Diagnosis performance of ultrasonography, dual-phase 99mTc-MIBI scintigraphy, early SPECT/CT and delayed SPECT/CT in preoperative localization of parathyroid gland in secondary hyperparathyroidism

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Abstract

Background: Secondary hyperparathyroidism (SHPT) usually need parathyroidectomy when drug regimens fail. However, obtaining an exact preoperative map of the locations of the parathyroid glands is a challenge. The purpose of this study was to compare the diagnostic performance of ultrasonography, dual-phase 99m Tc-MIBI scintigraphy, early SPECT/CT and delayed SPECT/CT in patients with SHPT. Methods: Sixty patients with SHPT who were undergoing dialysis were evaluated preoperatively with ultrasonography, dual-phase 99m Tc-MIBI scintigraphy, early SPECT/CT and delayed SPECT/CT. Postoperative pathology served as the gold standard. The sensitivity, specificity, and accuracy rate were determined for each method. Spearman correlation analysis was used to analyze the correlation of the hyperplastic parathyroid calcification with serum alkaline phosphatase (AKP) and parathyroid hormone (PTH). Results: 229 lesions in 60 patients were pathological confirmed to be parathyroid hyperplasia with 209 lesions in typical sites, 15 lesions in upper mediastinum and 5 lesions in the thyroid. 88.33% (53/60) patients had four lesions. US, early and delayed SPECT/CT had significantly higher sensitivity and accuracy rate (P < 0.001) than did dual-phase 99m Tc-MIBI scintigraphy. Furthermore, early SPECT/CT had significantly higher sensitivity ($\chi^2 = 17.521, P < 0.001$, $\chi^2 = 35.027, P < 0.001$) and accuracy rate ($\chi^2 = 11.076, P = 0.001$, $\chi^2 = 16.289, P < 0.001$) than did US and delayed SPECT/CT. In ectopic hyperplastic parathyroid, the sensitivity of early SPECT/CT (90%) was significantly higher than US (55%) and dual-phase planar (50%) (P = 0.039 and P = 0.039). Spearman correlation results showed a significant linear association between the calcification and serum PTH ($r = 0.398, P = 0.002$) and AKP ($r = 0.415, P = 0.002$). Conclusion: The ability of early SPECT/CT to detect hyperplastic parathyroid in patients with SHPT is superior to US, 99m Tc-MIBI scintigraphy and delayed SPECT/CT, and dual-phase SPECT/CT is not essential. Calcification of parathyroid gland is related to the levels of PTH and AKP and may help provide an evidence for the identification of SHPT.

Background

Secondary hyperparathyroidism (SHPT) is a complex disease due to increase parathyroid hormone (PTH) production which affect the metabolism of calcium or phosphorus, causing abnormal
parathyroid hormone secretion, usually leading to 4-gland hyperplasia [1]. Severe SHPT mainly occurs in chronic kidney disease (CKD), claimed as a key causal factor for bone disease, muscle weakness, neurologic dysfunction, soft tissue and vascular calcifications, which increased cardiovascular morbidity and mortality [2, 3]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) suggested parathyroidectomy to treat severe secondary hyperparathyroidism when drug regimens fail[4] and total parathyroidectomy had minimum risk of postoperative relapse (0-4%) [5]. However, parathyroidectomy for SHPT are less satisfactory, and the occurrence of persistent SHPT after parathyroidectomy is reported to be 0.4–25%[6]. Surgical failure is mainly due to the difficulty to resect all parathyroid glands especially because of the existence of supernumerary (more than 4) and ectopic parathyroid glands. It is reported that the incidences of ectopic and supernumerary glands reported in patients with end-stage kidney disease are 17.5-39.3% and 6.3-37%, respectively[7-9].Therefore, preoperative imaging and accurate localization is critical to a successful operation.

Parathyroid glands can be detected with multiple methodologies such as ultrasonography (US), computer tomography (CT) and magnetic resonance imaging (MRI), but the performance of these anatomical examinations is not satisfactory[10]. Different from the above anatomical imaging, technetium-99m methoxyisobutylisonitrile ($^{99\text{m}}$Tc-MIBI) scintigraphy is a functional exploration and regarded as the main preoperative localizing method for patients with PHPT or SHPT[11]. When combined with single photon emission computed photography/computed photography (SPECT/CT), functional and anatomical, the sensitivity of scintigraphy was increased. Multiple studies have reported $^{99\text{m}}$Tc-MIBI scintigraphy superior to US especially combined with SPECT/CT in patient with hyperparathyroidism[12-14], but these studies do not separate SHPT from primary hyperparathyroidism (PHPT) for statistics and analysis. For PHPT, several investigations had reported $^{99\text{m}}$Tc-MIBI SPECT/CT superior to scintigraphy [11, 15, 16].

However, different from PHPT mostly due to parathyroid adenoma which most often able to be identified, SHPT usually has more than one lesion and it is difficult to highlight all the abnormal
parathyroid glands because parathyroid hyperplasia is an asynchronous and asymmetrical process[17]. For the SHPT, Jae Bok et al.[17] reported US (91.5%) had the higher sensitivity than $^{99m}$Tc-MIBI scintigraphy (56.1%), while Vulpio et al.[18] reported a little higher sensitivity of $^{99m}$Tc-MIBI scintigraphy (62%) than US (55%). When combined with SPECT/CT, $^{99m}$Tc-MIBI SPECT/CT had a higher sensitivity than US[19, 20] and $^{99m}$Tc-MIBI scintigraphy[6]. However, all these studies have acquired only a single set of SPECT/CT imaging, either early or delayed. One prior investigation directly compared early and delayed SPECT/CT and indicated both early and delayed phase should be performed[21]. Whatever all of them affirmed the SPECT/CT value in patients of SHPT, but which phase of SPECT/CT better in SHPT remains to be elucidated.

The purpose of this investigation was to directly compare the diagnostic performance of US, dual-phase $^{99m}$Tc-MIBI scintigraphy (or planar imaging), early SPECT/CT and delayed SPECT/CT to obtain an exact preoperative map of the localization of SPTH and to determine whether dual phase SPECT/CT is essential.

Methods

Clinical Materials

From May 2017 to November 2019, a total of 60 CKD patients who were undergoing dialysis and parathyroidectomy for SPTH in the Sixth Affiliated Hospital of Sun Yat-sen University were included in this study. All patients received US, dual-phase $^{99m}$Tc-MIBI scintigraphy, early SPECT/CT and delayed SPECT/CT, and SHPT were confirmed by pathological results. Patient demographics (gender, age, dialysis vintage), imaging, laboratory values, operative and pathological results were collected. Laboratory values conclude serum calcium, phosphorus, creatinine, alkaline phosphatase (AKP), preoperative parathyroid hormone (PTH) and postoperative PTH within the first week.

Imaging Methods

All patients with SHPT received an intravenous injection of 555 MBq of $^{99m}$Tc-MIBI. Dual-phase $^{99m}$Tc-MIBI scintigraphy was obtained at 15 min and 120 min after injection. SPECT/CT integrated imaging was performed immediately after the early and delayed planar imaging. The imaging acquisition was
using Symbia Intevo 6, Siemens Healthcare. The acquisition was set at energy peak of 140 keV, window width of 20%, matrix of 128x128, magnification of 1-fold, and counts of 600 k per frame with low-energy high resolution collimation. The CT scanning parameter was set at FOV of 40 cm, CT tube current of 200 mA, CT tube voltage of 130 kV, slice thickness of 2.5 mm, reconstruction matrix of 128x128, and reconstruction thickness of 2.5 mm. Imaging data were reconstructed using flash 3D. Ultrasonography was performed using the equipment (LOGIQ E9; GE Healthcare, USA), equipped with a linear probe 9L (8.4-9 MHz) and ML6-15 (10-15MHz).

**Image analysis**

**Dual-phase ⁹⁹ᵐTc-MIBI scintigraphy**

The images were analyzed by 2 experienced nuclear medicine doctors who were blinded to the laboratory, surgical, and pathological results. The image was considered positive on visual analysis when it met one of the following criteria: (1) Abnormal ⁹⁹ᵐTc-MIBI uptake was observed on both the early and the delayed image. (2) Abnormal ⁹⁹ᵐTc-MIBI uptake was observed on either the early or the delayed image. It was considered negative when abnormal ⁹⁹ᵐTc-MIBI uptake was observed on neither early nor delayed image[13].

**Early SPECT/CT and delayed SPECT/CT**

SHPT was diagnosed positive on the early or delayed SPECT/CT if CT indicated parenchyma space occupying lesion at the parathyroid region, while SPECT image showed abnormal ⁹⁹ᵐTc-MIBI accumulation compared to neck muscles and blood vessels. It was considered negative if abnormal ⁹⁹ᵐTc-MIBI uptake was observed on neither early nor delayed SPECT when CT indicated parenchyma space occupying lesion at the parathyroid region, and if abnormal ⁹⁹ᵐTc-MIBI uptake was observed on both early and delay phase but no parenchyma space occupying lesion at the parathyroid region on CT image[19].

**Ultrasonography**

The images were assessed by experienced ultrasound doctors blind to the laboratory, surgical, and pathological results. Typical ultrasound image was demonstrated as an oval or asymmetrical
hypoechoic mass at the upper and lower pole of the thyroid back, having variable dimensions, separated by the thyroid gland. It may rarely present with cystic degeneration. Color doppler examination showed parathyroid vascular pedicle and a vascular arch located at the periphery of the gland[22].

**Definition of ectopic parathyroid glands**

It was considered parathyroid glands position normal when the lower glands were related to the lower pole of the thyroid gland, and when the upper glands were found near the upper pole of the thyroid. Hyperplastic parathyroid gland located inside the superior mediastinum regions and thyroid gland was regarded as ectopic parathyroid gland[6, 23].

**Parathyroidectomy and final diagnosis**

Parathyroidectomy was performed in severe SHPT patients who failed to respond to medical therapy. Our operative indications included: persistent serum PTH >800 pg/mL, and at least one enlarged parathyroid gland discovered by US, or $^{99m}$Tc-MIBI scintigraphy or SPECT/CT[24]. In our study, serum PTH levels less than 300 pg/mL detected at the first postoperative week was identified as successful parathyroidectomy [25]. All patients were submitted to surgery by the same surgical team. Subtotal or total parathyroidectomy with auto-transplantation was performed on patients. In subtotal parathyroidectomy, 3 glands and half of the fourth gland were removed and half of the normal gland was left in situ. Hyperplastic parathyroid glands resected in operation were confirmed by pathological examination regarded as the golden standard for final diagnosis. The US, dual-phase $^{99m}$Tc-MIBI scintigraphy, early SPECT/CT and delayed SPECT/CT findings for each gland were defined as true positive, false positive, true negative, or false negative on the basis of the pathology results. Comparisons of sensitivity, specificity and accuracy rate between different groups were made according to the parathyroid pathology results.

**Statistical analysis**

Metric data are expressed as mean ± SD. Categorical variables were analyzed using the $\chi^2$ or Fisher’s exact test. Spearman correlation was used for statistical analysis. A $P$ value less than 0.05 was
considered to indicate statistical significance. Statistical analysis was performed using the IBM SPSS version 20.0 statistical software.

Results
For the all 60 patients included in the study, the primary diseases of all patients were stage 5 chronic kidney disease. The clinical pathological characters of the patients with SHPT who underwent surgery are summarized in Table 1. There were 34 males and 26 females with an average age of 47.8 ± 11.1 years and an average dialysis age of 6.58 ± 3.16 years. 51 patients received regular hemodialysis, 5 peritoneal dialysis, and 4 both hemodialysis and peritoneal dialysis. All patients had significantly increased serum PTH preoperatively (1838.37±894.13pg/ml) and decreased postoperatively (38.25±75.04pg/ml). 23.33% (14/60), 95.00% (57/60) and 74.07% (40/54) patients showed higher serum calcium, phosphorus and AKP levels, respectively. Moreover, 23 patients had punctate and annular calcification in the hyperplastic parathyroid glands, and the correlation between calcification and laboratory test items such as serum PTH, calcium, phosphorus, AKP and creatinine were analyzed. Spearman correlation results showed a significant linear association between the calcification and serum PTH (r = 0.398, P = 0.002) and serum AKP (r = 0.415, P = 0.002), while no significant correlation was observed between the calcification and serum calcium, phosphorus, and creatinine. Besides, a significant linear association was seen between serum PTH and AKP (r = 0.349, P = 0.011).

In all, 59 of the 60 patients underwent total parathyroidectomy with auto-transplantation, and one patient underwent subtotal parathyroidectomy. Meanwhile, 9 of the 60 patients underwent partial thyroidectomy and one accompanied by papillary carcinoma of thyroid. As shown in Figure 1, a total of 243 lesions were resected in the surgery of the 60 patients, 229 lesions were pathological confirmed to be parathyroid hyperplasia, 5 were normal parathyroid glands, 4 were lymph nodes, 4 were thyroid nodules and 1 was bone tissue. In the confirmed 229 lesions, 209 were in typical sites, 15 in upper mediastinum and 5 in the thyroid gland. Among the 60 patients, four lesions were identified in 53 patients (88.33%), two lesions in 4 patients (6.67%), and the other three patients had 1, 3, 5 lesions respectively. US showed 178 positive lesions in 60 patients, and 175 lesions confirmed
to be true positive. The three false positive lesions were confirmed to be lymph nodes. Dual-phase planar detected 116 positive lesions and there were 2 false positive lesions. One was confirmed to be thyroid nodule and another one was the focal $^{99m}$Tc-MIBI uptake of the manubrium sterni without destruction of bone on the SPECT/CT images. Early SPECT/CT showed 210 positive lesions, and 205 lesions confirmed to be true positive. For the 5 false positive lesions, three lesions were confirmed to be lymph nodes and two lesions were thyroid nodules. Delayed SPECT/CT showed 171 positive lesions concluding 168 true positive and 3 false positive of which two lesions were confirmed to be lymph nodes and the other one was thyroid nodule. A representative imaging showed in the Figure 2.

Analyzed by case numbers, the sensitivity of US, dual-phase planar, early and delayed SPECT/CT was 93.33% (56/60), 76.67% (46/60), 98.33% (59/60), 98.33% (59/60). Analyzed by lesion numbers and as shown in Table 2, early SPECT/CT had the highest sensitivity and accuracy rate while dual-phase planar had the lowest (89.5% vs. 49.8% and 88.0% vs. 51.9%) among the 4 modalities. US, early and delayed SPECT/CT had significantly higher sensitivity and accuracy rate ($P < 0.001$) than did dual-phase planar. Furthermore, early SPECT/CT had significantly higher sensitivity ($\chi^2 = 17.521, P < 0.001$, $\chi^2 = 35.027, P < 0.001$) and accuracy rate ($\chi^2 = 11.076, P = 0.001$, $\chi^2 = 16.289, P < 0.001$) than did US and delayed SPECT/CT. There was no significant difference of sensitivity and accuracy rate between US and delayed SPECT/CT. The specificity of US, dual-phase planar, early and delayed SPECT/CT was 78.6%, 85.7%, 64.3% and 78.6%.

Then, the sensitivity of preoperative eutopic and ectopic parathyroid imaging was compared (Table 3). Twenty ectopic parathyroid glands (20/229, 8.73%) were detected in 16 patients (16/60, 26.67%). The sensitivity of preoperative eutopic parathyroid imaging had the similar results compared with preoperative overall parathyroid imaging. However, in ectopic parathyroid, the sensitivity of early SPECT/CT was significantly higher than US and dual-phase planar ($P < 0.05$). Delayed SPECT/CT was not significantly superior to US and dual-phase planar for sensitivity.

Discussion

SHPT is a common complication in CKD, and it is followed by disorders of calcium and phosphorus metabolism, abnormal PTH secretion, and parathyroid hyperplasia. Serum PTH plays a critical role in
the maintenance of calcium and phosphate levels. Unlike patients with PHPT which is independent secretion of PTH by the parathyroid tissue, patients with SHPT have a compensatory PTH secretion due to hypocalcaemia [20]. Therefore, in patients with SHPT, the serum calcium level can be increased or remain normal. In our study all patient had higher serum PTH but only 23.33% patients showed higher serum calcium. We found 23 patients had punctate and annular calcification in the hyperplastic parathyroid glands and annular calcification might be a special sign of SHPT [26-28]. Soft tissue and vascular calcifications are commonly present in end-stage CKD patients, secondary to disturbances in calcium and phosphate balance and secondary to hyperparathyroidism, which may explain why the parathyroid glands were more prone to appear calcification in patients with SHPT [29, 30]. Previous study showed an association between serum AKP and vascular calcification via modulation of the pyrophosphate pathway[31, 32]. Serum PTH can increase the bone metabolic conversion to elevate the serum AKP level[20]. Therefore, as we reported calcification of parathyroid glands might be correlated with serum PTH and AKP.

For severe SHPT parathyroidectomy remains the best treatment option when drug treatment fails. However, surgical results among SHPT patients are less satisfactory than those among patients with PHPT due to incomplete intraoperative identification of all parathyroid glands [21]. Therefore, preoperative imaging and localization are critical to a successful operation. US is the most used imaging investigation for the advantage of low cost and simple manipulation, but limited in the detection of ectopic parathyroid glands and in the dependence on the examiner’s experience[22]. CT may be necessary to locate parathyroid glands precisely, especially for the ectopic glands of mediastinum, to avoid recurrent laryngeal nerve injuries caused by unnecessary dissections[7]. MRI has the advantage of no radiation and has a discreetly increased sensitivity than CT, and it is especially useful in detecting mediastinal parathyroid glands[22]. Different from the above anatomical imaging, ⁹⁹ᵐTc-MIBI imaging is a functional exploration with the advantage of detecting ectopic glands and it is based on the different washout rate between the thyroid tissue and parathyroid hyperplasia[33]. ⁹⁹ᵐTc-MIBI scintigraphy has high sensitivity and specificity, but also has
multiple limitation, such as lacks precise anatomical location of the lesion [34], making the differential diagnosis of parathyroid hyperplasia from thyroid lesions difficult. SPECT/CT is significantly superior to $^{99m}$Tc-MIBI scintigraphy in the detection of parathyroid abnormalities because it can provide more precise anatomic localization particularly for localizing ectopic lesions, identification of supernumerary glands and parathyroid glands with the lowest $^{99m}$Tc-MIBI uptake [11, 35].

In our study, we directly compared US, dual-phase $^{99m}$Tc-MIBI scintigraphy, early SPECT/CT and delayed SPECT/CT in the SHPT patients. The overall sensitivity and accuracy of early phase SPECT/CT was higher than the other techniques and also slightly higher than the previous studies[21, 22]. For detecting ectopic parathyroid glands, the sensitivity of early SPECT/CT was significantly higher than US and $^{99m}$Tc-MIBI scintigraphy, and the percentage was similar to that of the previous study (90.5%) [6]. Our results showed that early SPECT/CT was superior to the other methodologies to detect parathyroid lesion in SHPT patients. Hybrid SPECT/CT can provide not only functional information acquired through SPECT but also the accurate and anatomic depiction of parathyroid gland location, size, and adjacent structures through CT, especially the ectopic and supernumerary parathyroid glands. With delayed SPECT/CT, two investigational group had reported a high sensitivity of 59.3% [20] and 85%[19], and in our study the sensitivity is 73.4%. In our investigation, we found that $^{99m}$Tc-MIBI uptake of some hyperplastic parathyroid glands on early SPECT/CT were slightly higher than the background but lower than the thyroid and further clearance in delayed SPECT/CT causing false negative on the delayed SPECT/CT imaging. Schachter et al. reported that delayed SPECT/CT may be nondiagnostic when similar washout rates between thyroid and parathyroid tissue are found[36]. So, we may suggest early SPECT/CT in combination with dual-phase $^{99m}$Tc-MIBI scintigraphy as the routine preoperative evaluation, and delayed SPECT/CT may not be necessary due to entailing more radiation than early SPECT/CT alone. Meanwhile $^{99m}$Tc-MIBI scintigraphy cannot be replaced by early SPECT/CT for the former is a rough indication of the presence of ectopic parathyroid gland and assists in determining SPECT/CT scan range.

Most patients in our study had four proved lesions which remind us to identify as many as four
parathyroid gland lesions as possible when diagnosing SHPT. As we found all of the calcified parathyroid glands (45 lesions) were confirmed to be parathyroid hyperplasia by pathology, reminding us that if calcified nodules were seen in the parathyroid region, parathyroid hyperplasia should be suspected. However large samples and multicenter studies are still needed to confirm these.

The main reason of low sensitivity of US is believed to be the frequent misdiagnosis of inferior parathyroid lesions, especially the mediastinal ectopic parathyroid glands. The manipulator’s experience for accurate determination of lesions is also one of the indispensable factors that can’t be ignored. It was reported that the sensitivity of US for SHPT diagnosis was ranging from 46.24% to 91.5%[17, 19, 20], which was similar to our result (75.65%).

Our observations show that the sensitivity of $^{99m}$Tc-MIBI scintigraphy is the lowest in the four methods. The reasons are as follows. First, although $^{99m}$Tc-MIBI scintigraphy can effectively detect the ectopic parathyroid gland, they can only show a general increase in radioactivity and cannot clearly distinguish the number of lesions when multiple parathyroid gland lesions are existed.

Secondly, some hyperplastic parathyroid glands p-glycoprotein was positive and $^{99m}$Tc-MIBI was quickly eliminated from the parathyroid glands leading to the negative uptake images of scintigraphy [37]. Thirdly, $^{99m}$Tc-MIBI scintigraphy was related to the size and weight of the parathyroid glands, and the smaller parathyroid gland lesions were easy to be omitted[22, 38]. Fourthly, the lesions located behind the thyroid gland and with the similar $^{99m}$Tc-MIBI uptake were difficult to detect on the scintigraphy but those lesions were identified on SPECT/CT. In a meta-analysis the pooled sensitivity of $^{99m}$Tc-MIBI scintigraphy in SHPT was 58% [39] which is a little higher than our result.

David Taieb et al. [38] reported the most common cause of false positive results on parathyroid scintigraphy was the presence of thyroid nodules, thymoma, metastatic or inflammatory lymph nodes, and skeletal brown tumors may also represent rare potential false-positive lesions. However, in our study multiple false positive lesions found on US, early and delayed SPECT/CT were mostly confirmed to be lymph nodes followed by thyroid nodules. The most likely explanation is that we have lesser false positive lesions and all our patients were SHPT not PHPT. One false positive lesion found
on the $^{99m}$Tc-MIBI scintigraphy was the focal $^{99m}$Tc-MIBI uptake of the manubrium sterni. Previous study supposed that the $^{99m}$Tc-MIBI uptake of bone might reflect the presence of active metabolic bone disease, but did not reflect the changes that occurred in microstructure of bone[40]. However, this remains to be evaluated further. Besides, the specificity of early SPECT/CT in our study is lower than the previous study (75%)[6] probably due to the small number of true negative cases. Our study is limited by its retrospective design and relatively small cohort of patients. Therefore, future prospective randomized studies of preoperative imaging modalities are needed for more accurate and objective investigations.

Conclusion
Our study demonstrated that the ability of early SPECT/CT to detect parathyroid lesion in SHPT patients is superior to US, $^{99m}$Tc-MIBI scintigraphy and delayed SPECT/CT. These findings strongly suggest that dual-phase $^{99m}$Tc-MIBI scintigraphy, with early SPECT/CT whenever possible, should be part of the routine preoperative evaluation of patients with SHPT and dual-phase SPECT/CT is not essential. Calcification of parathyroid gland is related to the levels of PTH and AKP and may help provide an evidence for the identification of SHPT

Abbreviations

$^{99m}$Tc-MIBI: Technetium-99m methoxyisobutylisonitrile; SHPT: Secondary hyperparathyroidism; PHPT: Primary hyperparathyroidism; AKP: Alkaline phosphatase; PTH: Parathyroid hormone; US: ultrasonography; CT: Computer tomography; MRI: Magnetic resonance imaging; SPECT/CT: Single photon emission computed photography/computed photography; CKD: Chronic kidney disease.

Declarations

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Authors’ contributions

Contribution to conception and design: RQZ, ZWZ and PH; Contribution to data acquisition and interpretation: RQZ, ZWZ, ZL, RH, WLQ and PBH; Contribution to performance of all statistical analyses: RQZ and PBH; Contribution to drafting of manuscript: RQZ, PBH, ZWZ and JZ; Contribution
to critical revision of manuscript: RQZ, PBH, ZWZ and PH. All authors have read and approved the manuscript.

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**Availability of data and materials**

The data that support the findings of this study are available from authors upon request and with permission of the Sixth Affiliated Hospital Ethics Committee.

**Ethics approval and consent to participate**

The study was approved by the ethical committee of the Sixth Affiliated Hospital. On the basis of the general research contentment form, the need for individual consent was waived.

**Consent for publication**

Not Applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Tominaga Y, Tanaka Y, Sato K, Nagasaka T, Takagi H: Histopathology, pathophysiology, and indications for surgical treatment of renal hyperparathyroidism. Semin Surg Oncol 1997, 13(2):78-86.

2. Trainor D, Borthwick E, Ferguson A: Perioperative management of the hemodialysis patient. Semin Dial 2011, 24(3):314-326.

3. Evans M, Methven S, Gasparini A, Barany P, Birnie K, MacNeill S, May MT, Caskey FJ, Carrero JJ: Cinacalcet use and the risk of cardiovascular events, fractures and
mortality in chronic kidney disease patients with secondary hyperparathyroidism. Scientific reports 2018, 8(1):2103.

4. Kidney Disease: Improving Global Outcomes CKD-MBDWG: KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney international Supplement 2009(113):S1-130.

5. Madorin C, Owen RP, Fraser WD, Pellitteri PK, Radbill B, Rinaldo A, Seethala RR, Shaha AR, Silver CE, Suh MY et al: The surgical management of renal hyperparathyroidism. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies 2012, 269(6):1565-1576.

6. Zeng M, Liu W, Zha X, Tang S, Liu J, Yang G, Mao H, Yu X, Sun B, Zhang B et al: (99m)Tc-MIBI SPECT/CT imaging had high sensitivity in accurate localization of parathyroids before parathyroidectomy for patients with secondary hyperparathyroidism. Renal failure 2019, 41(1):885-892.

7. Hiramitsu T, Tomosugi T, Okada M, Futamura K, Tsujita M, Goto N, Narumi S, Watarai Y, Tominaga Y, Ichimori T: Pre-operative Localisation of the Parathyroid Glands in Secondary Hyperparathyroidism: A Retrospective Cohort Study. Scientific reports 2019, 9(1):14634.

8. Schneider R, Waldmann J, Ramaswamy A, Fernandez ED, Bartsch DK, Schlosser K: Frequency of ectopic and supernumerary intrathymic parathyroid glands in patients with renal hyperparathyroidism: analysis of 461 patients undergoing initial parathyroidectomy with bilateral cervical thymectomy. World journal of surgery 2011, 35(6):1260-1265.

9. Taterra D, Wong LM, Vikse J, Sanna B, Pekala P, Walocha J, Cirocchi R, Tomaszewski
K, Henry BM: The prevalence and anatomy of parathyroid glands: a meta-analysis with implications for parathyroid surgery. Langenbeck's archives of surgery 2019, 404(1):63-70.

10. Kettle AG, O'Doherty MJ: Parathyroid imaging: how good is it and how should it be done? Seminars in nuclear medicine 2006, 36(3):206-211.

11. Lavely WC, Goetze S, Friedman KP, Leal JP, Zhang Z, Garret-Mayer E, Dackiw AP, Tufano RP, Zeiger MA, Zissman HA: Comparison of SPECT/CT, SPECT, and planar imaging with single- and dual-phase (99m)Tc-sestamibi parathyroid scintigraphy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2007, 48(7):1084-1089.

12. Kobylecka M, Plazinska MT, Chudzinski W, Fronczewska-Wieniawska K, Maczewska J, Bajera A, Karlinska M, Krolicki L: Comparison of scintigraphy and ultrasound imaging in patients with primary, secondary and tertiary hyperparathyroidism - own experience. Journal of ultrasonography 2017, 17(68):17-22.

13. Zhou J, Lu DY, Xia L, Cheng XJ: Diagnosis performance of (99m)Tc-MIBI and multimodality imaging for hyperparathyroidism. Journal of Huazhong University of Science and Technology Medical sciences = Hua zhong ke ji da xue xue bao Yi xue Ying De wen ban = Huazhong keji daxue xuebao Yixue Yingdewen ban 2017, 37(4):582-586.

14. Kim YI, Jung YH, Hwang KT, Lee HY: Efficacy of (9)(9)mTc-sestamibi SPECT/CT for minimally invasive parathyroidectomy: comparative study with (9)(9)mTc-sestamibi scintigraphy, SPECT, US and CT. Annals of nuclear medicine 2012, 26(10):804-810.

15. Slater A, Gleeson FV: Increased sensitivity and confidence of SPECT over planar imaging in dual-phase sestamibi for parathyroid adenoma detection. Clinical nuclear medicine 2005, 30(1):1-3.
16. Moka D, Voth E, Dietlein M, Larena-Avellaneda A, Schicha H: Technetium 99m-MIBI-SPECT: A highly sensitive diagnostic tool for localization of parathyroid adenomas. Surgery 2000, 128(1):29-35.

17. Lee JB, Kim WY, Lee YM: The role of preoperative ultrasonography, computed tomography, and sestamibi scintigraphy localization in secondary hyperparathyroidism. Annals of surgical treatment and research 2015, 89(6):300-305.

18. Vulpio C, Bossola M, De Gaetano A, Maresca G, Bruno I, Fadda G, Morassi F, Magalini SC, Giordano A, Castagneto M: Usefulness of the combination of ultrasonography and 99mTc-sestamibi scintigraphy in the preoperative evaluation of uremic secondary hyperparathyroidism. Head & neck 2010, 32(9):1226-1235.

19. Yuan LL, Kan Y, Ma DQ, Yang JG: Combined application of ultrasound and SPECT/CT has incremental value in detecting parathyroid tissue in SHPT patients. Diagnostic and interventional imaging 2016, 97(2):219-225.

20. Li P, Liu Q, Tang D, Zhu Y, Xu L, Sun X, Song S: Lesion based diagnostic performance of dual phase (99m)Tc-MIBI SPECT/CT imaging and ultrasonography in patients with secondary hyperparathyroidism. BMC medical imaging 2017, 17(1):60.

21. Yang J, Hao R, Yuan L, Li C, Yan J, Zhen L: Value of dual-phase (99m)Tc-sestamibi scintigraphy with neck and thoracic SPECT/CT in secondary hyperparathyroidism. AJR American journal of roentgenology 2014, 202(1):180-184.

22. Strambu V, Bratucu M, Garofil D, Paic V, Zurzu M, Tigora A, Popa F, Radu P, Costin P: The Value of Imaging of the Parathyroid Glands in Secondary Hyperparathyroidism. Chirurgia 2019, 114(5):541-549.

23. Andrade JS, Mangussi-Gomes JP, Rocha LA, Ohe MN, Rosano M, das Neves MC, Santos Rde O: Localization of ectopic and supernumerary parathyroid glands in patients with
secondary and tertiary hyperparathyroidism: surgical description and correlation with preoperative ultrasonography and Tc99m-Sestamibi scintigraphy. Brazilian journal of otorhinolaryngology 2014, 80(1):29-34.

24. Zhang L, Xing C, Shen C, Zeng M, Yang G, Mao H, Zhang B, Yu X, Cui Y, Sun B et al: Diagnostic Accuracy Study of Intraoperative and Perioperative Serum Intact PTH Level for Successful Parathyroidectomy in 501 Secondary Hyperparathyroidism Patients. Scientific reports 2016, 6:26841.

25. Kara M, Tellioglu G, Bugan U, Krand O, Berber I, Seymen P, Eren PA, Ozel L, Titiz I: Evaluation of intraoperative parathormone measurement for predicting successful surgery in patients undergoing subtotal/total parathyroidectomy due to secondary hyperparathyroidism. The Laryngoscope 2010, 120(8):1538-1544.

26. Li X, Xie X, Wang R, Liu Y, Fu X, Han X: Comparative analysis of calcification features of primary and secondary hyperparathyroidism by 99Tcm-MIBI SPECT/CT imaging. Journal of third military medical university 2014, 36(15):1626-1629.

27. Peng S, Li P, Zhang A, Liu Q, Xu L, Sun X, Huang G, Song S: Importance of 99Tcm-MIBI SPECT/CT fusion imaging in primary and secondary hyperparathyroidism. International Journal of Radiation Medicine and Nuclear Medicine 2018, 42(3):195-200.

28. Liang XX, Li F, Gao F, Liu Y, Qiao XH, Zhang Z, Du LF: The Value of the Model and Quantitative Parameters of Contrast-Enhanced Ultrasound in Judging the Severity of SHPT. Biomed Res Int 2016, 2016:6064526.

29. Yeh SM, Hwang SJ, Chen HC: Treatment of severe metastatic calcification in hemodialysis patients. Hemodialysis international International Symposium on Home Hemodialysis 2009, 13(2):163-167.

30. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, Ott S, Sprague S,
31. Shantouf R, Kovesdy CP, Kim Y, Ahmadi N, Luna A, Luna C, Rambod M, Nissenson AR, Budoff MJ, Kalantar-Zadeh K: Association of serum alkaline phosphatase with coronary artery calcification in maintenance hemodialysis patients. Clinical journal of the American Society of Nephrology : CJASN 2009, 4(6):1106-1114.

32. Lomashvili KA, Garg P, Narisawa S, Millan JL, O'Neill WC: Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification. Kidney international 2008, 73(9):1024-1030.

33. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, Townsend DW, Berland LL, Parker JA, Zubal G et al: Procedure Guideline for SPECT/CT Imaging 1.0. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2006, 47(7):1227-1234.

34. Greenspan BS, Dillehay G, Intenzo C, Lavely WC, O'Doherty M, Palestro CJ, Scheve W, Stabin MG, Sylvestros D, Tulchinsky M: SNM practice guideline for parathyroid scintigraphy 4.0. J Nucl Med Technol 2012, 40(2):111-118.

35. Thomas DL, Bartel T, Menda Y, Howe J, Graham MM, Juweid ME: Single photon emission computed tomography (SPECT) should be routinely performed for the detection of parathyroid abnormalities utilizing technetium-99m sestamibi parathyroid scintigraphy. Clinical nuclear medicine 2009, 34(10):651-655.

36. Schachter PP, Issa N, Shimonov M, Czerniak A, Lorberboym M: Early, postinjection MIBI-SPECT as the only preoperative localizing study for minimally invasive parathyroidectomy. Archives of surgery 2004, 139(4):433-437.

37. Yamaguchi S, Yachiku S, Hashimoto H, Kaneko S, Nishihara M, Niibori D, Shuke N,
Aburano T: Relation between technetium 99m-methoxyisobutylisonitrile accumulation and multidrug resistance protein in the parathyroid glands. World journal of surgery 2002, 26(1):29-34.

38. Taieb D, Hindie E, Grassetto G, Colletti PM, Rubello D: Parathyroid scintigraphy: when, how, and why? A concise systematic review. Clinical nuclear medicine 2012, 37(6):568-574.

39. Caldarella C, Treglia G, Pontecorvi A, Giordano A: Diagnostic performance of planar scintigraphy using (99m)Tc-MIBI in patients with secondary hyperparathyroidism: a meta-analysis. Annals of nuclear medicine 2012, 26(10):794-803.

40. Zhao Y, Wang Q: Bone uptake of Tc-99m MIBI in patients with hyperparathyroidism. Annals of nuclear medicine 2014, 28(4):349-355.

Tables
Due to technical limitations the Tables are available as downloads in the Supplementary Files.

Figures
Figure 1

Flow chart of lesions analyzed by US, Dual-phase planar, Early SPECT/CT and Delayed SPECT/CT. PH, parathyroid hyperplasia; PG, parathyroid gland; LN, lymph node; TN, thyroid nodule; BN, bone tissue.
A middle-aged patient was suffered with SHPT. Dual-phase 99mTc-MIBI scintigraphy (A and B) showed 4 hyperplastic parathyroid glands. Ultrasonography image (C) showed a typical enlarged parathyroid on the right. Early SPECT/CT (D) showed the right inferior and left inferior hyperplastic parathyroid glands with 99mTc-MIBI uptake. Delayed SPECT/CT (E) showed the right inferior hyperplastic parathyroid glands with 99mTc-MIBI uptake while left inferior hyperplastic parathyroid glands without 99mTc-MIBI uptake. Pathological examination (F) confirmed nodular parathyroid hyperplasia.

Supplementary Files
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Table 2.xlsx
Table 1.xlsx