ORIGINAL ARTICLE

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

Elena Scagliori[1], Laura Evangelista[2], Annalori Panunzio[1], Fiorella Calabrese[3], Nazarena Nannini[3], Roberta Polverosi[4] & Fabio Pomerri[1]

1 Oncologic Radiology Unit, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy
2 Radiotherapy and Nuclear Medicine Unit, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy
3 Department of Cardiac, Thoracic and Vascular Science, University of Padua, Padua, Italy
4 Department of Radiology, Hospital of San Donà di Piave, Venice, Italy

Abstract

Background: To evaluate the role of computed tomography (CT) and positron emission tomography (PET)/CT in patients with thymic cancer and thymoma at initial staging.

Methods: We retrospectively reviewed CT and PET/CT scans of 26 patients with a thymic cancer ($n = 9$) or thymoma ($n = 17$). Chest CT findings documented were qualitative and quantitative. Both qualitative and semiquantitative data were recovered by PET/CT. The comparisons among histological entities, outcome, and qualitative data from CT and PET/CT were made by non-parametric analysis.

Results: PET/CT resulted positive in 15/17 patients with thymoma. CT was available in 5/9 (56%) patients with thymic cancer and in 3/17 with thymoma. All quantitative CT parameters were significantly higher in patients with thymic cancer than thymoma (maximum axial diameter: 45 vs. 20 mm, maximum longitudinal diameter: 69 vs. 21 mm and volume: 77.91 vs. 4.52 mL; all $P < 0.05$). Conversely, only metabolic tumor volume (MTV) and total lesion glycolysis were significantly different in patients with thymic cancer than thymoma (126.53 vs. 6.03 cm3 and 246.05 vs. 20.32, respectively; both $P < 0.05$). After a median follow-up time of 17.45 months, four recurrences of disease occurred: three in patients with thymic cancer and one with a type B2 thymoma. CT volume in patients with recurrent disease was 102.19 mL *versus* a median value of 62.5 mL in six disease-free patients. MTV was higher in the recurrent than disease-free patient subset (143.3 vs. 81.13 cm^3), although not statistically significant ($P = 0.075$).

Conclusion: Our preliminary results demonstrated that both morphological and metabolic volume could be useful from a diagnostic and prognostic point of view in thymic cancer and thymoma patients. A large multi-center clinical trial experience for confirming the findings of this study seems mandatory.

Introduction

Thymoma is a rare tumor accounting for <1% of all adult malignancies, although it is the most common primary neoplasm of the anterior mediastinum. Thymoma is the most common thymic epithelial neoplasm; however, thymic carcinoma and thymic carcinoid are also recognized. Because thymoma is a rare disease, an international collaboration and a dedicated work group have been created, the International Thymic Malignancy Interest Group (ITMIG). To facilitate collaborative research efforts and formation of a uniform thymoma database, ITMIG has adopted the Masaoka-Koga staging system as the official staging system for thymoma. This system is based on gross operative findings with microscopic confirmation of invasive tumor properties. Conversely, the World Health Organization (WHO) classification

distinguishes thymic lesions according to their histological pattern. Both the WHO histologic classification of thymic epithelial tumor[1,2] and the clinic-pathologic staging system proposed by Masaoka *et al.*[3] have been reported to reflect the oncological behavior of thymoma and, hence, the prognosis.

Imaging plays a role in thymoma identification, extension, global staging, restaging, and evaluation of response to treatment. Initial investigation of thymoma starts with a chest radiograph followed by chest-computed tomography (CT) and is rarely completed by magnetic resonance imaging (MRI) or nuclear medicine studies (such as 111In-octreoscan scintigraphy or positron emission tomography [PET] with 18F-Fluorodeoxyglucose [FDG]).

The purposes of the present study were: (i) to evaluate the role of CT and FDG PET/CT in thymic lesions in initial staging, (ii) to correlate imaging findings with the prognosis of thymic lesions, and (iii) to compare our findings with current literature.

Materials and methods

Patient population

From April 2008 to December 2012, we retrospectively reviewed a total of 90 FDG PET/CT scans that were performed on 56 patients with a known or suspected thymic disease. Moreover, in 32 subjects of the same population, we collected 38 CT scans performed within three months of the PET/CT studies. Thirty-five PET/CT scans were performed at initial staging, 28 for restaging, 17 for evaluation of response to therapy, and 10 for long term follow-up. Out of 38 CT scans, 14 were made at initial staging, eight for restaging, six for response to therapy, and 10 for follow-up. For the end points of the present study, we considered 26 patients at initial staging of thymoma or thymic cancer. There were eight male and 18 female patients (30.8 vs. 68.2%, respectively). The median age was 57.5 years (31–78 years). All patients had a PET/CT scan, while only eight subjects had an available CT in the same setting. The defined diagnosis was obtained by surgical specimens after thymectomy. The surgical specimens were reviewed by two experienced pathologists, and the tumors were divided into six subtypes on the basis of WHO classification: type A, type AB, type B1, type B2, type B3, and thymic carcinoma. All of the tumors were staged on the basis of the presence and extent of transcapsular invasion into adjacent mediastinal tissues as determined by surgical findings and confirmed by microscopic examination:[3] stage I, encapsulated tumor without microscopic evidence of capsular invasion; stage II, microscopic or macroscopic invasion of the surrounding fatty tissue or the mediastinal pleura; stage III, macroscopic invasion of neighboring organs, such as the pericardium, lung or the great vessels; and stage IV, pericardial or pleural dissemination (IVa) and lymph node or distant metastases (IVb). This study was approved by the local institutional review board for retrospective analysis, and was conducted according to the Declaration of Helsinki (2000).

Computed tomography (CT) imaging

All chest CT examinations were acquired from the lung apices through the middle portions of both kidneys. Three examinations were made using a 40-row detector CT (Somatom Definition AS; Siemens Medical Systems, Erlangen, Germany) using the following parameters: section thickness 3 mm, reconstruction 2 mm, gantry rotation time 0.5 seconds, pitch 0.8, tube potential 120 kV, and mAs setting adjusted for body weight. All patients received intravenous contrast medium (2 mL/kg; flow rate 3 mL/second; Omnipaque 350; GE Healthcare, Milan, Italy). Imaging data of hard copies in five patients whose CT scans were obtained at other hospitals were scanned and uploaded to a picture archiving and communication system. All monitors showed images obtained using both mediastinal (width, 400 H; level, 20 H) and lung (width 1.500 H, level −700 H) window settings. Multiplanar reconstruction images were assessed for lesion shape and size. CT images were reviewed and interpreted by two radiologists with at least five years experience of chest CT interpretation. Both specialists were presented with the patients' clinical history, but were unaware of histological findings. Chest CT scans were also retrieved to a commercially available stand-alone workstation loaded with commercial volume CT software (syngo.via, Siemens, Hoffman Estates, IL, USA) which automatically measured the tumor volume by calculating the space that is enclosed within the segmented tumor. Qualitative and quantitative chest CT findings were documented for each patient; in particular, the tumor shape was classified as round if the long-to-short axis ratio was less than or equal to 1.5, oval if the ratio was greater than 1.5 but less than 3.0, and plaque-shaped if the ratio was greater than 3.0. Marginal characteristics were subclassified as smooth, lobulated or irregular. Tumor necrosis and calcifications were considered. The pattern of enhancement was recorded as homogeneous or heterogeneous and the degree of enhancement was classified as low or high compared to that of the chest wall muscle. Fatty mediastinal infiltration, great vessel invasion (such as the degree of abutment), pleural and pericardial effusion, and enlarged lymph nodes were evaluated. Among quantitative variables, tumor size (two maximal axial diameters and maximal longitudinal diameter measured by multi planar reconstruction (MPR) and volume (in mL) were computed.

Positron emission tomography (PET)/CT protocol

Whole body FDG PET/CT was performed using a dedicated PET/CT scanner (Biograph 16 HT, Siemens Medical Solu-

tions, Hoffman Estates, IL, USA). The PET component is a high-resolution scanner with a spatial resolution of 4.7 mm and has no septa, thus allowing only 3-dimensional (3D) acquisitions. The CT portion of the scanner is the Somatom Sensation 16-slice CT. Together with the PET system, the CT scanner is used both for attenuation correction of PET data and for localization of FDG-uptake in PET images. All patients were advised to fast for at least six hours before the integrated PET/CT examination. After injection of 3.0 MBq of FDG per kg/bw, patients rested for a period of approximately 60 minutes in a comfortable chair. A low dose CT was performed for the attenuation correction. Emission images ranging from the proximal femur and the base of the skull were acquired for three minutes per bed position. Acquired images were reconstructed using the attenuation weighted-ordered subset expectation maximization iterative reconstruction, with two iterations and eight subsets. Fourier rebinning was used to reduce the 3D dataset to a 2D equivalent dataset, and a 4-mm full width at half maximum Gaussian filter was applied to the image after reconstruction along the axial and transaxial directions. The data were reconstructed over a 128×128 matrix with 2 mm pixel size and slice thickness. Processed images were displayed in coronal, transverse, and sagittal planes. Two experienced nuclear medicine physicians interpreted the PET/CT images, unaware of previous findings. At visual analysis, increased FDG uptakes not corresponding to physiological uptake patterns or in any foci of increased uptake corresponding to a CT abnormality were recorded as positive. The absence of an uptake was used to define a negative PET/CT finding.

The metabolic tumor volume (MTV), maximum, minimum, and average standardized uptake value (SUVmax, SUVmin and SUVavg, respectively) were determined by drawing iso-volumetric regions of interest (VOI) on the attenuation corrected PET/CT images around suspected thymic lesions. Moreover, the SUVmax of the aortic arch was taken as a reference region for background mediastinal activity (or blood-pool activity). Therefore, the tumor/mediastinum ratio was calculated by the ratio of thymic lesion SUVmax (T) and blood pool SUVmax (M). Finally, the total lesion glycolysis (TLG) of thymic lesions was computed according to the formula: TLG = MTVxSUVavg.

Follow-up

Data was collected via scripted telephone interviews by a researcher blinded to the patient's test result and then confirmed by the revision of medical archives or by contacting the patient's general practitioner. To determine follow-up time, the date of the last examination or consultation was used. Defined events included local or distant recurrence confirmed by biopsy or conventional imaging modalities.

Literature research strategy

A computer literature analysis on studies in human subjects was performed to identify articles that evaluated the role of PET or PET/CT, CT, and MRI in thymic disease.

Pubmed and Web of Knowledge were used to compile data from 2004 to January 2014, with the following key words: "THYMOMA or Thymic carcinoma" AND" CT" AND "MRI", "THYMOMA" AND "CT" NOT "PET" and "THYMOMA AND PET."

Reviews, clinical reports, and editor comments were excluded. Moreover, articles that did not evaluate the role of CT or MRI or FDG PET or PET/CT in adult thymic lesions were also excluded. We found 91 articles for thymoma and CT and MRI without any filters; when we added HUMANS/JOURNALS ARTICLE/ENGLISH LANGUAGE as filters, a total of 24 articles were obtained. Considering the words thymoma AND CT NOT PET, 419 articles were found, for a total of 91 after filters. Of all of the research compiled, eight articles on thymoma and radiologic examinations for initial assessment were recovered. Similarly, 77 reports evaluated the role of FDG PET or PET/CT in thymic disease, but only 12 met the inclusion criteria.

Statistical analysis

A non-parametric statistical analysis was used, such as the chi-square, U-Mann Whitney or Wilcoxon test, as appropriate. A *P*-value <0.05 was defined as significant. Survival curves were constructed using the Kaplan-Meier method to account for censored survival times and were compared with the log rank test. Progression-free survival was defined as the length of time from the date of PET/CT to any relapse (local or distance recurrence). Statistical analysis was performed with SPSS software (SPSS Inc. Chicago, IL, USA).

Results

Clinical and histopathological data

Table 1 reports the clinical and histopathological characteristics of the study population. Seventeen (65.4%) patients had a histologically proven thymoma, while nine (34.6%) had a thymic cancer. WHO classification was type A/B in three (11.5%) patients, type B1 in three (11.5%), type B1/B2 in one (3.8%), type B2 in three (11.5%), and type B3 in seven (26.9%) patients. The Masaoka-Koga system was stage I in three (11.5%) patients, stage IIa in six (23%), stage IIb in one (3.8%), stage III in six (23%), stage IVa in four (15.7%), and stage IVb in six (23%) patients. Among nine patients with thymic cancer, one (11.1%) was stage IIB, two (22.2%) were stage III, two (22.2%) were stage IVA, and four (44.5%) were stage IVB.

Table 1 Characteristics of study population

Characteristics	
Median age (range), years	57.5 (31–78)
Histological subtype, *n (%)*	
Thymoma AB	3 (11.5%)
Thymoma B1	3 (11.5%)
Thymoma B1/B2	1 (3.8%)
Thymoma B2	3 (11.5%)
Thymoma B3	7 (26.9%)
Thymic cancer	9 (34.6%)
Stage, *n (%)*	
I	3 (11.5%)
II	7 (26.9%)
III	6 (23.1%)
IVA	14 (15.4%)
IVB	6 (23.1%)
Gender, *n (%)*	
Male	8 (30.8%)
Female	18 (69.2%)
Median volume (range)	
CT (morphological), mL	62.5 (3.30–306.9)
PET/CT (metabolic), cm3	83.5 (0.06–690)
Following treatments, *n (%)*	
Surgery†	26 (100%)
Systemic treatment‡	13 (50%)
Radiotherapy	5 (19.2%)

†Radical and non-radical. ‡Neoadjuvant or adjuvant chemotherapy. CT, computed tomography; PET, positron emission tomography.

PET/CT and CT findings

Of the 17 patients with thymoma, 15 (88.2%) showed a positive PET/CT scan, whereas two had a false-negative finding. On the other hand, 100% of patients with thymic cancer had a positive scan. CT was available in 5/9 (56%) patients with thymic cancer and in 3/17 (17.6%) with thymoma. In all cases, CT clearly identified the primary tumor.

Tumor necrosis, calcifications, fat infiltration, and pleural effusion were more frequent in thymic cancer compared to thymoma. Conversely, infiltration of vessels was reported both in thymic cancer and in thymoma, as illustrated in Table 2. All quantitative CT parameters were significantly higher in patients with thymic cancer than thymoma (median maximum axial diameter: 45 vs. 20 mm, median maximum longitudinal diameter: 69 vs. 21 mm, and median volume: 77.91 vs. 4.52 mL; all $P < 0.05$). Conversely, among semiquantitative PET/CT features, only MTV and TLG were significantly different in patients with thymic cancer than thymoma (Table 3), while SUVmax, SUVavg, and T/B ratio was similar, although with a trend to increase in thymic cancer. Figure 1 illustrates two examples of CT and PET/CT images in patients with thymic and thymoma cancer, respectively. According to Masaoka clinical staging, 10 (38.5%) patients were at stage I-II and 16 (61.5%) were at stage III-IV. Table 4 demonstrates that maximum longitudinal diameter,

Table 2 Computed tomography characteristics

	Thymic cancer (*n* = 5)	Thymoma (*n* = 3)	*P*-value
Necrosis	2 (60%)	0	*0.673**
Calcifications	2 (40%)	0	*0.673**
Fat infiltration	4 (80%)	0	*0.144**
Infiltration of vessels	3 (60%)	3 (100%)	*0.673**
Pleural effusion	2 (40%)	0	*0.673**
Median maximum axial diameter (in mm)	45 (28–80)	20 (15–27)	*0.025***
Median maximum longitudinal diameter (in mm)	69 (24–109)	21 (3–22)	*0.025***
Median volume (in mL)	77.91 (10.5–251)	4.52 (3.30–7.10)	*0.025***

*Chi-square test corrected for Yates. **U-Mann Whitney.

Table 3 PET/CT characteristics

	Thymic cancer (*n* = 9)	Thymoma (*n* = 17)	*P*-value*
SUVmax	9.34 (3.2–23.5)	4.84 (1.5–25.9)	*0.100*
SUVavg	4.75 (2.98–8.28)	3.39 (0.78–8.85)	*0.247*
T/B ratio	3.07 (1.67–3.79)	2.06 (0.63–5.05)	*0.112*
MTV	126.53 (0.4–690.02)	6.03 (0.06–240.21)	*0.043*
TLG	642.05 (1.10–3374.20)	20.32 (0.05–1570.97)	*0.056*

*U-Mann-Whitney test. CT, computed tomography; MTV, metabolic tumor volume; PET, positron emission tomography; SUV avg, standardized uptake value average; SUVmax, SUVmaximum; T/B tumor/background; TLG, total lesion glycolysis.
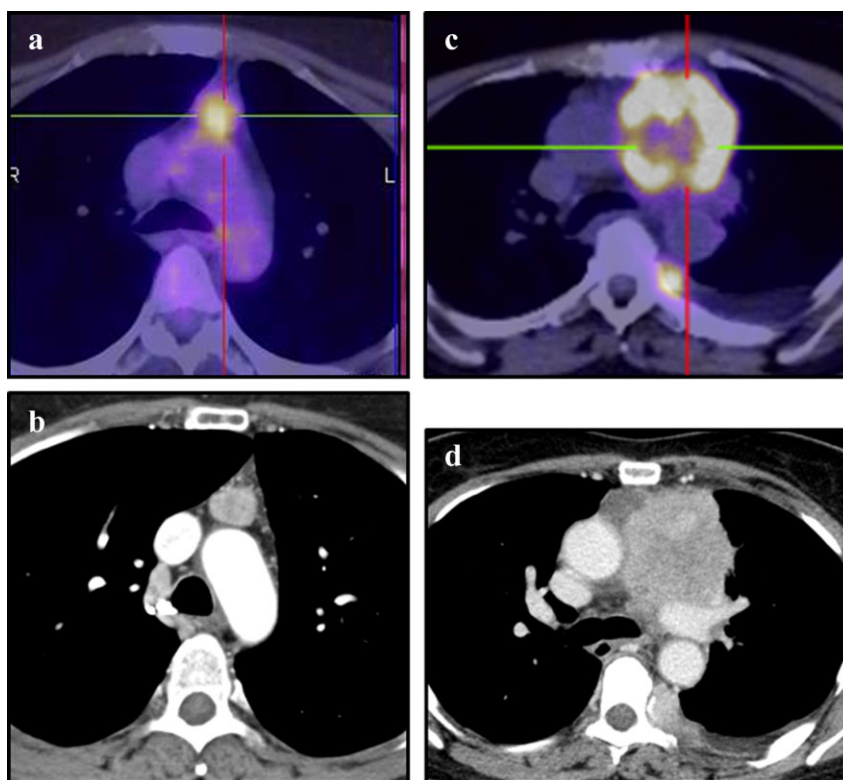
Figure 1 Positron emission tomography/computed tomography (CT) and CT images of (**a,b**) a thymoma, and (**c,d**) thymic cancer.

volume at CT, MTV, and TLG at PET were significantly higher in patients at stage III-IV than those at stage I-II.

Analysis of literature research

From the collection of published papers on FDG PET/CT, it emerged that four studies have compared mean SUVmax among low and high-risk thymoma, and thymic cancer patients.[4–7] The median SUVmax in 175 patients were 4.48, 6.75, and 10.80 for low and high-risk thymoma, and thymic cancer, respectively. As shown in Figure 2a, a slight overlap was found between the three categories. Conversely, the median SUVmax of thymoma and thymic cancer, obtained from 95 patients enrolled in another four studies,[8–11] were 3.37 and 8.68, showing a large gap (Fig 2b). Moreover, considering studies that evaluated the relationship between CT

measures and thymic disease, we found that in non-invasive thymoma, morphological characteristics were substantially similar to the results of Priola *et al.*[12] and Tomiyama *et al.*[13] In particular, smooth contour, homogeneous enhancement, and partial mediastinal fat infiltration were detected in >50% of patients. Conversely, only the presence of lobulated contours was equally distributed in both patient populations, while the residual CT data (such as necrotic or cystic component and calcifications) were different. Studies by Sadohara *et al.*,[14] Jeong *et al.*,[15] and Liu *et al.*[16] focused on the differentiation among low and high-risk thymoma, and thymic cancer. According to their results, a similar distribution was found for homogeneous contours in low-risk thymoma, for lobulated contours in high-risk thymoma, and for the presence of necrotic or cystic components and heterogeneous enhancement in thymic cancer.

Table 4 Masaoka clinical staging and semiquantitative imaging findings

	CT		PET/CT	
	MLD	Volume	MTV	TLG
Stage I-II	21.5 (3–69)	5.81 (3.30–54.78)	0.34 (0.06–118.91)	1.15 (0.05–912.04)
Stage III-IV	73 (24–109)	77.9 (10.5–306.9)	95.08 (0.34–690.02)	466.45 (1.01–3374.20)
P-value	*0.026*	*0.013*	*0.003*	*0.003*

CT, computed tomography; MLD, ***; MTV, metabolic tumor volume; PET, positron emission tomography; TLG, total lesion glycolysis.
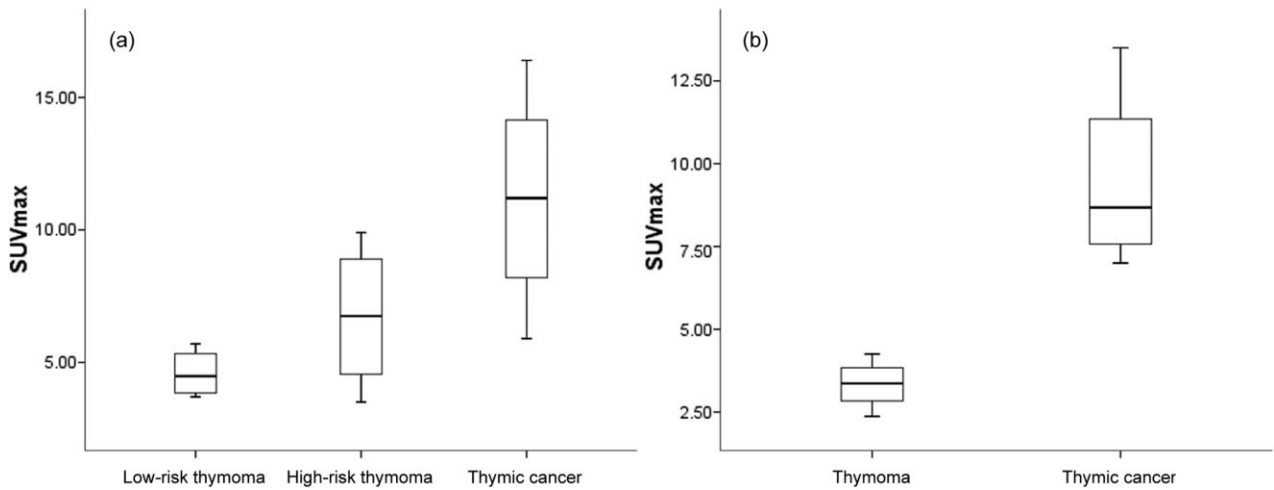
Figure 2 Box-plots of semiquantitative positron emission tomography/computed tomography data obtained from literature research.

Outcome

After a median follow-up of 17.45 months (range: 1–50 months), four patients experienced a recurrence of disease: three in patients with thymic cancer and one with a type B2 thymoma. Follow-up data were lost in three subjects. The median CT volume in two patients with recurrent disease was 102.19 mL *versus* 62.50 mL in six disease-free patients ($P = 0.865$). MTV and TLG were higher in the recurrent than in the disease-free patient subset (143.3 vs. 81.13 and 756.8 cm^3 vs. 322.31, respectively); however, these results were not statistically significant ($P = 0.075$ and 0.118). In Kaplan-Meier analysis, a MTV and a TLG higher than 83.5 cm^3 and 371.3, respectively, was associated with a poor prognosis (Fig 3).

Discussion

In the present study, we retrospectively analyzed the morphological and metabolic measurements of a patient series with thymoma and thymic cancer using CT and PET/CT examinations at initial staging of disease. The main purpose of our study was to define the role of CT and PET/CT in patients with thymoma and thymic cancer, in order to help clinicians and surgeons in the management of these diseases, considering the strong support of histological data. Nowadays, both CT and PET/CT are employed in patients with thymic cancer, particularly for defining the extension of disease and for determining the clinical stage. We would like to underline that PET/CT and CT can be interpreted both by visual analy-
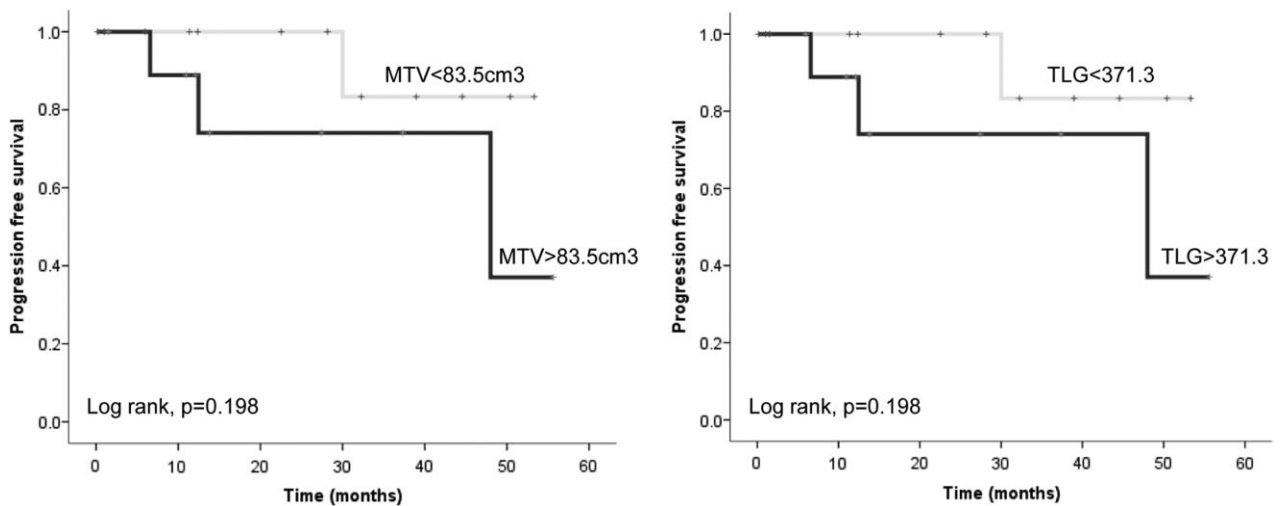

Figure 3 Progression-free survival curves in accordance with metabolic positron emission tomography measures.

sis and by a semiquantitative/quantitative point of view. These latter criteria could be useful in clinical practice to distinguish between low and high disease staging and between poor and good prognoses.

Table 5 reports the list of studies in the literature research.[4–23] The majority of reports concerning FDG PET or PET/CT focused on the differences between semiquantitative data and histological patterns.[4,6–9,14–17,19,22,23] In particular, Igai *et al.*,[8] Sung *et al.*,[7] Benveniste *et al.*,[4] Fukumoto *et al.*,[6] and Lococo *et al.*[17] concluded that there was a significant difference in SUVmax between the thymoma and thymic carcinoma groups, indicating that this parameter may be useful for discriminating thymoma from thymic carcinoma. In an analysis of 95 patients, SUVmax differentiated patients with thymoma from thymic cancer (see Fig 2b). It is probable that the inclusion of low-risk thymoma patients in the analysis of semiquantitative PET data could lead to lower SUVmax results than if the study only included high-risk thymoma and thymic cancer patients (see Fig 2a). Conversely, in the present study we observed an increasing tendency of SUVmax and tumor/background (T/B) ratio according to thymoma and thymic carcinoma, although this was not statistically significant. On the other hand, MTV shows a significantly different value in thymoma patients when compared to thymic cancer patients (6.03 vs. 126.53 cm³; $P = 0.043$). Therefore, this latter parameter could be more appropriate than SUVmax for the differential diagnosis between malignant and potentially malignant thymic lesions.

Table 5 summarizes the findings of eight studies focusing on the role of CT in thymoma and thymic cancer.[12–16,18,20,21] All studies reported quantitative data, essentially tumor size measured as maximum trans-axial diameters, and qualitative data (i.e. shape, contour, density, pattern of enhancement, infiltration of fat surrounding tumor and great vessel invasion, pleural and pericardial effusion, and lymph node involvement). Only Maroom *et al.* reported data including tumor volume; however, no definitive finding was clearly discussed.[20] Analysis of the collected CT data revealed that homogeneous contours are typical of non-invasive and low-risk thymoma, while lobulated contour and heterogeneous enhancement are linked with high-risk thymoma or thymic cancer. In our study, we found that tumor volume can differentiate thymoma from thymic cancer and distinguish patients at stage I-II from those at stage III-IV. In accordance with Maroom *et al.*,[20] we considered MPR, whereas the majority of studies based their measurement on axial plane alone.

The advantage of using both anatomical and metabolic volumes would be evident in a more accurate evaluation of disease extension. In fact, stage I is classified as completely encapsulated tumor, stage II as microscopic transcapsular invasion (IIa) or macroscopic invasion into thymic or surrounding fatty tissue (IIb), stage III as macroscopic invasion into neighboring organ (i.e. pericardium, great vessel or lung), and stage IV as pericardial or pleural metastases (IVa) or lymphogeneous or hematogenous metastases (IVb). Therefore, stage I and IIa tumors are confined in the thymic capsule while stage IIb –III and IV are characterized by an infiltrative form that can be associated with a longitudinal extension, rather than posterior-anterior growth. Therefore, CT image measurement based on three perpendicular diameters should be used for the evaluation of thymic lesions. Similarly, metabolic volume by PET could prompt more clinical data.

None of the studies listed in Table 5 evaluated the prognostic role of CT or PET/CT in thymic neoplasms. As reported by Lococo *et al.*,[17] while there is a body of evidence suggesting that PET SUVmax could reflect the rate of proliferation and degree of invasiveness of thymic neoplasms – thus providing a useful index for diagnosis and treatment – its prognostic role is still debated and remains controversial. Following the lines of extreme simplification we may suppose with a logical assertion that SUVmax and SUVmax/T index may indeed have a prognostic value in thymic neoplasms, directly associated to the different risk classes; however, to date there is no evidence or robust data supporting this assumption. In our study we found that high MTV and TLG (>83.5 cm3 and 371.3, respectively) were associated with a poorer prognosis in this setting of patients. A low rate of recurrence ($n = 4/26$; 15.4%) was reported in the present study. Although no unique prognostic factor has been identified, several studies have indicated the importance of clinical features (i.e. age and the presence or absence of myasthenia gravis), Masaoka staging, the completeness of surgical resection, WHO histologic type, size of tumor, and great vessel or mediastinal invasion as predictors of recurrence and survival after surgical resection. Patients in stage I and II with a high-risk thymoma have a significantly poorer prognosis (higher recurrence rate and reduced survival) than those with a low-risk thymoma.[24] Based on this data, we found that MLD, volume at CT, MTV and TLG at PET were significantly higher in patients at stage III-IV than those at stage I-II and, therefore, directly correlated with prognosis. In addition, we found that after 18 months of follow-up in two patients with disease recurrence, the volume of the tumor in CT images was larger than in patients free of disease.

All selected patients were treated by surgical resection, in some cases associated with chemotherapy ($n = 13$; as neoadjuvant or adjuvant) and/or adjuvant radiotherapy ($n = 5$). Although the association between prognosis and therapeutic regimen is beyond the aim of the present study, we indirectly found that combined therapeutic modalities have an important impact on the event-free survival rate. In fact, in our patient population, only four recurrences occurred after 18 months of follow-up.

Table 5 The list of collected studies (*in publication date order*)

Authors, ref	Year	N. PTS	Histology (thymoma/thymic cancer)	Imaging	Aim of the study	Conclusions
Benveniste et al.[4]	2013	51	37/12 (2 thymic carcinoid)	FDG PET	To assess whether the amount of FDG uptake can predict advanced thymoma and if it can separate thymoma from thymic cancer.	Focal FDG uptake cannot predict advanced thymoma but is helpful in distinguish thymoma from thymic carcinoma or more aggressive forms, such as thymoma B3.
Toba et al.[5]	2013	33	25/8	FDG PET/CT	To evaluate the usefulness of FDG PET/CT and the relationship among the expression of HIF-1alfa, Glut-1 and VEGF.	The expression of HIF-1, Glut-1 and VEGF might be associated with malignancy of thymic epithelial tumors.
Lococo et al.[17]	2013	47	40/7	FDG PET/CT	To determine the performance of combined FDG PET/CT as a predictor of the WHO classification based malignancy grade in thymic epithelial tumors.	A significant correlation between FDG PET/CT and WHO classification was found.
Qu et al.[18]	2013	129	129/0	CT	To investigate the relationships between preoperative CT staging and postoperative surgical Masaoka clinical staging.	This study documented a close relationship between preoperative CT thymoma staging and postoperative Masaoka clinical staging. Thus, preoperative CT findings can be beneficial for determining the proper management and prognosis of thymoma patients.
Liu et al.[16]	2012	105	84/21	CT	To explore the relationship between CT manifestations of thymoma and its WHO pathological classification.	Distinctive CT features of thymomas may reflect their pathological types.
Fukumoto et al.[6]	2012	58	44/14	FDG PET/CT	To assess the utility of FDG PET/CT for predicting the histologic type and stage of thymic epithelial tumors.	PET/CT is a useful modality for predicting the histologic type and tumor stage of thymic epithelial tumors.
Terzi et al.[19]	2011	26	18/8	FDG PET/CT	To assess the usefulness FDG PET/CT for differentiating the grade of malignancy of thymic epithelial neoplasm, and to modify treatment strategy.	PET/CT could be used to identify patients with a high-risk thymoma and modify clinical management following histological confirmation or modify surgical approach (open vs. thoracoscopic surgery).
Igai et al.[8]	2011	13	8/5	FDG PET	To investigate whether SUVmax can predict the grade of malignancy of thymic epithelial tumors based on the WHO classification.	SUVmax is a useful parameter for differentiating between thymic epithelial tumor subgroups and for evaluating the extent of disease.
Marom et al.[20]	2011	99	99/0	CT	To identify preoperative CT findings associated with thymoma invasiveness before surgical resection.	CT imaging features can differentiate between stage I/II and stage III/IV disease and, thus, help identify patients more likely to benefit from neoadjuvant therapy.
Priola et al.[12]	2010	58	58/0	CT	To assess the CT imaging findings of thymoma and to correlate these features with Masaoka staging system and prognosis.	CT is useful in differentiating invasive from non-invasive thymomas and plays an important role in evaluating and treating these patients for multimodal therapy with neoadjuvant approaches.
Totanarungroj et al.[21]	2010	28	27/1	CT	To characterize the CT features of common anterior mediastinal tumors and evaluate CT findings that may help in suggesting specific diagnosis among these tumors.	The CT findings that help in giving specific diagnosis of anterior mediastinal tumor are fat attenuation and associated mediastinal lymphadenopathy.
Kumar et al.[9]	2009	23	19/4	FDG PET/CT	To evaluate if FDG PET-CT can help differentiate various thymic lesions noted on conventional imaging modalities.	FDG PET/CT can characterize and differentiate various thymic lesions and it can distinguish between high risk and low risk thymoma.
Luzzi et al.[10]	2009	19	13/6	FDG PET	To explore the usefulness of FDG PET-CT in the preoperative assessment of isolated anterior mediastinal lesions.	Anterior mediastinal lesions with SUVmax <5 indicate a susceptible lesion for upfront surgery, in the absence of other clinical indications. For lesions with SUVmax >5 and with CT evidence of gross morphology, a biopsy must be obtained.
Shibata et al.[11]	2009	40	37/3	FDG PET	To clarify the usefulness of PET) using FDG and 11C-acetate for predicting the histologic types and tumor invasiveness of thymoma.	The FDG-SUV and 11C-acetate-SUV in PET can be used to predict the histologic type of thymoma.
Tomiyama et al.[13]	2009	60	48/12	CT and MRI	To compare the diagnostic accuracy for anterior mediastinal tumors among CT, MRI, and both CT and MRI, and to determine the optimal CT and MRI procedures for the diagnosis of anterior mediastinal tumors.	CT is equal or superior to MRI in the diagnosis of anterior mediastinal tumors except for thymic cysts. CT should be considered the modality of choice following chest radiography.
Endo et al.[22]	2008	36	36/0	FDG PET	To assess the value of FDG PET in thymic epithelial tumors according to the WHO histologic classification.	FDG PET accumulation in thymic epithelial tumors significantly correlated with a simplified WHO classification.
El-Bawab et al.[23]	2007	37	37/0	FDG PET	To evaluate the utilization of PET scan with FDG in thymic pathology.	FDG PET is a very sensitive diagnostic tool in detecting residual, recurrence, and metastatic disease in patients who underwent thymoma excision.
Sadohara et al.[14]	2006	60	48/12	CT and MRI	To assess the CT and MRI findings of thymic epithelial tumors classified according to the current WHO histologic classification and to determine useful findings in differentiating the main subtypes.	The presence of irregular contour, necrotic or cystic component, heterogeneous enhancement, lymphadenopathy, and great vessel invasion on CT or MRI are strongly suggestive of thymic carcinomas.
Sung et al.[7]	2006	33	17/16	FDG PET/CT	To assess the usefulness of integrated PET/CT using FDG for distinguishing thymic epithelial tumors according to the WHO classification.	FDG PET/CT proved to be useful in differentiating thymic epithelial tumor subgroups and in evaluating the extent of disease.
Jeong et al.[15]	2004	91	76/15	CT	To describe the CT findings of thymic epithelial tumors and to correlate these findings with histopathologic subtypes and prognosis.	CT findings may serve as predictors of postoperative recurrence or metastasis for thymic epithelial tumors.

CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; SUVmax, standardized uptake value maximum; VEGF, vascular endothelial growth factor; WHO, World Health Organization.

The present study has some limitations: (i) different types of CT scanner were used, including hard copies of scans in five patients; (ii) a small number of patients were included and a retrospective design was used; and (iii) a short period of follow-up could be correlated with a lower number of events. Particularly, the fact of the small sample size cannot, therefore, determine a solid conclusion, and should be considered a major limitation. The low incidence of the disease also represents a limit to clinical trials.

Conclusions

Both morphological and metabolic volume can be useful from a diagnostic and prognostic point of view in thymic cancer and thymoma patients. The association of CT and PET/CT images in a single step examination employing a dedicated protocol, such as respiratory gating, could be useful for providing complete tumor information. A large multi-center clinical trial for confirming the findings of this study is mandatory.

Disclosure

No authors report any conflict of interest.

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