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ORIGINAL ARTICLE

Positron emission tomography/computed tomography as a clinical diagnostic tool for anterior mediastinal tumors

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Abstract

Purpose The purpose of this study was to assess the usefulness of positron emission tomography/computed tomography (PET/CT) in the differential diagnosis of anterior mediastinal tumors.

Methods A total of 94 patients with anterior mediastinal masses or nodules (male, $n=41$; female, $n=53$; age, 17–84 years) were retrospectively evaluated. All patients were evaluated by PET/CT and the masses or nodules were histologically diagnosed in our institution.

Results Anterior mediastinal masses and nodules were classified into two disease categories: Low (thymic hyperplasia, thymoma, mature teratoma, and MALT lymphoma) and High (thymic carcinoid, thymic cancer, diffuse large B-cell lymphoma, T-cell lymphoblastic lymphoma, Hodgkin's lymphoma, and malignant germ cell tumors) groups. The sensitivity and specificity of maximum standardized uptake value (SUV_{max}) 7.5 for the detection of High group were 77% and 100%, respectively. The SUV_{max} distributions of the WHO histological thymoma types and Masaoka stage thymomas extensively overlapped. Masaoka stage III thymomas had significantly higher SUV_{max} than Masaoka stage I thymomas. Regarding the TNM classification, the SUV_{max} of T3 and T1b thymomas was higher than T1a thymoma.

Conclusion Although the SUVmax of each disease overlapped, PET/CT findings provided useful information for the differential diagnosis of anterior mediastinal masses.

Keywords PET/CT · Anterior mediastinal mass · Thymoma · Malignant lymphoma

Introduction

Clinicians need noninvasive diagnostic tools for diseases in anterior mediastinum since various diseases arise there. Thymomas account for approximately half of the various pathological types of primary anterior mediastinal masses and nodules [1, 2]. Thymic cancer, mediastinal germ cell tumors, and lymphomas are relatively rare diseases in the anterior component of the mediastinum. Cysts and thymic hyperplasia are typical benign diseases found in the mediastinum. Surgery may be indicated for benign diseases—most can be excised endoscopically. Most thymomas are also eligible for excision by minimally invasive surgery, as long as the tumors are small [3]. The treatment of thymomas of advanced clinical stage, thymic carcinoids, and thymic cancers varies according to their clinical characteristics. Lymphomas and malignant germ cell tumors are generally treated with chemotherapy rather than surgery.

Obtaining a pathological diagnosis of mediastinal masses helps to establish the therapeutic strategy; however, this is not always technically possible and is considered too invasive for patients in a poor physical condition. Noninvasive diagnostic approaches are therefore important and useful for selected patients with anterior mediastinal masses. The patient's age, sex, and symptoms often suggest a clinical diagnosis [4]. Computed tomography (CT) and magnetic resonance imaging can provide detailed information on

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masses, including their size, location, relationship to surrounding structures, and tissue characteristics. Tumor markers further support the diagnostic work-up. Despite the information obtained by these diagnostic tools, obtaining a pathological diagnosis of anterior mediastinal masses in addition to the clinical diagnosis is not always easy.

In 1996, Kubota et al. reported the ^{18}Fluorine-fluorodeoxyglucose–positron emission tomography (FDG–PET) findings in mediastinal tumors [5]. ^{18}Fluorine-fluorodeoxyglucose–positron emission tomography (PET/CT), which combines an FDG–PET scanner and X-ray computed tomography, has emerged as a powerful diagnostic tool for the diagnosis, staging, and restaging of neoplasms. More recently, a number of small studies have reported on the efficacy of PET/CT in the diagnosis of anterior mediastinal masses [6–8], including thymomas [9, 10]. This study describes the clinical experience in a series of patients at a single center for whom both PET/CT findings of anterior mediastinal masses and a histological diagnosis were available. The aim was to determine the diagnostic value of PET/CT and its potential role in the selection of therapeutic strategies.

Materials and methods

Between February 2005 and April 2013, 94 patients with anterior mediastinal masses or nodules male, $n=41$; female, $n=53$; median age, 55 years (range, 17–84 years) were evaluated by PET/CT and then underwent surgical resection or biopsy. The masses were resected in 78 patients, diagnosed by surgical biopsy in 7 patients, and diagnosed by needle biopsy in 9 patients. The anterior mediastinum was defined as a prevascular compartment based on the CT findings [11]. All resected masses and biopsy tissue were evaluated histologically. Patients with metastatic tumors, mediastinal invasion of primary lung cancers, and recurrence of mediastinal diseases were excluded from this study. Patients with benign congenic cysts were not included. The Institutional Review Board of Tohoku University Hospital approved the study (No. 2018-1-324), which was conducted in accordance with the Declaration of Helsinki and the Declaration of Istanbul 2013.

Surgery

Lesions with CT findings compatible with resection were resected without a preoperative diagnosis. Tumors that invaded the major mediastinal structures and that were judged clinically unsuitable for initial surgical treatment were biopsied (core needle biopsy or surgical biopsy) to obtain a sufficient quantity of tissue for a pathological diagnosis. The Masaoka stage of thymoma [12] was determined after reviewing the operative and pathological findings. Two thymomas were diagnosed by needle biopsy and were not treated by surgical resection because of the patient's poor general condition; the Masaoka stage and TNM classification were not obtained.

The PET/CT protocol

All integrated PET/CT images were obtained at our institution using a Biograph Duo or a Biograph 40 PET/CT system [Siemens AG, Erlangen, Germany] and a standard clinical protocol. Patients fasted for at least 4 h before receiving an intravenous injection of 185–370 MBq (5–10 mCi) FDG. Blood samples were collected to measure the blood glucose level before the injection of the radioactive tracer. The patients rested in a reclining chair in a quiet room for approximately 1 h between the tracer injection and the initiation of the PET/CT scan. No oral or intravenous contrast agent was used. During the scan, FDG–PET data were obtained for 2 min in each bed position. Patients were instructed to continue shallow breathing during PET acquisition. FDG–PET images were reconstructed using the CT transmission map for attenuation correction, and the images were interpreted in standard clinical fashion by two nuclear radiologists. The maximum standardized uptake value (SUV_{max}) of the early phase (1 h after injection) was calculated for mediastinal lesions using the commercially available software provided by the manufacturer and installed in the imaging machinery. The two PET/CT systems are carefully calibrated and monitored, and the imaging protocols were consistent, which was shown to reduce variability in the SUV_{max} between scans in phantom studies.

Histology

The histological interpretations and immunohistochemical examinations were made by pathologists. The histological types of thymoma were determined according to the World Health Organization (WHO) classification. The stages of the thymoma were determined by Masaoka's staging system [12] and the 8th edition of TNM classification of malignant tumors [13]. Thymomas, thymic cancer, and thymic carcinoid were considered to represent thymic malignancies [13]. Primary mature teratomas and malignant germ cell tumors were considered to represent distinct disease entities [4]. Mediastinal lymphoma was diagnosed pathologically by immunohistochemistry and/or flow cytometry.

Statistical analysis

The SUV_{max} data were expressed as mean ± standard deviation (SD). The significance of differences were tested by an analysis of variance (ANOVA) for the comparison of more than three groups and the Mann–Whitney test for the comparison of two groups. The analysis was performed using the GraphPad PRISM 6 software program (GraphPad Software Inc., San Diego, CA, USA). p values < 0.05 were considered to indicate statistical significance.

Results

Ninety-four patients with anterior mediastinal masses or nodules were included in this study. The diagnoses (Table 1) included thymic hyperplasia ($n = 7$), teratoma ($n = 8$), thymoma ($n = 55$; type A, $n = 4$; type AB, $n = 12$; B1, $n = 16$; type B2, $n = 17$; and type B3, $n = 6$), thymic cancer (n = 4), thymic carcinoid (n = 4), malignant germ cell tumor ($n = 3$;seminoma, $n = 2$; embryonal carcinoma, $n = 1$), lymphoma ($n = 13$; diffuse large B-cell lymphoma, $n = 5$; T-cell lymphoblastic lymphoma, $n = 2$; Hodgkin's lymphoma, $n = 4$; and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type (MALT), $n = 2$). Fifteen thymomas and six thymic hyperplasias were combined with myasthenia gravis. The blood glucose level just before the administration of FDG was < 200 mg/dl in all patients. The ages and sex ratios of the patients with each disease and the size of the nodules and masses are shown in Table 1.

The SUV_{max} of each disease

The mean SUV_{max} for each disease was as follows (Fig. 1): thymic hyperplasia, 1.4 ± 0.7; mature teratoma, 3.0 ± 1.7; thymoma, 3.7 ± 1.5; thymic carcinoid, 7.0 ± 1.5; thymic cancer, 11.4 ± 2.8; malignant germ cell tumor, 9.4 ± 5.3; and

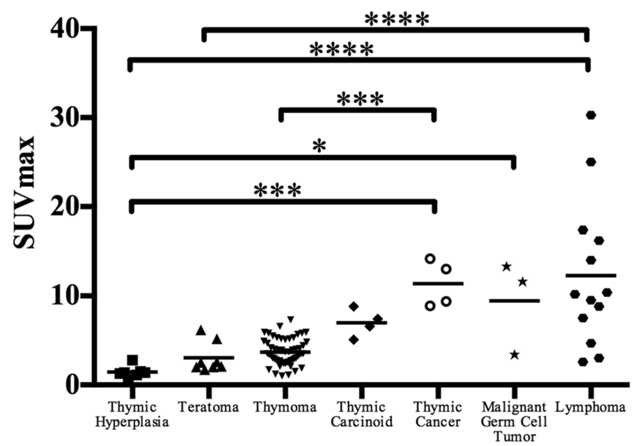

Fig. 1 The SUV_{max} distribution of each histological type of anterior mediastinal mass and nodule. The mean $SUV_{max} \pm$ SD was 1.4 ± 0.7 for thymic hyperplasia, 3.0 ± 1.7 for teratoma, 3.7 ± 1.5 for thymoma, 7.0 ± 1.5 for thymic carcinoid, 11.4 ± 2.6 for thymic cancer, 9.4 ± 5.3 for malignant germ cell tumors, and 12.3 ± 8.3 for lymphoma. $^{*}p < 0.05$, $^{***}p < 0.005$, $^{****}p < 0.001$

Table 1 The characteristics of each anterior mediastinal mass

Histology	Number of cases	Male	Female	Median age (minimum and maximum)	Median MTD (minimum and maximum)	Range of SUV_{max} (minimum and maximum)
Thymic malignancy	63	40	23	57.0 (19–84)	45 (20–120)	1.2–5.1
Thymoma	55	34	21	58.0 (19–84)	43 (20–102)	1.0–5.9
A	4	2	2	74.0 (57–82)	44 (20–102)	1.2–5.1
AB	12	6	6	67.5 (31–77)	50 (20–80)	1.1–5.2
B1	16	14	2	55.5 (19–68)	39 (20–83)	1.0–5.9
B2	17	9	8	58.0 (34–80)	41 (21–83)	1.7–7.3
B3	6	2	4	57.0 (53–84)	55 (43–100)	3.0–5.8
Thymic cancer	4	3	1	63.0 (54–73)	49.5 (36–70)	8.9–14.2
Thymic carcinoid	4	3	1	51.5 (37–57)	76.5 (20–120)	5.1–8.8
Malignant germ cell tumor	3	3	0	26.0 (22–40)	72 (70–80)	3.4–13.3
Lymphoma	13	6	7	27.0 (18–73)	69 (36–100)	1.5–30.3
DLBCL	5	3	2	34.0 (19–73)	57.0 (36–94)	9.5–25.0
TLL	2	2	0	25.5 (24–27)	68.5 (55–82)	3.0-30.3
Hodgkin's lymphoma	4	1	3	21.5 (18–25)	93.5 (69–100)	7.5–16.2
MALT	2	0	2	56.5 (54–59)	67 (64–70)	2.6–4.7
Benign disease	15	4	11	33.5 (17–66)	33.5 (17–66)	0.6–6.2
Thymic hyperplasia	7	3	4	50.0 (17–66)	35 (10–60)	0.6–2.8
Mature teratoma	8	1	7	25.5 (17–41)	53.5 (31–125)	1.7–6.2

MTD maximum transverse diameter; *Thymic malignancy* thymoma, thymic cancer and thymic carcinoid; *DLBCL* diffuse large B-cell lymphoma; *TLL* T-cell lymphoblastic lymphoma, *MALT* extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type lymphoma, 12.3 ± 8.3. The SUV_{max} of thymic hyperplasia was < 3.0. The SUV_{max} of mature teratomas and all thymomas was < 7.4, and the individual values partially overlapped with those of thymic carcinoids but not thymic cancer. The SUV_{max} of malignant germ cell tumors (3.4–13.3) and lymphomas (2.6–30.3) varied widely.

The SUV_{max} of thymomas according to the WHO histological classification, Masaoka stage, and TNM classification 8th edition

The distributions of SUV_{max} for thymoma (WHO histological classification) are shown in Fig. 2a. The mean ± SD SUV_{max} was 3.1 ± 1.8 in type A, 3.4 ± 1.5 in type AB, 3.8 ± 1.5 in type B1, 3.7 ± 1.6 in type B2, and 4.3 ± 1.0 in type B3. The distributions of SUV_{max} observed in the different WHO histological types overlapped.

The distributions of SUV_{max} in thymomas according to the Masaoka stage are shown in Fig. 2b, and were 3.0 ± 1.2 in stage I ($n = 22$), 3.8 ± 1.6 in stage II ($n = 21$), 4.8 ± 1.0 in stage III ($n = 7$), and 4.4 ± 1.2 in stage IV ($n = 3$). The SUV_{max} distribution in each stage overlapped; however, the distribution of stage III thymomas was significantly greater than that of Stage I thymoma. The SUV_{max} of stage III and IV thymomas were ≥ 3.

The distributions of SUV_{max} in thymomas according to T classification (TNM classification) are shown in Fig. 2c. The SUV_{max} was 3.2 ± 1.3 in T1a ($n = 40$), 5.4 ± 2.0 in T1b ($n = 3$), 5.1 ± 0.9 in T2 ($n = 2$), 4.6 ± 1.1 in T3 ($n = 8$). T3 and T1b thymomas had significantly higher SUV_{max} than T1a thymomas. The SUV_{max} distribution in thymomas according to TNM stage were as follows: Stage I ($n = 43$: SUV_{max}, 3.4 ± 1.4), Stage II ($n = 1$: SUV_{max}, 4.4), Stage IIIa ($n = 6$: SUV_{max}, 4.9 ± 1.0), and Stage IVa ($n = 3$: SUV_{max}, 4.4 ± 1.2).

The SUV_{max} of lymphoma

The SUV_{max} of each pathological type of lymphoma is shown in Fig. 3, and was 15.2 ± 6.3 for diffuse large B-cell lymphoma, 16.7 ± 19.3 for T-cell lymphoblastic lymphoma, 10.7 ± 3.8 for Hodgkin's lymphoma, and 3.7 ± 1.5 for MALT. All diffuse large B-cell lymphomas and Hodgkin's lymphomas had an SUV_{max} of > 9.5 and 7.5, respectively. Thus, the SUV_{max} of these two histological types of lymphoma never overlapped with that of MALT. The SUV_{max} of T-cell lymphoblastic lymphomas ranged significantly from 3.0 to 30.3. The SUV_{max} of all cases of MALT was < 4.7.

Proposed classification of anterior mediastinal masses and nodules

Given the study findings, we propose classifying anterior mediastinal masses into two groups (Fig. 4a). The Low

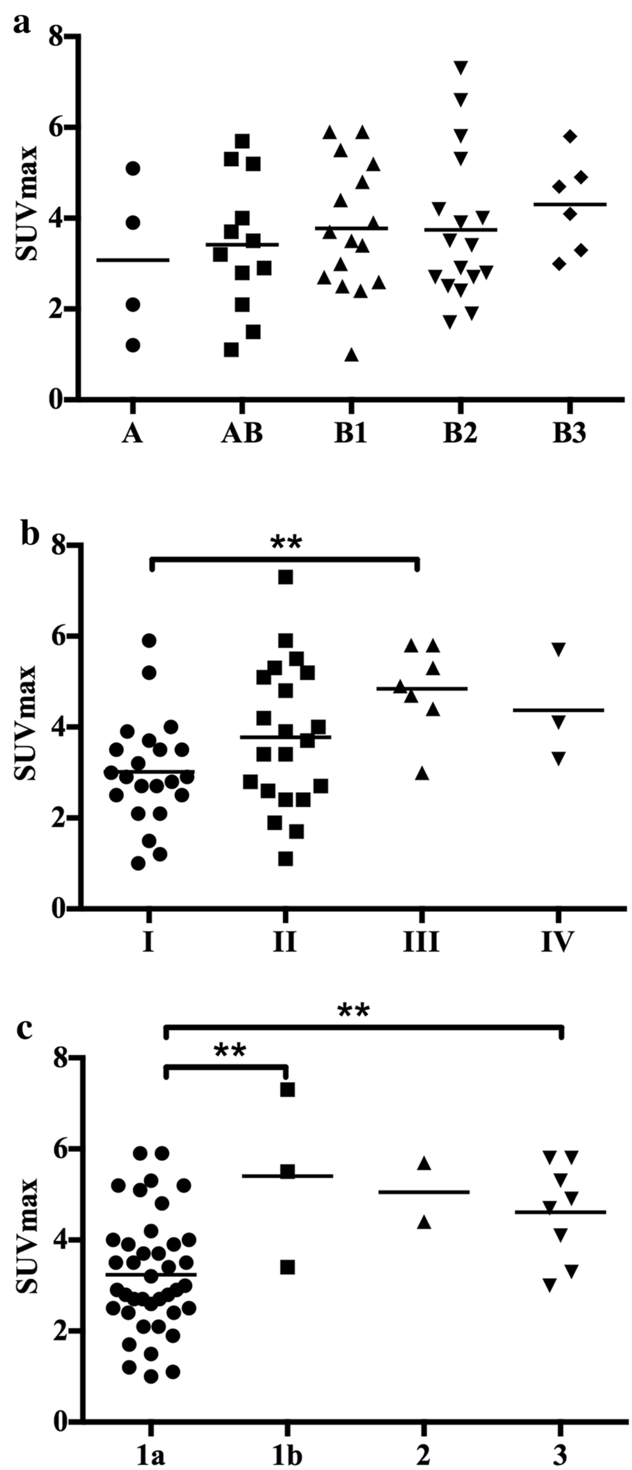

Fig. 2 **a** The SUV_{max} distribution of thymomas according to the WHO classification and Masaoka Stage. **a** The mean SUV_{max} ± SD of the thymomas according to the WHO classification was 3.1 ± 1.8 for type A, 3.4 ± 1.5 for type AB, 3.8 ± 1.4 for type B1, 3.7 ± 1.6 for type B2, and 4.2 ± 1.0 for type B3. No significant differences were observed among the groups. **b** The SUV_{max} distribution in thymoma according to the Masaoka stage. The mean SUV_{max} ± SD was 3.0 ± 1.2 for stage I, 3.8 ± 1.6 for stage II, 4.8 ± 1.0 for stage III, and 4.4 ± 1.2 for stage IV. **c** The SUV_{max} distribution of thymoma according to the T stage of the TNM classification. The mean SUV_{max} ± SD was 3.2 ± 1.3 for T1a, 5.4 ± 2.0 for T1b, 5.1 ± 0.9 for T2, 4.6 ± 1.1 for T3. $^{**}p < 0.01$

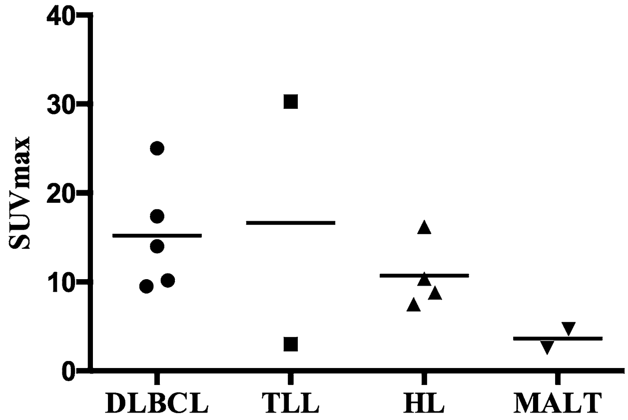

Fig. 3 The SUV_{max} distribution of lymphoma for each histological type. The mean SUV_{max} ± SD was 15.2 ± 6.3 for diffuse large B-cell lymphoma (DLBCL), 16.7 ± 19.3 for T-cell lymphoblastic lymphoma (TLL), HL: 10.7 ± 3.8 for Hodgkin's lymphoma (HL), and 3.7 ± 1.5 for extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT). No significant differences were observed among the groups

group includes thymic hyperplasia, thymoma, mature teratoma, and, MALT. The High group includes thymic carcinoid, thymic cancer, diffuse large B-cell lymphoma, T-cell lymphoblastic lymphoma, Hodgkin's lymphoma and malignant germ cell tumors. The receiver operating characteristic (ROC) curve showed that the sensitivity and specificity of SUV_{max} 7.5 in the detection of the High group were 77% and 100%, respectively (Fig. 4b).

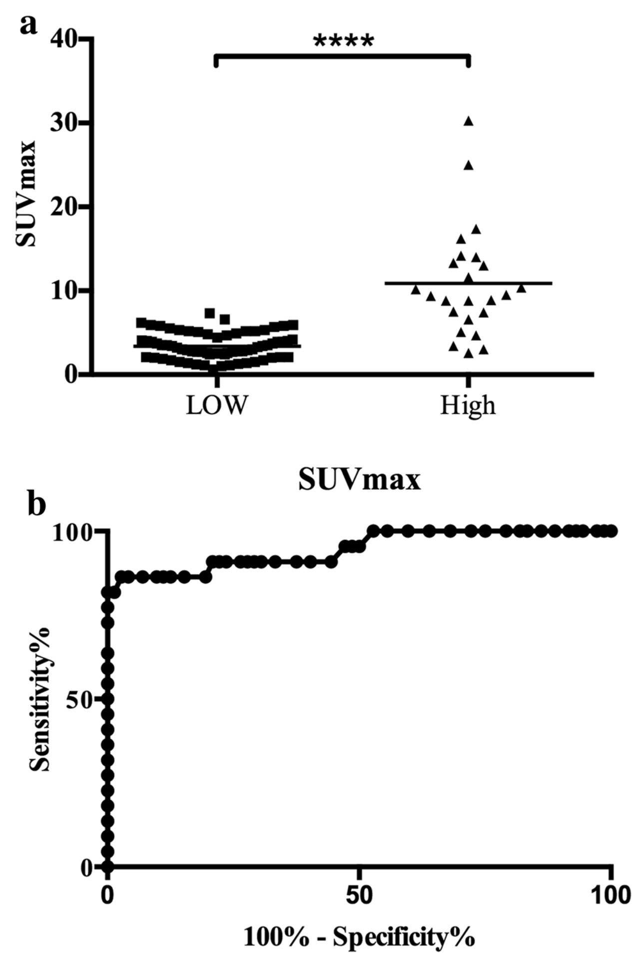

Fig. 4 **a** The SUV_{max} distribution of the two anterior mediastinal mass groups. The Low group: included patients with thymic hyperplasia, thymoma, mature teratoma, and MALT. The High group included patients with thymic carcinoid, thymic cancer, diffuse large B-cell lymphoma, T-cell lymphoblastic lymphoma, Hodgkin's lymphoma, and malignant germ cell tumors. **b** The ROC curves of the Low and High groups of anterior mediastinal masses. ****$p < 0.001$

Discussion

An important finding of this study, which included a relatively large number of patients with anterior mediastinal masses and nodules, was that PET/CT could distinguish thymoma from thymic cancer, diffuse large B-cell lymphoma, and Hodgkin's lymphoma. The highest SUV_{max} of thymomas was 7.3, whereas the lowest SUV_{max} of the other three diseases was 7.5; the SUV_{max} distributions did not overlap. This suggests that a pathological diagnosis of an anterior mediastinal mass should be obtained before surgery if the SUV_{max} is ≥ 7.5 because chemotherapy is specifically indicated as the initial treatment of diffuse large B-cell and Hodgkin's lymphomas, and occasionally indicated as the initial treatment of thymic cancer. The study results are in line with previous reports that showed the usefulness of PET/CT in the differential diagnosis of thymoma and thymic cancer [7, 14–17]. On the other hand, the SUV_{max} did not predict the histological diagnosis of thymoma. Previous researchers had tried to investigate the correlation of the biological activity of thymomas using the Ki-67 labeled index [18] and the combination of tumor size and SUV_{max} [19]. Contrary to our expectation, the SUV_{max} distributions of all WHO histological types of thymoma overlapped significantly. Some previous studies have demonstrated the usefulness of PET/CT in the differentiation of thymomas (classified according to the WHO system) [20] and others have not [15, 21–23]. Our results were consistent with the latter group in terms of the WHO histological classification of thymoma.

PET/CT has been proposed for the staging of thymomas. The SUV_{max} of Masaoka stage thymomas showed considerable variation in this study. The SUV_{max} of Masaoka stages I and II were distributed over a relatively wide range between 1.0 and 7.3, and significantly overlapped with the observed distributions of stage III and IV thymomas. It is difficult to determine the stage of thymoma based on PET/CT; however, our result showed that Masaoka stage III thymomas had significantly higher SUV_{max} in comparison to Masaoka stage I thymomas. The assessment of the T stage in accordance with the recently published 8th edition of the TNM classification of malignant tumors revealed that T3 and T1b thymomas showed significantly higher SUV_{max} than T1a thymomas. T2 thymomas tended to show a higher SUV_{max} in comparison to T1a thymomas; however, the statistical power was not sufficient. The role of PET/CT in the staging of thymoma is also controversial. Some investigators have reported that it was not possible [9, 18, 24], whereas others found that Masaoka stage III and IV thymomas showed higher SUV_{max} in comparison to stage I and II thymomas [18, 21]. Our results indicated that the SUV_{max} from PET/CT potentially reflected the local invasiveness of thymomas, which was also suggested from other researchers [7, 14–16]; however, the SUV_{max} could not provide a clear cutoff value for either the Masaoka or the TNM classification.

The study results led to the proposal to categorize anterior mediastinal masses and nodules into two groups according to the SUV_{max} range. The Low group included thymic hyperplasia, mature teratomas, thymoma, and MALT lymphoma; the High group included thymic carcinoid, thymic cancer, diffuse large B-cell lymphoma, T-cell lymphoblastic lymphoma, Hodgkin's lymphoma, and malignant germ cell tumors. On one hand, this classification showed that the sensitivity and specificity of SUV_{max} 7.5 in the detection of the High group was 77% and 100%, respectively. On the other hand, our data showed that the SUV_{max} of two groups of high malignancy tumors, T-cell lymphoblastic lymphoma and malignant germ cell tumors was highly variable. Some of these cases could be included in the Low group, although their initial treatment was thought to be other than definitive surgery. Another point is that the SUV_{max} of thymic carcinoid (SUV_{max}: 7.0 ± 1.5) was close to the proposed cutoff value; thus, thymic carcinoid can be included in both groups. In addition, a subtype of mediastinal lymphoma, MALT lymphoma, was included in the Low group. Thus, this classification will very useful for establishing a differential diagnosis of anterior mediastinal masses and nodules, if it is used with clinical information and other diagnostic tools, including tumor markers, which are considered to be standard diagnostic methods [4]. In High group patients, every effort should be made to obtain sufficient specimens by any procedure, including endoscopic surgery, mediastinoscopy, and anterior mediastinotomy, before proceeding with definitive surgical excision.

The present study was associated with some limitations. First, two different PET/CT imaging machines were used in this study, and cystic lesions and nodules were included, these factors might have affected the individual SUV_{max}. However, we tried to reduce variability by utilizing quantitative PET/CT imaging in a network of calibrated PET/CT scanners [25]. Second, the present study was observational and retrospective in nature. Nevertheless, the present study confirmed a role for PET/CT in the differential diagnosis of anterior mediastinal masses and nodules in a relatively large patient population.

Conclusions

This retrospective, single center study of anterior mediastinal masses in 94 patients revealed that the PET/CT SUV_{max} helped to facilitate the differential diagnosis of anterior mediastinal masses. The SUV_{max} may reflect the invasiveness of thymoma. We therefore conclude that PET/CT is a useful diagnostic modality for establishing therapeutic strategies for anterior mediastinal masses.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

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