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Diagnosis Performance of ^{99m}Tc-MIBI and Multimodality Imaging for Hyperparathyroidism

Jun ZHOU (周 俊), Di-yu LU (陆涤宇)[#], Liang XIA (夏 亮), Xiao-jie CHENG (程小杰)
Department of Nuclear Medicine, Wuhan Central Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430014, China

Summary: This study aimed to examine the diagnosis performance of ^{99m}Tc-methoxyisobutylisonitrisonitrile (^{99m}Tc-MIBI) and multimodality imaging [ultrasound, single-photon emission computed tomography/computed tomography (SPECT/CT)] for hyperparathyroidism (HPT). From Nov. 2009 to Dec. 2015, clinical data of a total of 43 HPT patients (16 males and 27 females; 26–70 years old, average age: 51.60±10.66 years old) were retrospectively analyzed. Among them, 19 patients with primary hyperparathyroidism (PHPT) underwent ^{99m}Tc-MIBI planar imaging, 24 [15 with PHPT and 9 with secondary hyperparathyroidism (SHPT)] underwent SPECT/CT hybrid imaging, and 41 (33 with PHPT and 8 with SHPT) had neck ultrasound imaging. Final diagnosis was determined by pathological examination after surgery. The positive rate was compared between different imaging modalities, and the correlation analysis was conducted between imaging results and lesion size or serum parathyroid hormone (PTH) level. The results showed that the total positive rates of ^{99m}Tc-MIBI imaging, ultrasound, and the two combined imaging in the 43 HPT cases were 90.70% (39/43), 58.54% (24/41), and 100% (41/41), respectively. According to lesion numbers, the positive rates were 79.10% (53/67), 53.23% (33/62), and 88.71% (55/62), respectively. SPECT/CT hybrid images were positive in all the 24 patients who underwent this examination. The mean maximum diameters of the lesions in ^{99m}Tc-MIBI positive and negative patients were 1.96±0.95 cm and 1.36±0.67 cm respectively, with statistically significant difference noted (P=0.03). The T/NT of ^{99m}Tc-MIBI imaging at the early phase was correlated positively with serum PTH level (r=0.40, P=0.01). The T/NT of ^{99m}Tc-MIBI imaging at both the early phase and the delay phase was correlated positively with lesion size (r=0.51, and r=0.45, respectively; P<0.01 for both). It was concluded that ^{99m}Tc-MIBI imaging presents significant value for location diagnosis of HPT, especially when combined with SPECT/CT hybrid imaging or ultrasound. The ^{99m}Tc-MIBI uptake correlates positively with serum PTH level and lesion size.
Key words: hyperparathyroidism; ^{99m}Tc-methoxyisobutylisonitrisonitrile; planar imaging; SPECT/CT hybrid; ultrasound

Hyperparathyroidism (HPT) is a calcium-phosphorus metabolism disorder syndrome caused by oversecretion of parathyroid hormone (PTH), which involves many organs and systems of the human body. The clinical manifestation of HPT is of diversity, and its morbidity has been increasing yearly in China[1]. The serum PTH level determination is applied clinically for preliminary screening and diagnosis, but it is hard to locate hyper-functional lesions with use of the serum PTH level. So far, high frequency ultrasound imaging and ^{99m}Tc-methoxyisobutylisonitrisonitrile (^{99m}Tc MIBI) double time phase imaging are the most commonly used methods for location diagnosis[2–4]. Ultrasound imaging offers information of morphological changes but not functional activities of the lesion, leading to suboptimal specificity. The ^{99m}Tc-MIBI double time phase planar imaging reveals functional information of HPT lesions, but lacks precise anatomical location of the lesion, making the differential diagnosis of HPT from thyroid adenoma and thyroid carcinoma difficult. Our research was to investigate the clinical value of ^{99m}Tc-MIBI double time phase imaging and multimodality imaging [ultrasound, single-photon emission computed tomography/computed tomography (SPECT/CT)] for HPT diagnosis, and to analyze their correlation factors.

1 MATERIALS AND METHODS

1.1 Clinical Materials

From Nov. 2009 to Dec. 2015, a total of 43 patients who were diagnosed with HPT and treated in the Central Hospital of Wuhan (16 males and 27 females; 26–70 years old, average age: 51.60±10.66 years old) were retrospectively analyzed. There were 34 cases of primary HPT (PHPT) and 9 cases of secondary HPT (SHPT). Nineteen patients underwent ^{99m}Tc-MIBI planar imaging. Twenty-four patients underwent SPECT/CT hybrid imaging (15 primary cases and 9 secondary cases), and 41 patients (33 primary cases and 8 secondary cases) underwent neck ultrasound imaging. Sixty-seven lesions were confirmed by pathological examination after surgery, including 45 lesions of parathyroid adenoma (PTA), 21 lesions of parathyroid hyperplasia (secondary lesions), and 1 lesion of parathyroid hypertrophy. In the PTA lesions, there were 35 primary lesions and 10 secondary

Jun ZHOU, E-mail: 595596405@qq.com
[#]Corresponding author, E-mail: diyulu2013@163.com

lesions. In the primary PTA lesions, there were 32 single lesions and 3 multiple lesions (in 1 case). In all 43 HPT patients, there were 26 cases complicated with thyroid nodule, of which 23 cases were complicated with nodular goiter (1 case with adenoma, and 1 case with anterior sternum ectopic goiter), 1 case with Hashimoto's thyroiditis, and 2 cases with thyroid papillary carcinoma. In all 43 HPT patients, there was 1 case of metabolic bone disease (brown tumor), 5 cases complicated with hypercalcemia, 1 osteoporosis, 3 cases of urinary tract calculi, and 9 cases of renal failure.

1.2 Imaging Methods

After intravenous administration of 740 MBq ^{99m}Tc-MIBI for each patient, neck anterior and posterior planar images were acquired at 15 min post-injection (the early phase) and 120 min post-injection (the delay phase). The acquisition was set at energy peak of 140 keV, window width of 20%, matrix of 128×128, magnification of 2–4 folds, and counts of 600 k per frame with low-energy high resolution collimation. SPECT/CT hybrid imaging was conducted at the delay phase by low-dose CT scan following SPECT tomography scan. The scanning parameter was set at FOV of 40 cm, CT tube current of 2.5 mA, CT tube voltage of 200 kV, slice thickness of 5 mm, reconstruction matrix of 128×128, and reconstruction thickness of 1.25 mm. The equipment for double time phase planar imaging was the Philips Vertex V60 MCD SPECT, NED and that for SPECT/CT hybrid imaging was the NM670 of GE, USA.

1.3 Image Analysis

1.3.1 ^{99m}Tc-MIBI Planar Image The images were assessed by 2 experienced nuclear medicine doctors together. The image was considered positive when it met one of the following criteria: (1) Abnormal radioactivity accumulation was observed at both the early phase and the delay phase. (2) Evident abnormal radioactivity accumulation was observed at the early phase but not the delay phase. It was considered negative when abnormal radioactivity accumulation was observed at neither early phase nor delay phase.

1.3.2 SPECT/CT Hybrid Image PTA was diagnosed when the planar image met the first criterion mentioned above, CT indicated parenchyma space occupying lesion at the parathyroid region, and SPECT tomography image showed abnormal radioactivity accumulation. It was also considered to be PTA when CT indicated parenchyma space occupying lesion at the parathyroid region, SPECT tomography image showed no evident abnormal radioactivity accumulation, but the serum PTH level increased.

1.3.3 ^{99m}Tc-MIBI Semi-quantitative Analysis The image T/NT ratio of planar imaging of the PHPT patients at the early phase and the delay phase was determined respectively (T as the mean radioactivity counts of the ROI at the abnormal accumulation lesion in the parathyroid, NT as that of the corresponding area at the opposite side). The maximum diameter (cm) and the volume (length×width×thickness×π/6) were also determined. Image semi-quantitative analysis of the SHPT patients was not performed due to the poor accuracy which was caused by multiple lesions of the SHPT.

1.3.4 Ultrasound Imaging The images were diagnosed by experienced ultrasound doctors. Typical ultrasound image of PTA was demonstrated as the solid hypoechoic mass at the upper and lower pole of the thyroid back, with the clear border and the shape of circle, ellipse, or strip-type. Color Doppler flow imaging showed that abundant blood flow surrounded the mass, or branch flow penetrated deep into the mass.

1.4 Final Diagnosis

Pathological examination following surgery was employed as the golden standard for final diagnosis.

1.5 Statistical Analysis

Software of SPSS 11.5 or SPSS 23 was applied for statistical analysis. The measurement data were analyzed by two independent sample *t* tests and variance analysis, and the enumeration data were analyzed by Chi-square test. It was considered statistically different when $\alpha<0.05$. The correlation analysis was performed by Pearson's correlation, and it was statistically different if $\alpha<0.01$.

2 RESULTS

2.1 Positive Rate of ^{99m}Tc-MIBI Imaging

Analyzed by case numbers, the positive rate of ^{99m}Tc-MIBI imaging was 90.70% (39/43). Analyzed by lesion numbers, its positive rate was 79.10% (53/67).

In the 43 HPT cases, the positive rate of the planar imaging of PHPT was 78.95% (15/19), and that of the SPECT/CT hybrid imaging was 100% (24/24). In the total 67 lesions, the positive rate of the planar imaging was 78.95% (15/19), and that of the SPECT/CT hybrid imaging was 79.17% (38/48). In the PHPT cases, the positive rate of the planar imaging was 78.95% (15/19), and that of the SPECT/CT hybrid imaging was 100% (17/17) (1 case with 3 multiple lesions); in the SHPT cases, the positive rate of SPECT/CT hybrid imaging was 67.74% (21/31).

2.2 Positive Rate of Ultrasound Imaging and the Combined Imaging of Ultrasound and ^{99m}Tc-MIBI

In the 43 HPT cases, the positive rate of ultrasound imaging was 58.54% (24/41), and that of the combined imaging of ultrasound and ^{99m}Tc-MIBI was 100% (41/41). In the total 67 lesions, the positive rate of ultrasound was 53.23% (33/62), and that of the combined imaging was 88.71% (55/62). The positive rate of the combined imaging was 100% (36/36) in the PHPT, and 73.08% (19/26) in the SHPT.

2.3 Semi-quantitative Analysis of ^{99m}Tc-MIBI Imaging and Its Correlation with PTH and Lesion Size

In the PHPT cases, the T/NT ratio at the early phase was 0.89–4.00 (average ratio: 1.85±0.70), and that at the delay phase was 0.85–3.90 (average ratio: 2.07±0.79). The maximum diameter of the lesions was 0.80–5.00 cm, and their maximum volume was 0.21–41.87 cm^3 (average volume: 5.26±9.34 cm^3). The serum PTH level was 7.60–282.70 pmol/L (normal 1.30–6.90pmol/L).

The T/NT ratios of ^{99m}Tc-MIBI imaging at the early phase correlated positively with the serum PTH level (r=0.40, P=0.01), while no significant correlation was observed between the serum PTH level and the T/NT ratios at the delay phase (r=0.13, P=0.24). There was a positive correlation between the lesion volume (cm^3) and the T/NT ratios at both early phase and delay phase, with statistical differences found (r=0.51, r=0.45, respectively; P=0.00, P=0.01, respectively).

The mean maximum diameters of positive and negative lesions in ^{99m}Tc-MIBI imaging were 1.96±0.95

cm and 1.36±0.67 cm, respectively, with statistical difference obtained (t=2.25, P=0.03). The mean maximum diameter of lesions in the planar imaging was 2.19±1.13 cm, while that in SPECT/CT hybrid imaging was 1.91±0.86 cm, with no statistical difference seen (t =1.10, P=0.28).

The serum PTH in the PHPT patients was 46.58±58.79 pmol/L, while that in the SHPT patients was 212.05±99.77 pmol/L, with statistical difference noted (t=4.76, P=0.00).

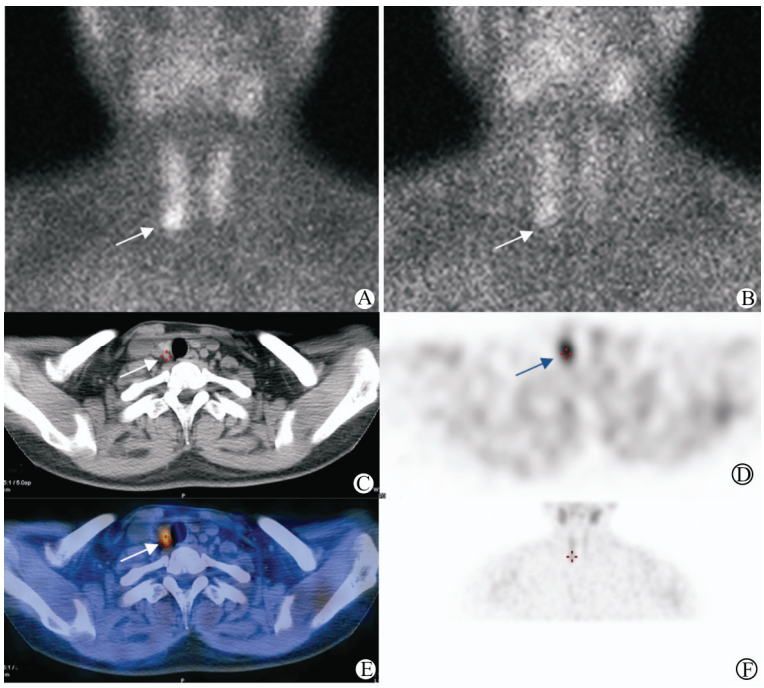

Fig. 1 Representative images of ^{99m}Tc-MIBI double time phase imaging of a patient with a parathyroid neoplasm
A: Radioactivity accumulation (0.6 cm×0.8 cm) was observed at the lower pole of the right thyroid (arrow) at the early phase, and radioactivity was slightly higher than that in the normal thyroid tissue. B: The radioactivity was distinctly cleared in both the lesion and the thyroid at the delay phase 2 h post-injection. C: The soft tissue nodule opacification (as indicated by the white arrow) was observed with CT. D: The radioactivity accumulation (black arrow) was observed in the transverse image of SPECT. E: The evident radioactivity accumulation was observed at the nodular lesion on a CT image with SPECT/CT hybrid imaging, indicating a positive lesion, which was confirmed to be right PTA pathologically after surgery. F: a three-dimensional result of fig. 1D

3 DISCUSSION

The conventional imaging strategies for HPT location so far have been ultrasound, CT, and MRI, of which ultrasound is the primary imaging used because of its simple manipulation and low cost. Recently, ^{99m}Tc-MIBI imaging is preferred in clinical practice for diagnosis of HPT[5]. ^{99m}Tc-MIBI imaging combined with SPECT/CT multimodality imaging is able to diagnose HPT precisely, qualitatively and locally before surgery by acquiring functional information of parathyroids as well as morphological and location information[6]. In recent years ^{99m}Tc-MIBI imaging has been highly regarded as a promising application.

It has been reported that ^{99m}Tc-MIBI imaging presents high location rate and positive predictive value for patients with high level of serum calcium and PTH[7, 8], which makes it a reliable method for HPT diagnosis. Many researchers believe that SPECT/CT imaging offers higher accuracy than the planar imaging, and it has peculiar value for detection of parathyroid hyperplasia lesions[9]. There are also other reports pointing out that no statistical differences are observed between the sensitivities of SPECT/CT hybrid imaging and planar imaging[9]. Our present investigation demonstrated that the total positive rate of ^{99m}Tc-MIBI imaging in the 43 HPT cases was 90.70%, and that in the 67 HPT lesions was 79.10%, proving its high sensitivity for HPT diagnosis as well as the presence of false positives and missed diagnosis. It is difficult to differentially diagnose clinical benign lesions, such as thyroid follicular adenoma, some nodular goiter complicated with fibrillation, and thyroid malignant tumor, from PTA by double time phase planar imaging. Our further analysis in the 43 HPT cases showed that the positive rate of the planar imaging was 78.95% (15/19), and that of the SPECT/CT hybrid imaging was 100% (24/24). In the 67 lesions, the positive rate of the planar imaging was 78.95% (15/19), and that of the SPECT/CT hybrid imaging was 79.17% (38/48). Two patients with slightly increased PTH levels had false negative results in the planar imaging. The focal radioactivity accumulation in the lesions at the under part of the thyroid was similar to that in normal thyroid tissue at the early phase, and the lesions were cleared almost simultaneously in the thyroid at the delay phase. In SPECT/CT hybrid imaging, however, soft tissue nodule opacification in the parathyroid area was spotted to diagnose PTA (fig. 1), which was confirmed by pathological examination after surgery. Therefore, ^{99m}Tc-MIBI SPECT/CT hybrid imaging provides higher sensitivity and accuracy than the planar im-

aging alone.

Studies have demonstrated that the disseminated or nodular parathyroid hyperplasia in the SHPT patients makes it difficult to diagnose HPT by the ^{99m}Tc-MIBI planar imaging[10], while SPECT/CT hybrid imaging can provide valuable quantitative and location information of parathyroid hyperplasia in the SHPT caused by chronic nephropathy[11, 12]. The ^{99m}Tc-MIBI imaging of PHPT and SHPT in our research showed that the positive rate in the PHPT was 78.95% (15/19) in the planar imaging and 100% (17/17) in the SPECT/CT hybrid imaging, while that in the SHPT was 67.74% (21/31) in the SPECT/CT imaging. The SPECT/CT hybrid imaging showed its advantages in the diagnosis of the solitary lesion in the PHPT. Additionally, lesions of parathyroid hyperplasia in the SHPT are usually multiple (2–5 in number), and are closely adjacent to each other, which are also well suitable for the use of diagnostic CT for determination of lesion location and numbers. So, the lesion detection rate was much higher in the SPECT/CT hybrid imaging than in the planar imaging, which is in accordance with other reports[11].

The main reason of low sensitivity for parathyroid lesions diagnosed by the morphology-relied ultrasound (34%–64%), is believed to be the frequent misdiagnosis of multiple thyroid nodules for parathyroid lesions[13]. The manipulator's experience for accurate determination of lesions is also one of the indispensable factors that can't be ignored[14, 15]. In the 67 lesions of our research, 26 lesions were found to be complicated with thyroid nodules, indicating the common appearance of HPT with thyroid nodules. It was reported that the sensitivity of ultrasound for PTA diagnosis is 50%–85%[16, 17], which is similar to our result (58.54%). It was demonstrated that the combined imaging of ^{99m}Tc-MIBI and ultrasound could reach a sensitivity of 90.4%, which increases the lesion detection rate, and is especially applicable to the precise location before surgery[18, 19]. Our result of the sensitivity (88.71%) generally accords with the reports, indicating the reduction of false positive and misdiagnosis by the combined imaging.

It is believed that the serum PTH level and the lesion size are the main factors to influence the MIBI uptake and its positive rate. The lesion accumulation appears along with more MIBI uptake by massive mitochondria in oxygenocytes, thus the MIBI uptake correlates positively with the quantity of oxygenocytes in the adenoma[20, 21]. Our research showed that the T/NT ratio in ^{99m}Tc-MIBI imaging correlated positively with serum PTH level at the early phase, and positively with lesion size at the early and the delay phases, which is consistent with the above-mentioned reports[22]. The mean maximum diameters of the positive and the negative lesions in ^{99m}Tc-MIBI imaging were 1.96±0.95 cm and 1.36±0.67 cm respectively, with statistical difference found. This means that larger lesion size leads to more MIBI accumulation and higher positive rate, while less MIBI accumulation in small lesions results in misdiagnosis. The cases in our group demonstrated that the serum PTH level in the SHPT was abnormally high (up to 6-fold), while that in the PHPT was relatively low, and there was statistically significant difference. The positive rate of lesions in PHPT was positively correlated with the serum PTH level, especially in the early phase. But the correlation of SHPT with the serum PTH level is uncertain, which needs further study.

In conclusion, ^{99m}Tc-MIBI imaging offers significant value for the HPT diagnosis, especially when SPECT/CT hybrid imaging combined with ultrasound imaging is complimentarily used. For the HPT patients, SPECT/CT hybrid imaging helps to increase the positive rate as compared with the planar imaging. The ^{99m}Tc-MIBI uptake correlates positively with the serum PTH level and lesion size.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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