Application values of $^{99m}$Tc-methoxyisobutylisonitrile imaging for differentiating benign and malignant thymic masses

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Abstract. The aim of the present study was to investigate the application value of $^{99m}$Tc-methoxyisobutylisonitrile (MIBI) imaging to differentiate between benign and malignant thymic masses. A total of 32 patients with space-occupying mediastinal masses were enrolled and early and delayed-phase images were collected following injection with the imaging agent. The tumor to background ratio (T/N) values at the different phases were also recorded. The sensitivity of the qualitative analysis to distinguish between benign and malignant thymic masses was 95.24%, with specificity as 90.91%. The T/N values in the early and delayed phases were not significantly different in the group with benign thymic masses, but demonstrated statistical significant differences in the groups with low- and intermediate-grade malignant thymic masses. The T/N values at the above early and delayed phase were significantly different between the benign and low-grade malignancy groups, as well as between low- and moderate-grade malignancy groups. Those between the benign and moderate-grade malignancy groups demonstrated no significant difference. $^{99m}$Tc-MIBI imaging was able to differentiate between benign and malignant thymic masses, and the simultaneous semi-quantitative analysis of the T/N values of the tumors may be able to initially determine the degree of malignancy of thymoma.

Introduction

Primary anterior mediastinal tumors account for 50% of mediastinal tumors, including thymic hyperplasia, thymoma, thymic cysts, mature type and immature type teratomas, germ cell tumors and lymphoma, however, thymoma is the most common primary tumor of the anterior mediastinum (1-4). At present, morphological examinations including computed tomography (CT) and magnetic resonance imaging (MRI) are advantageous in that they are able to identify the anatomical locations of tumors and their relationships with adjacent tissues and organs. Although CT is able to make relatively specific diagnoses for certain mediastinal masses by identifying the fat, calcified or cystic components, it is often difficult to distinguish benign and malignant thymoma, and although benign and malignant thymic masses demonstrate similar CT results their treatment programs differ substantially (5). Therefore, identifying the benign or malignant nature of these masses would have great significance for assessing the condition of patients, making treatment decisions and evaluating prognosis (5-8).

Biopsies provide strong evidence for differentiating between benign and malignant tumors and their use has become more common (9), but they remain an invasive examination. Biopsies are likely to increase the risk of disseminating the tumor cells along the needle tract, and patients with thymoma and myasthenia gravis are more likely to enter myasthenic crisis (10,11). Therefore, the development of a non-invasive, simple and economical examination method would have clinical significance. Positron emission tomography (PET)/CT has previously been reported to exhibit certain value for grading the malignancies of thymic tumors (12,13), but this method would face difficulties spreading in developing countries due to economic factors. Images of thymoma have also previously been reported to be discovered in $^{99m}$Tc-methoxyisobutylisonitrile (MIBI) myocardial perfusion imaging by accident (14,15), which provided certain guidance for the present study. A functional imaging method, MIBI single-photon emission computed tomography (SPECT), was able to reflect the metabolic activities of tumors, thus helping to preliminarily determine the natures of the tumors. This method is simple, economical, and readily accepted by patients, so it is worthy of further research and application. In the present study, postoperative pathologies were used as the basis to investigate the application value of $^{99m}$Tc-MIBI imaging to differentiate between benign and malignant thymic masses, thus providing the basis for clinical diagnosis and treatment.

Materials and methods

Study subjects. A total of 32 patients diagnosed with mediastinal space-occupying masses in the thymic region by CT or MRI between February 2014 and December 2015 at The Affiliated Hospital of Qingdao Medical University (Qingdao, China) were selected, including 13 males and 19 females, aged 27 to 74 years, with a mean of (50.6±11.1) years. The present study
was conducted in accordance with the declaration of Helsinki. The present study was conducted with approval from the Ethics Committee of Qingdao Medical University (Qingdao, China) and written, informed consent was obtained from all participants. Following \(^{99m}\text{Tc}\)-MIBI radionuclide imaging, all patients underwent surgical removal of the thymic masses, which were then used for postoperative biopsies. According to the postoperative pathological results, these patients were divided into three groups as follows: Those with benign thymic masses (the BT group, including 9 cases of thymic hyperplasia, 1 case of mature cystic teratom, and 1 case of thymic cyst; n=11), those with low-grade malignant thymoma (LRT group, including 1 case of type A, and 9 cases of type AB, n=10), and those with intermediate-grade malignant thymoma (IRT group, 2 cases of type B1, 6 cases of type B2, and 3 cases of type B3; n=11) (16).

\(^{99m}\text{Tc}\)-MIBI-SPECT. Following intravenous injection of 740 megabecquerels of the imaging agent \(^{99m}\text{Tc}\)-MIBI (provided by Shihong Drug Development Center, Beijing Normal University, Beijing, China, with a chemical purity of 95-98%), a Hawkeye Millennium VG type SPECT device (GE Healthcare, Chicago, IL, USA) was then used for imaging. This was accompanied by a low-energy, high-resolution, parallel-hole collimator (GE Healthcare), with the energy peak set as 140 KeV, window width as 20%, acquisition matrix as 512x512 and magnification as 1.0, to perform planar and SPECT imaging of local lesions. The planar images in the early phase (15 min following injection) and the delayed phase (2 h following injection) were collected, as well as fusion imaging to assist positioning if necessary.

Imaging interpretation. The equivalent irregular regions of interest delineating the tumor and the background (lung) were manually drawn by two experienced nuclear medicine physicians. For each lesion, the uptake index was determined by dividing the average counts/pixel within a lesion over the average counts/pixel in normal tissues. Then the ratio of tumor to background (T/N) was calculated. This generated T/N ratios for the early phase (e) and the delayed phase (d). The 2-h washout index (WI) was calculated according to the following formula: \[ WI = \frac{\text{T/N (e)} - \text{T/N (d)}}{\text{T/N (e)}} \times 100\% \]. The 2-h retention index (RI) was calculated according to the following formula: \[ RI = \frac{\text{T/N} \times \text{T/N (d)}}{\text{T/N (e)}} \times 100\% \]. The final results were decided by the consensus of at least two nuclear physicians.

Statistical analysis. The mean and standard deviation of the T/N ratio, RI and WI were calculated. The intragroup comparisons between T/N(e) and T/N(d) were performed using paired Student’s t tests. Multiple comparisons between the three groups was performed using one-way analysis of variance. P<0.05 was considered to indicate a statistically significant difference. SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA) was used for analysis.

Results

Comparison of MIBI uptake between benign and malignant groups. Among the 12 patients of the BT group, the majority of the masses revealed no significant radioactivity uptake in the early and delayed phases, with the exception of a single case with multilocular thymic cysts. Radioactivity uptake was similar to the background radioactivity count. A representative case from the BT group was depicted in Fig. 1. Among the 21 patients included in the LRT and IRT groups, the majority exhibited various degrees of radioactivity uptake, with the exception of a single case of B3-type thymoma, with the sensitivity as 95.24%, and the specificity as 90.91% (Table I). A representative case from the malignant groups was depicted in Fig. 2.

Comparison of semi-quantitative analysis of MIBI uptake among three groups. There was no statistically significant difference between T/N(e) and T/N(d) in the BT group (P=0.253), but the differences between T/N(e) and T/N(d) in the LRT and IRT groups were statistically significant (P=0.045 and P=0.001, respectively).

The comparison of T/N(e) between the three groups revealed a statistically difference (P<0.001; Table II), among which the differences between the BT and LRT groups, as well as between the LRT and IRT groups, were statistically significant (P<0.001; Table II). The comparison of T/N(d) between the three groups revealed a statistically significant difference (P<0.001; Table II), among which the differences between the BT and LRT groups, as well as between the LRT and IRT groups, were statistically significant (P<0.001; Table II), while the difference between the BT and IRT groups was not significant (P=0.08; Table II).

The present study also revealed that T/N(e) and T/N(d) of the patient with multilocular thymic cysts exhibited apparent radioactivity uptake, so this case was seen as a false positive and removed from the BT group when performing semi-quantitative analysis. Another case with B3-type thymoma from the IRT group revealed no significant radioactivity uptake in the early or delayed phase, so it was seen as a false negative and removed from the IRT group when performing semi-quantitative analysis.

Fig. 1 depicted a representative case from the BT group. The 10 min and 2 h \(^{99m}\text{Tc}\)-MIBI images revealed no abnormal radioactivity concentration shadow in the mediastinum (Fig. 1A). Fusion CT imaging revealed a soft tissue mass in the anterior mediastinum, and SPECT/CT fusion imaging revealed no significant radioactivity uptake in this soft tissue mass (Fig. 1B). The diagnosis was an anterior mediastinal mass, with a high probability of being a benign lesion. Postoperative pathology revealed the presence of thymic cysts and the cyst wall was primarily composed of proliferated fibrous connective tissues, which contained more lymphoid tissues, and was consistent with the diagnosis of space-occupying thymic cysts. Fig. 2 depicted a representative case

### Table I. \(^{99m}\text{Tc}\)-methoxyisobutylisonitrile imaging results for the benign and malignancy groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign group</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Malignancy groups</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>
The 10 min $^{99m}$Tc-MIBI image revealed an abnormal dumbbell-shaped radioactivity uptake shadow in the mediastinum, and the 2 h image revealed that the mass was still clear, without significant regression (Fig. 2A). Fusion CT imaging revealed that the thymus was irregularly increased, and the abnormal dumbbell-shaped radioactivity uptake shadow in the mediastinum was concentrated in the thymus (Fig. 2B). The diagnosis was a thymic mass, with a 10-min T/N value 2.74, 2 h T/N value 2.88, and it was not possible to rule out the probability of malignancy. Postoperative pathology revealed the presence of thymoma (type AB).
Discussion

At present, 99mTc-MIBI imaging is the most common non-specific imaging method for tumors in China, and it has important application value for differentiating between benign and malignant lesions in the chest, and while its applications for the diagnosis of thymic masses are rarely reported it is more commonly used for patients with breast cancer, lung cancer, thyroid cancer, and malignant soft tissue metastases (14,15).

MIBI is positively charged, lipophilic molecule, so its uptake by cells occurs through trans-membrane potential difference, and may become concentrated inside the mitochondria and cytoplasm. Malignant cells have a rich metabolism and abundant mitochondria, so they have higher negative trans-membrane potentials. Therefore, it may be possible to use this imaging technique for differential diagnosis of benign and malignant tumors (8,17). The results of the present study revealed that the majority of thymic benign lesions demonstrated no apparent MIBI uptake, while the thymoma groups demonstrated various degrees of increased or concentrated MIBI uptake in the mass regions, with the diagnostic sensitivity set at 95.24%, and the specificity as 90.91%. This indicated that 99mTc-MIBI imaging may also potentially be used to distinguish between benign and malignant thymic masses.

Certain previous studies have confirmed that the uptake of 99mTc-MIBI is not only associated with the blood supply, capillary permeability and density of tumor cells, but also with the vitality of mitochondria (13,14,17). Patients with rapid tumor proliferation, high metabolism and low tissue differentiation normally exhibited high uptake of 99mTc-MIBI in the early phase (18,19). Fiorelli et al (17) reported that the uptake of MIBI by thymoma was increased with the increasing degree of malignancy of the tumor (the T/N values of type A, B and C were 1.3±0.2, 1.8±0.3 and 2.7±0.5, respectively). The present study revealed that the uptake ratio in the early phase of the thymoma group was not associated with the degree of malignancy. It was not possible to diagnose mild uptake in the early phase as benign, as certain highly malignant thymoma also demonstrated mild uptake in the early phase, and patients with higher degrees of malignancy demonstrated a gradual concentration of radioactivity uptake within a certain period, namely higher RI. The patients with low-grade malignancies demonstrated a greater concentration of radioactivity uptake in the early phase, while the uptake was reduced in the delayed phase, namely higher WI. Therefore, low uptake with high retention of 99mTc-MIBI in the early phase may indicate a higher degree of malignancy and poor prognosis, so greater clinical attention should be paid and the appropriate treatment programs should be selected. Conversely, high uptake and high washout of 99mTc-MIBI in the early phase may indicate a lower degree of malignancy and an improved prognosis. Previous studies (18,20-23) demonstrated that MIBI was the common transport substrate of phosphoric acid glycoprotein (Pgp) and multidrug resistance-associated protein (MRP), and were actively transported out of the tumor cells by Pgp and MRP. Therefore, overexpression of Pgp or MRP may decrease the concentration of MIBI uptake inside the tumor cells. To determine whether Pgp or MRP were more highly expressed in the group with high-grade malignant thymoma requires additional large-sample studies at the molecular level.

There were certain limitations associated with the present study. The cohort of patients included one case of multilocular thymic cysts-which demonstrated apparent radioactivity uptake in the early and delayed phases. This may be because the cystic components altered the membrane permeability and the potential difference on each side of the cell membrane (24). Another patient with B3-type thymoma demonstrated no significant uptake of MIBI in the early or delayed phase, and this may be due to the presence of an increased number of necrotic components inside the tumor tissues. In addition, the present study had a small sample size, and lacked the cases of thymic cancer (C-type). However, MIBI imaging may still be a potential method for the diagnosis of thymoma.

In short, 99mTc-MIBI imaging was able to accurately discriminate between benign and malignant thymic masses, and has the potential to be used to assess the malignancy of thymoma at a preliminary stage. Thus, it may have significance for the clinical treatment and evaluation of thymoma.

References