

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

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Abstract

Objective

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 4 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 a special sign of SHPT and correlated with serum PTH and AKP.

Introduction

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 regimes fail[4] and total parathyroidectomy had minimum risk of postoperative relapse (0-4%)[5]. However, parathyroidectomy for SHPT are less satisfactory, and the rates of persistent and recurrent disease after parathyroidectomy is ranging between 10% and 30%[6]. Surgical failure is mainly due to the difficulty to resect all parathyroid glands especially because of the existence of supernumerary and ectopic parathyroid glands. It is reported that the prevalence of ectopic parathyroids ranges from 35.1% to 45.7% [7-9] and supernumerary glands (more than 4) are present in 16.5% to 30% of patients in SHPT [10, 11]. 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 nuclear magnetic resonance (MRI), but the performance of these anatomical examinations is not satisfactory[12]. Different from the above anatomical imaging, technetium-99m methoxyisobutylisonitrile (^{99m}Tc -MIBI) scintigraphy is a functional exploration and regarded as the best preoperative localizing method for patients with PHPT or SHPT[6] and when combined with single photon emission computed photography/ computed photography (SPECT/CT), functional and anatomical, the sensitivity of scintigraphy can be able to increase. Multiple studies have reported ^{99m}Tc -MIBI scintigraphy superior to US especially combined with SPECT/CT in patient with hyperparathyroidism[13-15], but these studies do not separate SHPT from primary hyperparathyroidism (PHPT) for statistics and analysis. For PHPT, several investigations had reported ^{99m}Tc -MIBI SPECT/CT superior to scintigraphy [16-18], although the other study did not find SPECT/CT superior to scintigraphy [19].

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[20]. For the SHPT, Jae Bok et al.[20] reported US (91.5%) had the higher sensitivity than ^{99m}Tc -MIBI scintigraphy (56.1%), while [Vulpio](#) et al.[21] 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[22, 23] and ^{99m}Tc -MIBI scintigraphy[24]. 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[25]. 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 imaing), 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.

Materials And Methods

Clinical Materials

From May 2017 to November 2019, a total of 60 patients who underwent parathyroidectomy 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 128×128, 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 128×128, 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 ^{99m}Tc -MIBI scintigraphy

The images were diagnosed 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 ^{99m}Tc -MIBI uptake was observed on both the early and the delayed image. (2) Evident abnormal ^{99m}Tc -MIBI uptake was observed on the early image even if not on the delayed image. It was considered negative when abnormal ^{99m}Tc -MIBI uptake was observed on neither early nor delayed image[26].

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 ^{99m}Tc -MIBI accumulation compared to neck muscles and blood vessels. It was considered negative if abnormal ^{99m}Tc -MIBI uptake was observed on neither early nor delayed SPECT when CT indicated parenchyma space occupying lesion at the parathyroid region, and if abnormal ^{99m}Tc -MIBI uptake was observed on both early and delay phase but no parenchyma space occupying lesion at the parathyroid region on CT image.

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

calcifications or cystic degeneration. Color doppler examination showed parathyroid vascular pedicle and a vascular arch located at the periphery of the gland.

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.

Parathyroidectomy and final diagnosis

All patients were submitted to surgery by the same surgical team. The surgical technique consisted of bilateral parathyroidectomy, bilateral recurrent laryngeal nerve exploration and forearm parathyroid gland transplantation. 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 \pm SD. Categorical variables were analyzed using the χ^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 47.82 ± 11.06 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 ± 894.13 pg/ml) and decreased postoperatively (38.25 ± 75.04 pg/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 have 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 total parathyroidectomy without auto-transplantation. Meanwhile, 9 of the 60 patients underwent partial thyroidectomy and one accompanied by papillary carcinoma of thyroid. A total of 243 lesions were resected in the surgery of the 60 patients and 229 lesions were pathological confirmed to be parathyroid hyperplasia with 209 lesions in typical sites, 15 lesions in upper mediastinum and 4 lesions 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 of which one was confirmed to be thyroid nodule and another one was radioactive uptake of manubrium sterni. 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 1.

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). 20 ectopic parathyroid glands (20/229, 8.73%) were detected in 16 patients (16/60, 26.67%). The sensitivity of preoperative eutopic parathyroid imaging has the similar results compared with preoperative total 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 [23]. 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. Soft tissue and vascular calcifications are commonly present in patients of end-stage renal disease, secondary to disturbances in calcium and phosphate balance and secondary to hyperparathyroidism[27]. In our study, 23 patients had punctate and annular calcification in the hyperplastic parathyroid glands, and annular calcification was a special sign of SHPT. Previous study showed an association between serum AKP and vascular calcification via modulation of the pyrophosphate pathway[28, 29]. Serum PTH can increase the bone metabolism conversion to elevate the serum AKP level. Therefore, as we report calcification of parathyroid glands was 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 [25]. 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 discovery of ectopic parathyroid glands and in the dependence on the examiner's experience[30]. CT is useful in cases where US does not detect the lesions, and the sensitivity is increased in detecting the ectopic glands of mediastinum but is lower for the glands located in the thyroid lobe[31]. 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[30]. Different from the above anatomical imaging, ^{99m}Tc -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[32]. ^{99m}Tc -MIBI scintigraphy has high sensitivity and specificity, but also has multiple limitation, such as lacks precise anatomical location of the lesion [33], 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 [18, 34].

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[25, 30]. For detecting ectopic parathyroid glands, the sensitivity of early SPECT/CT was significantly higher than US and ^{99m}Tc -MIBI scintigraphy which is similar to the previous study(90.5%)[24]. All of these data showed that early SPECT/CT is 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%[23] and 85%[22], 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[35]. 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. Calcification (especially annular calcification) of parathyroid gland is a special sign of SHPT which can be shown on SPECT/CT, reminding us that as calcified nodules are seen in the parathyroid region parathyroid hyperplasia should be highly suspected, even if no radioactive uptake is present. 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 is ranging from 46.24% to 91.5%[20, 22, 23], which is similar to our result (75.65%).

Our observations show that the sensitivity of ^{99m}Tc -MIBI scintigraphy was 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 is quickly eliminated from the parathyroid glands leading to the negative uptake images of scintigraphy [36]. 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 misdiagnosed. 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% [26] which is a little higher than our result.

David Taieb et al. [37] reported the most common cause of false positive results on parathyroid scintigraphy was the presence of thyroid nodules, and 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 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 confirmed locating on manubrium sterni with SPECT/CT anatomical location, whether this is related to skeletal brown tumor remains to be seen. Besides, the specificity of early SPECT/CT in our study is lower than the previous study (75%)[24] probably due to the small number of true negative cases.

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 a special sign of SHPT and correlated with serum PTH and AKP.

Declarations

Funding

None.

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.

Authors' contributions

Rongqin Zhang, Zhanwen Zhang and Pin Hu participated in the study design, Rongqin Zhang, Zhanwen Zhang and Pinbo Huang carried out the data collection and statistical analysis and drafting of the manuscript. Rongqin Zhang, Zhi Li, Rui Hu, Jie Zhang and Wanglin Qiu performed drafting and clinical review of the manuscript. All authors read and approved the final manuscript.

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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.

Competing interests

The authors declare that they have no competing interests

References

1. Tominaga, Y., et al., *Histopathology, pathophysiology, and indications for surgical treatment of renal hyperparathyroidism*. Semin Surg Oncol, 1997. **13**(2): p. 78-86.
2. Trainor, D., E. Borthwick, and A. Ferguson, *Perioperative management of the hemodialysis patient*. Semin Dial, 2011. **24**(3): p. 314-26.
3. Evans, M., et al., *Cinacalcet use and the risk of cardiovascular events, fractures and mortality in chronic kidney disease patients with secondary hyperparathyroidism*. Sci Rep, 2018. **8**(1): p. 2103.
4. Kidney Disease: Improving Global Outcomes, C.K.D.M.B.D.W.G., *KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)*. Kidney Int Suppl, 2009(113): p. S1-130.
5. Madorin, C., et al., *The surgical management of renal hyperparathyroidism*. Eur Arch Otorhinolaryngol, 2012. **269**(6): p. 1565-76.
6. Giordano, A., D. Rubello, and D. Casara, *New trends in parathyroid scintigraphy*. Eur J Nucl Med, 2001. **28**(9): p. 1409-20.
7. Gomes, E.M., et al., *Ectopic and extranumerary parathyroid glands location in patients with hyperparathyroidism secondary to end stage renal disease*. Acta Cir Bras, 2007. **22**(2): p. 105-9.
8. Schneider, R., et al., *Frequency of ectopic and supernumerary intrathymic parathyroid glands in patients with renal hyperparathyroidism: analysis of 461 patients undergoing initial parathyroideectomy with bilateral cervical thymectomy*. World J Surg, 2011. **35**(6): p. 1260-5.
9. Zeze, F., H. Itoh, and K. Ohsato, [Hyperplasia and adenoma of the ectopic parathyroid gland]. Nihon Rinsho, 1995. **53**(4): p. 920-4.
10. Pattou, F.N., et al., *Supernumerary parathyroid glands: frequency and surgical significance in treatment of renal hyperparathyroidism*. World J Surg, 2000. **24**(11): p. 1330-4.
11. Numano, M., et al., *Surgical significance of supernumerary parathyroid glands in renal hyperparathyroidism*. World J Surg, 1998. **22**(10): p. 1098-102; discussion 1103.

12. Kettle, A.G. and M.J. O'Doherty, *Parathyroid imaging: how good is it and how should it be done?* Semin Nucl Med, 2006. **36**(3): p. 206-11.
13. Kobylecka, M., et al., *Comparison of scintigraphy and ultrasound imaging in patients with primary, secondary and tertiary hyperparathyroidism - own experience.* J Ultrason, 2017. **17**(68): p. 17-22.
14. Zhou, J., et al., *Diagnosis performance of (99m)Tc-MIBI and multimodality imaging for hyperparathyroidism.* J Huazhong Univ Sci Technolog Med Sci, 2017. **37**(4): p. 582-586.
15. Kim, Y.I., et al., *Efficacy of (9)(9)mTc-sestamibi SPECT/CT for minimally invasive parathyroidectomy: comparative study with (9)(9)mTc-sestamibi scintigraphy, SPECT, US and CT.* Ann Nucl Med, 2012. **26**(10): p. 804-10.
16. Slater, A. and F.V. Gleeson, *Increased sensitivity and confidence of SPECT over planar imaging in dual-phase sestamibi for parathyroid adenoma detection.* Clin Nucl Med, 2005. **30**(1): p. 1-3.
17. Moka, D., et al., *Technetium 99m-MIBI-SPECT: A highly sensitive diagnostic tool for localization of parathyroid adenomas.* Surgery, 2000. **128**(1): p. 29-35.
18. Lavelly, W.C., et al., *Comparison of SPECT/CT, SPECT, and planar imaging with single- and dual-phase (99m)Tc-sestamibi parathyroid scintigraphy.* J Nucl Med, 2007. **48**(7): p. 1084-9.
19. Chen, C.C., et al., *Comparison of parathyroid imaging with technetium-99m-pertechnetate/sestamibi subtraction, double-phase technetium-99m-sestamibi and technetium-99m-sestamibi SPECT.* J Nucl Med, 1997. **38**(6): p. 834-9.
20. Lee, J.B., W.Y. Kim, and Y.M. Lee, *The role of preoperative ultrasonography, computed tomography, and sestamibi scintigraphy localization in secondary hyperparathyroidism.* Ann Surg Treat Res, 2015. **89**(6): p. 300-5.
21. Vulpio, C., et al., *Usefulness of the combination of ultrasonography and 99mTc-sestamibi scintigraphy in the preoperative evaluation of uremic secondary hyperparathyroidism.* Head Neck, 2010. **32**(9): p. 1226-35.
22. Yuan, L.L., et al., *Combined application of ultrasound and SPECT/CT has incremental value in detecting parathyroid tissue in SHPT patients.* Diagn Interv Imaging, 2016. **97**(2): p. 219-25.
23. Li, P., et al., *Lesion based diagnostic performance of dual phase (99m)Tc-MIBI SPECT/CT imaging and ultrasonography in patients with secondary hyperparathyroidism.* BMC Med Imaging, 2017. **17**(1): p. 60.
24. Zeng, M., et al., *(99m)Tc-MIBI SPECT/CT imaging had high sensitivity in accurate localization of parathyroids before parathyroidectomy for patients with secondary hyperparathyroidism.* Ren Fail, 2019. **41**(1): p. 885-892.
25. Yang, J., et al., *Value of dual-phase (99m)Tc-sestamibi scintigraphy with neck and thoracic SPECT/CT in secondary hyperparathyroidism.* AJR Am J Roentgenol, 2014. **202**(1): p. 180-4.
26. Caldarella, C., et al., *Diagnostic performance of planar scintigraphy using (9)(9)mTc-MIBI in patients with secondary hyperparathyroidism: a meta-analysis.* Ann Nucl Med, 2012. **26**(10): p. 794-803.

27. Yeh, S.M., S.J. Hwang, and H.C. Chen, *Treatment of severe metastatic calcification in hemodialysis patients*. Hemodial Int, 2009. **13**(2): p. 163-7.
28. Shantouf, R., et al., *Association of serum alkaline phosphatase with coronary artery calcification in maintenance hemodialysis patients*. Clin J Am Soc Nephrol, 2009. **4**(6): p. 1106-14.
29. Lomashvili, K.A., et al., *Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification*. Kidney Int, 2008. **73**(9): p. 1024-30.
30. Strambu, V., et al., *The Value of Imaging of the Parathyroid Glands in Secondary Hyperparathyroidism*. Chirurgia (Bucur), 2019. **114**(5): p. 541-549.
31. Mitchell, B.K., R.C. Merrell, and B.K. Kinder, *Localization studies in patients with hyperparathyroidism*. Surg Clin North Am, 1995. **75**(3): p. 483-98.
32. Delbeke, D., et al., *Procedure Guideline for SPECT/CT Imaging 1.0*. J Nucl Med, 2006. **47**(7): p. 1227-34.
33. Greenspan, B.S., et al., *SNM practice guideline for parathyroid scintigraphy 4.0*. J Nucl Med Technol, 2012. **40**(2): p. 111-8.
34. Thomas, D.L., et al., *Single photon emission computed tomography (SPECT) should be routinely performed for the detection of parathyroid abnormalities utilizing technetium-99m sestamibi parathyroid scintigraphy*. Clin Nucl Med, 2009. **34**(10): p. 651-5.
35. Schachter, P.P., et al., *Early, postinjection MIBI-SPECT as the only preoperative localizing study for minimally invasive parathyroidectomy*. Arch Surg, 2004. **139**(4): p. 433-7.
36. Yamaguchi, S., et al., *Relation between technetium 99m-methoxyisobutylisonitrile accumulation and multidrug resistance protein in the parathyroid glands*. World J Surg, 2002. **26**(1): p. 29-34.
37. Taieb, D., et al., *Parathyroid scintigraphy: when, how, and why? A concise systematic review*. Clin Nucl Med, 2012. **37**(6): p. 568-74.

Tables

Table 1. Patient baseline characteristics.

Patient characteristics	Total (n = 60)
Age (yr) *	47.82 ± 11.06
Male sex, no. (%) **	34 (56.7%)
Type of dialysis, n (%)	
Hemodialysis	51 (85.0%)
Peritoneal dialysis	5 (8.3%)
Peritoneal and Hemodialysis	4 (6.7%)
Years of dialysis (yr)	6.58 ± 3.16
Preoperative PTH level (pg/ml)	1838.37±894.13
Postoperative PTH level (pg/ml)	38.25±75.04
Creatinine (μmol/L)	977.78±276.73
AKP (U/L)	574.63±627.30
Ca level (mmol/l)	2.44±0.22
P level (mmol/l)	2.55±0.61
Location	
Eutopic	209
Ectopic	20
Superior mediastinum	15
Intrathyroid	5

*Mean ± standard deviation (SD) **Number (%).

Table 2. Preoperative imaging and postoperative parathyroid pathology results

	Ultrasonography	^{99m} Tc-MIBI Planar	Early SPECT/CT	Delayed SPECT/CT
TP	175	114	205	168
FP	3	2	5	3
FN	54	115	24	61
TN	11	12	9	11
Sensitivity (%)	76.4%	49.8%	89.5%	73.4%
Specificity (%)	78.6%	85.7%	64.3%	78.6%
Accuracy rate (%)	76.5%	51.9%	88.0%	73.7%

TP: True Positive; FP: False Positive; FN: False Negative; TN: True Negative.

Table 3. Comparison of eutopic and ectopic parathyroids for the four techniques

		US	^{99m}Tc -MIBI Planar	Early SPECT/CT	Delayed SPECT/CT
Eutopic parathyroids	TP	164	104	187	153
	FN	45	105	22	56
	Sensitivity (%)	78.5%	49.8%	89.5%	73.2%
Ectopic parathyroids	TP	11	10	18	15
	FN	9	10	2	5
	Sensitivity (%)	55.0%	50.0%	90.0%	75.0%

TP: True Positive; FP: False Positive; FN: False Negative; TN: True Negative.

Figures

Figure 1

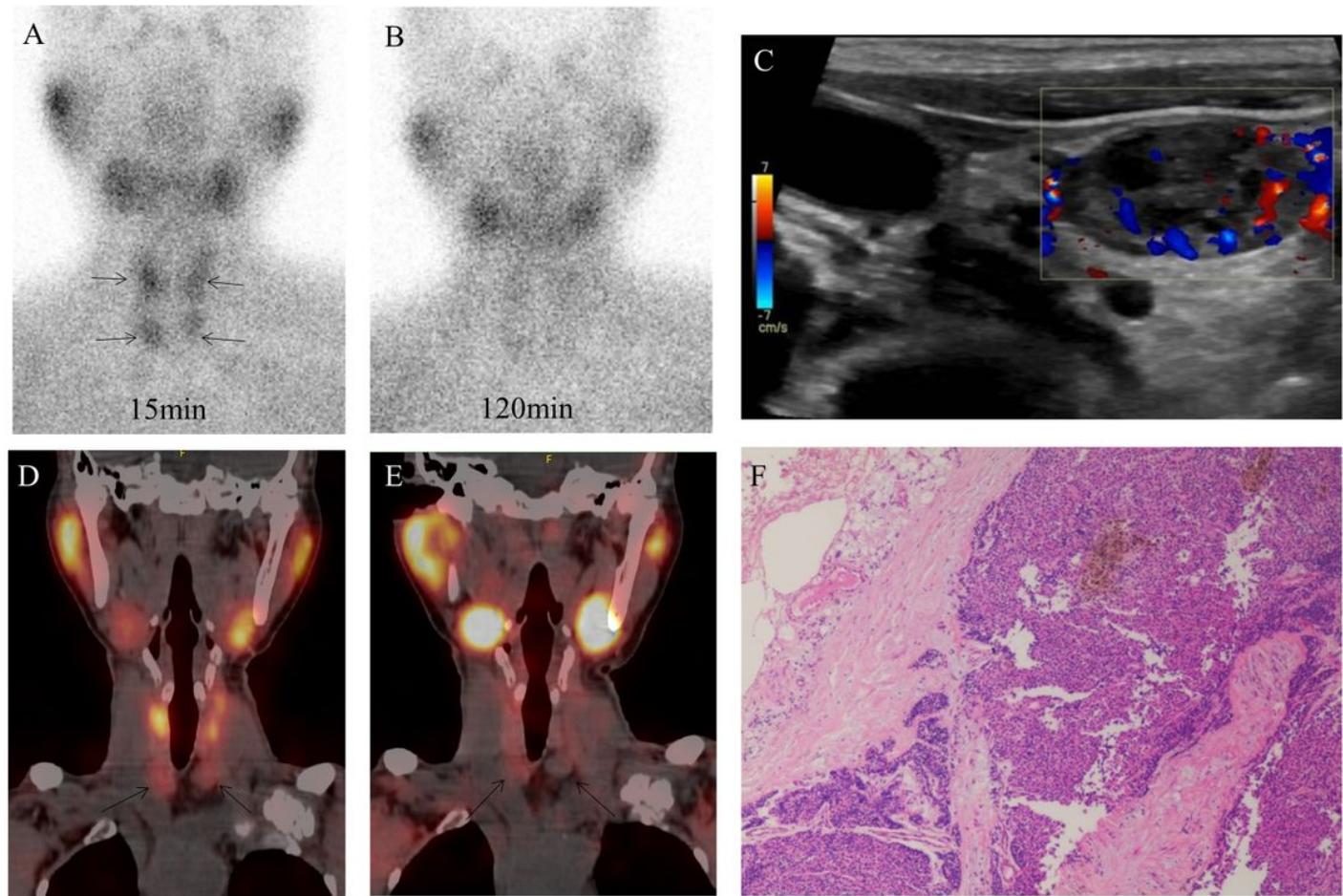


Figure 1

A middle-aged patient was suffered with SHPT. Dual-phase ^{99m}Tc -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 ^{99m}Tc -MIBI uptake. Delayed SPECT/CT (E) showed the right inferior hyperplastic parathyroid glands with ^{99m}Tc -MIBI uptake while left inferior hyperplastic parathyroid glands without ^{99m}Tc -MIBI uptake. Pathological examination (F) confirmed nodular parathyroid hyperplasia.