Previous study reported that overall sensitivity of parathyroid scintigraphy depending on serum PTH levels in hyperparathyroidism [35,36]. The third limitation is that we did not follow up the patient's outcomes, such as rate of recurrence and hypoparathyroidism. We would follow-up these patients in the future. The fourth limitation is that patients with positive 99mTc-sestamibi SPECT/CT or ultrasound result would perform the surgery, which would decrease the sensitivity values of preoperative imaging modalities. On the other hand, some new radiotracers, including ^{11}C-methionine PET and ^{18}F-choline PET, have been used in the diagnosis of hyperparathyroidism [37,38]. ^{11}C-methionine PET seems to be a sensitive method for hyperparathyroidism patients before reoperation.

Conclusions

Our study demonstrates that the combined application of ultrasound and 99mTc-sestamibi SPECT/CT has incremental value in accurately detecting parathyroid tissue in patients with SHPT over either method alone. Ultrasound is largely used in clinical practice as it is noninvasive, easily repeatable and has acceptable sensitivity and specificity. SPECT/CT cannot only detect more PTGs, but also more accurately depicts the precise location of PTGs. At the same time, dual phase SPECT/CT did not add the radiation dose than early or delayed phase SPECT/CT scan.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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