SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 14: 2417-2421, 2017

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

CHENGHUI LU, XUFU WANG, BIN LIU, XINFENG LIU, GUOMING WANG and QIN ZHANG

Department of Nuclear Medicine, The Affiliated Hospital of Qingdao University, Qingdao, Shandong 266003, P.R. China

Received October 5, 2015; Accepted March 3, 2017

DOI: 10.3892/ol.2017.6447

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

Correspondence to: Professor Xufu Wang, Department of Nuclear Medicine, The Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao, Shandong 266003, P.R. China
E-mail: xufuwangdoc@163.com

Key words: ^{99m}Tc-MIBI, SPECT, thymus tumor

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}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}Tc-MIBI-SPECT. Following intravenous injection of 740 megabecquerels of the imaging agent ^{99m}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=[T/N (e)-T/N (d)]/T/N (e) x 100%]. The 2-h retention index (RI) was calculated according to the following formula: RI=[T/N(d)-T/N (e)]/T/N (e) x 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.

Table I. ^{99m}Tc-methoxyisobutylisonitrile imaging results for the benign and malignancy groups.

Group	Positive	Negative
Benign group	1	10
Malignancy groups	20	1

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). However, the difference between the BT and IRT groups was not significant (P=0.339; 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}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 II. Comparison of semi-quantitative indexes of radioactivity uptake among the three groups.

Group	T/N (e)	T/N (d)	WI, %	RI, %
BT group	1.033±0.163	1.011±0.143[a]		
LRT group	2.750±1.149[b]	1.011±0.143[c]	5.778±7.716	-5.778±7.71
IRT group	1.317±0.182[d]	1.482±0.155[e]	-13.315±9.410	13.315±9.410

[a]P=0.253 vs. BT group T/N(e); [b]P<0.001 vs. BT group and IRT group; [c]P=0.010 vs. LRT group T/N(e); [d]P>0.05 vs. BT group; [e]P<0.001 vs. IRT group T/N(e). Data are expressed as the mean ± standard deviation. There was no significant difference between T/N (e) and T/N (d) in the BT group, so it was not possible to calculate WI or RI. BT, benign thymic mass; LRT, low-grade malignant thymoma; IRT, intermediate-grade malignant thymoma; T/N, tumor to background ratio; e, early phase; d, delayed phase; WI, 2-h washout index; RI, 2-h retention index.

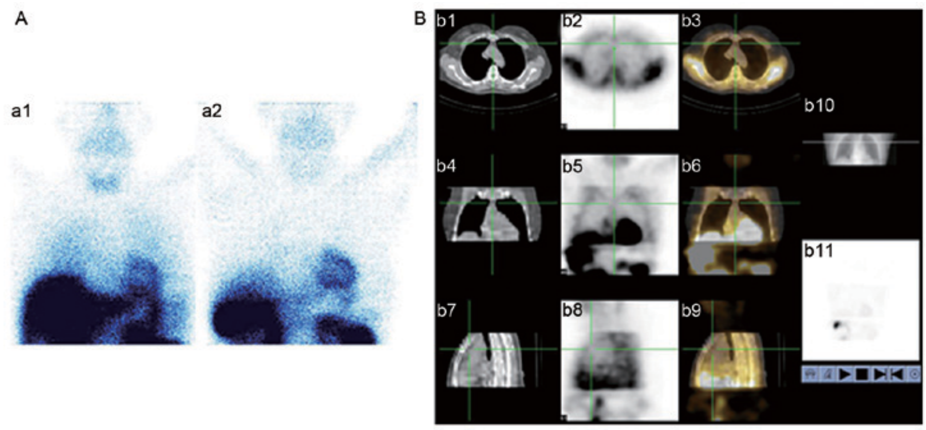

Figure 1. A representative case from the benign thymic mass group. The depicted patient is female (58 years old). Physical examination revealed the presence of an anterior mediastinal mass. (A) ^{99m}Tc-methoxyisobutylisonitrile imaging. a1, early stage; a2, delayed stage. There was almost no uptake in the two stages. (B) single-photon emission computed tomography/computed tomography fusion imaging. b1-b3, transverse view of CT, SPECT and fusion image, respectively. b4-b6, cronal view of CT, SPECT and fusion image, respectively. b7-b9, sagittal view of CT, SPECT and fusion image, respectively. b10, location image. b11, 3D of SPECT image. SPECT, single-photon emission computed tomography.

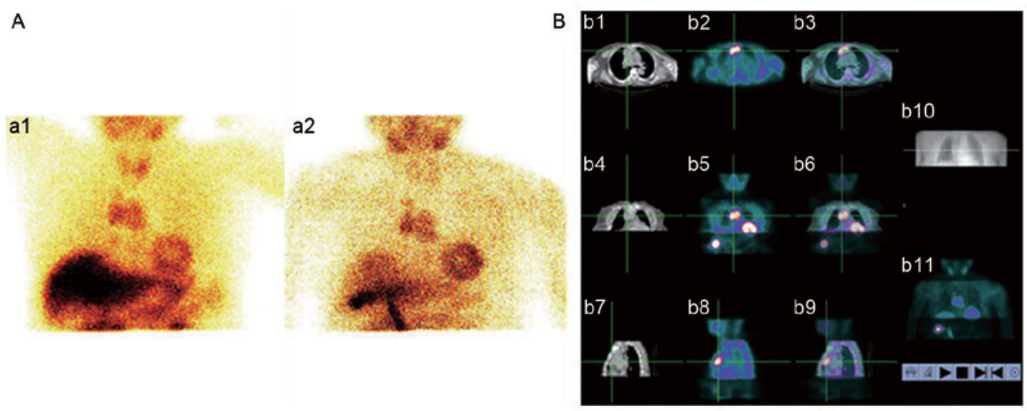

Figure 2. A representative case from the malignant groups. The depicted patient is female (63 years old). Physical examination revealed the presence of a thymic mass. It was confirmed to be thymoma (type AB) by postsurgical pathology. (A) ^{99m}Tc-methoxyisobutylisonitrile imaging. a1, early stage; a2, delayed stage. (B) Single-photon emission computed tomography/computed tomography fusion imaging. b1-b3, transverse view of CT, SPECT and fusion image, respectively. b4-b6, cronal view of CT, SPECT and fusion image. b7-b9, sagittal view of CT, SPECT and fusion image. b10, location image. b11, 3D of SPECT image. SPECT, single-photon emission computed tomography; CT, computed tomography.

from the malignant groups. 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, ^{99m}Tc-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 as 95.24%, and the specificity as 90.91%. This indicated that ^{99m}Tc-MIBI imaging may also potentially be used to distinguish between benign and malignant thymic masses.

Certain previous studies have confirmed that the uptake of ^{99m}Tc-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 ^{99m}Tc-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 ^{99m}Tc-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 ^{99m}Tc-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, ^{99m}Tc-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

1. Suster S and Moran CA: Primary thymic epithelial neoplasms showing combined features of thymoma and thymic carcinoma. A clinicopathologic study of 22 cases. Am J Surg Pathol 20: 1469-1480, 1996.
2. Priola AM, Priola SM, Cardinale L, Cataldi A and Fava C: The anterior mediastinum: Diseases. Radiol Med 111: 312-342, 2006 (In English, Italian).
3. Venuta F, Anile M, Diso D, Vitolo D, Rendina EA, De Giacomo T, Francioni F and Coloni GF: Thymoma and thymic carcinoma. Eur J Cardiothorac Surg 37: 13-25, 2010.
4. Aroor AR, Prakasha SR, Seshadri S, S T and Raghuraj U: A study of clinical characteristics of mediastinal mass. J Clin Diagn Res 8: 77-80, 2014.
5. Tomiyama N, Honda O, Tsubamoto M, Inoue A, Sumikawa H, Kuriyama K, Kusumoto M, Johkoh T and Nakamura H: Anterior mediastinal tumors: Diagnostic accuracy of CT and MRI. Eur J Radiol 69: 280-288, 2009.
6. Molina PL, Siegel MJ and Glazer HS: Thymic masses on MR imaging. AJR Am J Roentgenol 155: 495-500, 1990.
7. de Jong WK, Blaauwgeers JL, Schaapveld M, Timens W, Klinkenberg TJ and Groen HJ: Thymic epithelial tumours: A population-based study of the incidence, diagnostic procedure and therapy. Eur J Cancer 44: 123-130, 2008.
8. Hoerbelt R, Keunecke L, Grimm H, Schwemmle K and Padberg W: The value of a noninvasive diagnostic approach to mediastinal masses. Ann Thorac Surg 75: 1086-1090, 2003.
9. Kesler KA, Wright CD and Loehrer PJ Sr: Thymoma: Current medical and surgical management. Semin Neurol 24: 63-73, 2004.
10. Higuchi T, Taki J, Kinuya S, Yamada M, Kawasuji M, Matsui O, Nonomura A, Bunko H and Tonami N: Thymic lesions in patients with myasthenia gravis: Characterization with thallium 201 scintigraphy. Radiology 221: 201-206, 2001.
11. Priola AM and Priola SM: Imaging of thymus in myasthenia gravis: From thymic hyperplasia to thymic tumor. Clin Radiol 69: e230-e245, 2014.
12. Scagliori E, Evangelista L, Panunzio A, Calabrese F, Nannini N, Polverosi R and Pomerri F: Conflicting or complementary role of computed tomography (CT) and positron emission tomography (PET)/CT in the assessment of thymic cancer and thymoma: Our experience and literature review. Thorac Cancer 6: 433-442, 2015.
13. Treglia G, Sadeghi R, Giovanella L, Cafarotti S, Filosso P and Lococo F: Is (18)F-FDG PET useful in predicting the WHO grade of malignancy in thymic epithelial tumors? A meta-analysis. Lung Cancer 86: 5-13, 2014.
14. Malek H, Ghaedian T, Yaghoobi N, Rastgou F, Bitarafan-Rajabi A and Firoozabadi H: Focal breast uptake of 99mTc-sestamibi in a man with spindle cell lipoma. J Nucl Cardiol 19: 618-620, 2012.

15. Gedik GK, Ergün EL, Aslan M and Caner B: Unusual extracardiac findings detected on myocardial perfusion single photon emission computed tomography studies with Tc-99m sestamibi. Clin Nucl Med 32: 920-926, 2007.
16. Rosai J: Histological typing of tumors of the thymus. 2nd edition. World Health Organization International Histological Classification of Tumors. Berlin, Springer-Verlag, 1999.
17. Fiorelli A, Vicidomini G, Laperuta P, Rambaldi P, Mansi L, Rotondo A and Santini M: The role of Tc-99m-2-Methoxy-Isobutyl-Isonitrile Single Photon Emission Computed Tomography in visualizing anterior mediastinal tumor and differentiating histologic type of thymoma. Eur J Cardiothorac Surg 40: 136-142, 2011.
18. García-Talavera P, Olmos R, Sainz-Esteban A, Ruiz MÁ, González ML and Gamazo C: Evaluation by SPECT-CT of an incidental finding of a thymoma and breast cancer in a myocardial perfusion SPECT with 99mTc-MIBI. Rev Esp Med Nucl Imagen Mol 32: 260-262, 2013.
19. Hashimoto T, Goto K, Hishinuma Y, Yachuda K, Sugioka Y, Arai K, Harada S and Goto M: Uptake of 99mTc-tetrofosmin, 99mTc-MIBI and 201Tl in malignant thymoma. Ann Nucl Med 14: 293-298, 2000.
20. Sasajima T, Shimada N, Naitoh Y, Takahashi M, Hu Y, Satoh T and Mizoi K: (99m)Tc-MIBI imaging for prediction of therapeutic effects of second-generation MDR1 inhibitors in malignant brain tumors. Int J Cancer 121: 2637-2645, 2007.
21. Sun SS, Hsieh JF, Tsai SC, Ho YJ, Lee JK and Kao CH: Expression of mediated P-glycoprotein multidrug resistance related to Tc-99m MIBI scintimammography results. Cancer Lett 153: 95-100, 2000.
22. Kurata S, Ushijima K, Kawahara A, Kaida H, Kawano K, Hirose Y, Kage M, Kamura T, Ishibashi M and Abe T: Assessment of 99mTc-MIBI SPECT(/CT) to monitor multidrug resistance-related proteins and apoptosis-related proteins in patients with ovarian cancer: A preliminary study. Ann Nucl Med 29: 643-649, 2015.
23. Baumert C and Hilgeroth A: Recent advances in the development of P-gp inhibitors. Anticancer Agents Med Chem 9: 415-436, 2009.
24. Araki T, Sholl LM, Gerbaudo VH, Hatabu H and Nishino M: Intrathymic cyst: Clinical and radiological features in surgically resected cases. Clin Radiol 69: 732-738, 2014.