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REVIEW

The role of [^{18}F]fluorodeoxyglucose positron emission tomography in thymic epithelial tumors

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Abstract

The purpose of this study was to systemically review the available literature regarding the diagnostic performance of positron emission tomography (PET) using 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) in patients with thymic epithelial tumors. We reviewed 13 studies that evaluated the diagnostic role of thymic epithelial tumors with [^{18}F]FDG-PET. [^{18}F]FDG-PET is a useful radiological modality for differentiating between thymomas and thymic carcinoma. However, [^{18}F]FDG-PET may not be useful for differentiating low-risk thymoma and high-risk thymoma. One paper reported that [^{18}F]FDG-PET has a predictive significance for treatment and prognosis in thymic epithelial tumors. Two papers reported that the degree of [^{18}F]FDG uptake in thymic epithelial tumors is based on glucose metabolism. [^{18}F]FDG-PET may have a further use for radiological differential diagnosis of thymomas and thymic carcinomas.

Keywords: *Thymic epithelial tumor; [^{18}F]FDG-PET; systemic review; differential diagnosis.*

Introduction

Thymic epithelial tumors are broadly classified into thymoma and thymic carcinoma and are the most common primary neoplasms of the anterior mediastinum. Tumors of the thymus are a heterogeneous group of tumors, ranging from relatively benign thymomas to highly aggressive carcinomas. The World Health Organization (WHO) published a new histologic classification of thymic epithelial tumors, dividing them into 3 subgroups: low-risk thymomas (types A, AB and B1), high-risk thymomas (types B2 and B3) and thymic carcinomas[1,2]. Several studies have documented that positron emission tomography (PET) using 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) is increasingly important for the imaging technique in the diagnosis, grading malignancy, staging and assessment of response to therapy in patients with thymic epithelial tumors[3–16]. According to these reports, [^{18}F]FDG-PET is effective in differentiating thymic carcinoma from other entities within the thymus. However, these published reports consisted of clinical trials with small sample size, and we cannot conclude on the diagnostic performance of [^{18}F]FDG-PET in thymic epithelial tumors from these results.

The purpose of this study is to systematically review the available literature regarding the diagnostic performance of [^{18}F]FDG-PET in patients with thymic epithelial tumors, which may contribute to the development of guidelines for the usefulness of PET.

Materials and methods

Search strategy

We addressed the performance of [^{18}F]FDG-PET as a diagnostic test for differentiating thymoma from thymic carcinoma and for the grade of malignancy in thymic epithelial tumors. We performed a systematic search of

Table 1 Characteristics of the 13 studies included

Study	Year	No. of patients	Sex (male/female)	Mean age, years (range)	Histology (thymoma/thymic carcinoma)	Mean tumor size (mm)	[^{18}F]FDG dose (MBq)	Measurement of [^{18}F]FDG uptake	Analysis according to Masaoka or WHO classification
Liu et al.[3]	1995	10	6/4	47 (30–66)	10/0	(–)	370	TLR	Non-invasive thymoma, and invasive thymoma
Kubota et al.[4]	1996	10	7/3	62 (35–83)	7/3	(–)	180	DUR	Non-invasive thymoma, invasive thymoma, and thymic carcinoma
Sasaki et al.[5]	1999	31	19/12	58 (19–85)	17/14	68	226	SUV	Non-invasive thymoma, invasive thymoma, and thymic carcinoma
Sung et al.[6]	2006	33	15/18	55 (34–68)	17/16	54	370	SUV	Low-risk thymoma, high-risk thymoma, and thymic carcinoma
El-Bawab et al.[7]	2007	17	4/13	40 (25–72)	14/3	(–)	370	SUV	Non-invasive thymoma, invasive thymoma, and thymic carcinoma
Inoue A et al.[11]	2009	46	29/17	58 (31–75)	35/11	(–)	370	SUV	Low-risk thymoma, high-risk thymoma, and thymic carcinoma
Luzzi et al.[10]	2009	13	(–)	(–)	7/6	59	355	SUV	Low-risk thymoma, high-risk thymoma, and thymic carcinoma
Kumar et al.[8]	2009	18	14/4	38 (19–58)	14/5	62	370	SUV	Low-risk thymoma, high-risk thymoma, and thymic carcinoma
Shibata et al.[9]	2009	39	16/23	56 (28–77)	36/3	52	4.6 (MBq/kg)	SUV	Low-risk thymoma, high-risk thymoma, and thymic carcinoma
Kaira et al.[12]	2010	49	23/26	64 (32–80)	38/11	60	200–250	T/M ratio	Low-risk thymoma, high-risk thymoma, and thymic carcinoma
Nakajo et al.[13]	2010	11	5/6	55 (41–71)	10/1	58	3.7 (MBq/kg)	SUV	Low-risk thymoma, high-risk thymoma, and thymic carcinoma
Igai et al.[14]	2010	13	6/7	59 (36–78)	8/5	47	3.5 (MBq/kg)	SUV	Low-risk thymoma, high-risk thymoma, and thymic carcinoma
Terzi et al.[15]	2011	26	14/12	56 (34–85)	18/8	79	330–400	SUV and T/M ratio	Low-risk thymoma, high-risk thymoma, and thymic carcinoma

DUR, differential uptake ratio, radioactivity concentration in the region of interest (Bq/mm^3)/injected dose (Bq)/weight of patients (g); SUV, standardized uptake value; TLR, tumor to lung ratio; T/M ratio is the ratio of the peak SUV of the tumor to the mean SUV of the mediastinum.

the MEDLINE and PubMed databases to identify all clinical trials regarding the relationship between [^{18}F]FDG-PET and thymic epithelial tumors. The search strategy included articles published between January 1995 and August 2011 using the following keywords: "PET" or "positron emission tomography"; "positron emission tomography/computer tomography" or "PET/CT"; "[^{18}F]FDG" or "fluorodeoxyglucose"; "thymic epithelial tumor", "thymoma", "thymic carcinoma" or "thymic". The search did not restrict the type of publication or periodical. We did not include preliminary results published as abstracts or meeting proceedings. We selected all published reports that clearly described the diagnostic performance of [^{18}F]FDG-PET in patients with thymic epithelial tumors. The search was restricted to material published in English.

Study selection

The inclusion criteria were as follows: [^{18}F]FDG-PET was used to identify or characterize thymic epithelial tumors; [^{18}F]FDG was used as tracer; scanner apparatus was [^{18}F]FDG-PET for use on humans; sample size with at least 10 participants in each study. Criteria for exclusion were insufficient information to construct 2×2 contingency tables, and duplicate studies on the same patients. Two reviewers independently selected studies for possible inclusion by checking titles and abstracts. The final decision regarding inclusion was based on the full article. Disagreement was resolved in a consensus meeting.

Results

Characteristics of the published reports

Based on our research criteria, we identified 13 studies that evaluated the diagnostic role of thymic epithelial tumors with [^{18}F]FDG-PET[3–15]. The characteristics of the studies are presented in Table 1. The total number of patients in a study ranged from 10 to 49 (median, 18 patients). Reported age ranged from 19 to 85 years, and the population of male patients ranged from 24% to 70%. Most studies comprised both thymoma ($n=231$) and thymic carcinoma ($n=86$). Mean tumor size range from 47 to 79 mm. Four studies were analyzed according to the Masaoka classification (non-invasive thymoma, invasive thymoma and thymic carcinoma), and 9 studies used a simplified WHO classification (low-risk thymoma, high-risk thymoma and thymic carcinoma). In 10 of 13 studies, measurement of [^{18}F]FDG uptake was performed by maximal standardized uptake value (SUV_{max}).

Diagnostic comparison of [^{18}F]FDG uptake

[^{18}F]FDG accumulation according to the Masaoka and WHO classifications is presented in Tables 2 and 3, respectively. Seven of 13 studies compared the

Table 2 Comparison of [^{18}F]FDG uptake according to the Masaoka classification

Study	Thymoma vs thymic carcinoma			Statistical analysis
	Non-invasive thymoma	Invasive thymoma	Thymic carcinoma	
Liu et al.[3]	5.7 ± 1.7		NA	
Kubota et al.[4]	2.30 ± 0.40	8.62 ± 2.31*	7.85 ± 0.69	*P < 0.005 compared with non-invasive thymoma. Not compared with thymic carcinoma
Sasaki et al.[5]	3.0 ± 1.0	3.8± 1.3	7.2 ± 2.9*	*P < 0.01 compared with non-invasive thymoma and invasive thymoma
El-Bawab et al.[7]	4.75 ± 0.88		NA	

NA, not available.

Table 3 Comparison of [^{18}F]FDG uptake according to the WHO classification

Study	Thymoma vs thymic carcinoma			Statistical analysis
	Low-risk thymoma	High-risk thymoma	Thymic carcinoma	
Sung et al.[6]	4.0 ± 0.42	5.6 ± 1.90**	10.5 ± 4.68*	*P < 0.001 compared with thymoma. **No difference was observed between low-risk and high-risk thymoma
Inoue et al.[11]	Early SUV^{max} 3.2 (1.1–5.3); delayed SUV^{max} 3.4 (1.8–6.4)	Early SUV^{max} 6.0 (2.2–12.9)*; Delayed SUV^{max} 7.4 (3.7–16.3)**		*P < 0.001 compared with low-risk thymoma. **P = 0.001 compared with low-risk thymoma
Luzzi et al.[10]	3.3 ± 0.5	13.5 ± 7.0*		*P < 0.01 compared with low-risk thymoma
Kumar et al.[8]	3.0 (1.7–3.9)	2.1(0.8–2.8)	7.0 (4.3–9.2) *	*P < 0.01 compared with thymoma
Shibata et al.[9]	Type A/AB, B1, B2 and B3; 3.2 ± 0.7, 4.8 ± 2.0, 3.7 ± 1.2, 5.0 ± 1.4		9.2 ± 2.4*	*P = 0.048, P = 0.007, P = 0.001, and P = 0.001 compared with type A/AB, B1, B2 and B3, respectively
Kaira et al.[12]	2.6 ± 0.9	4.3 ± 1.6**	8.9 ± 3.6*	*P < 0.01 compared with high-risk thymoma. **P < 0.01 compared with low-risk thymoma
Nakajo et al.[13]	3.05 ± 0.55	5.24 ± 2.44*		*P = 0.008 compared with low-risk thymoma
Igai et al.[14]	3.43 ± 2.19		8.15 ± 7.88*	*P = 0.0084 compared with thymoma
Terzi et al.[15]	SUV^{max} 4.0 ± 1.7; T/M ratio 2.0 ± 0.5	SUV^{max} 14.1 ± 8.3*; T/M ratio 7.8 ± 5.2**	SUV^{max}17.1 ± 8.5***; T/M ratio 9.6 ± 5.5***	*P = 0.005 and **P < 0.001 compared with low-risk thymoma. ***No difference was observed between low-risk and high-risk thymoma

T/M ratio is the ratio of the peak SUV of the tumor to the mean SUV of the mediastinum.

measurement of [^{18}F]FDG uptake between thymoma and thymic carcinoma[5,6,8,9,12,14,15], and these 7 studies demonstrated that [^{18}F]FDG uptake in thymic carcinoma was significantly higher than in thymoma. [^{18}F]FDG-PET images are shown in Fig. 1[16]. In the analysis of the 8 studies according to the WHO classification (Table 3), the median values for the mean SUV in low-risk thymoma, high-risk thymoma and thymic carcinoma were 3.2 (range, 2.6–4.0), 5.0 (range, 2.1–14.1) and 9.2 (range, 7.0–17.1), respectively. Seven of these 9 studies showed a statistically significant higher [^{18}F]FDG uptake in high-risk thymoma or thymic carcinoma than in low-risk thymoma[6,8–13,15], and 4 studies revealed that [^{18}F]FDG uptake was significantly higher in thymic carcinoma than in high-risk thymoma[6,8,9,12]. Although 2 studies described the usefulness of [^{18}F]FDG-PET for differentiating between low-risk thymoma and high-risk thymoma[12,15], 2 studies reported that no statistically significant difference was found among these groups[6,8]. Fig. 2 shows the distribution of [^{18}F]FDG uptake on PET in patients with thymic epithelial tumors. Three of 13 studies investigated the relationship between [^{18}F]FDG uptake and the grading of the WHO classification and between [^{18}F]FDG uptake and the grading of the Masaoka classification, demonstrating a statistically significant correlation[10,12,15].

To differentiate thymic carcinoma from thymoma, the sensitivity, specificity and SUV cutoff values were 84.9%,

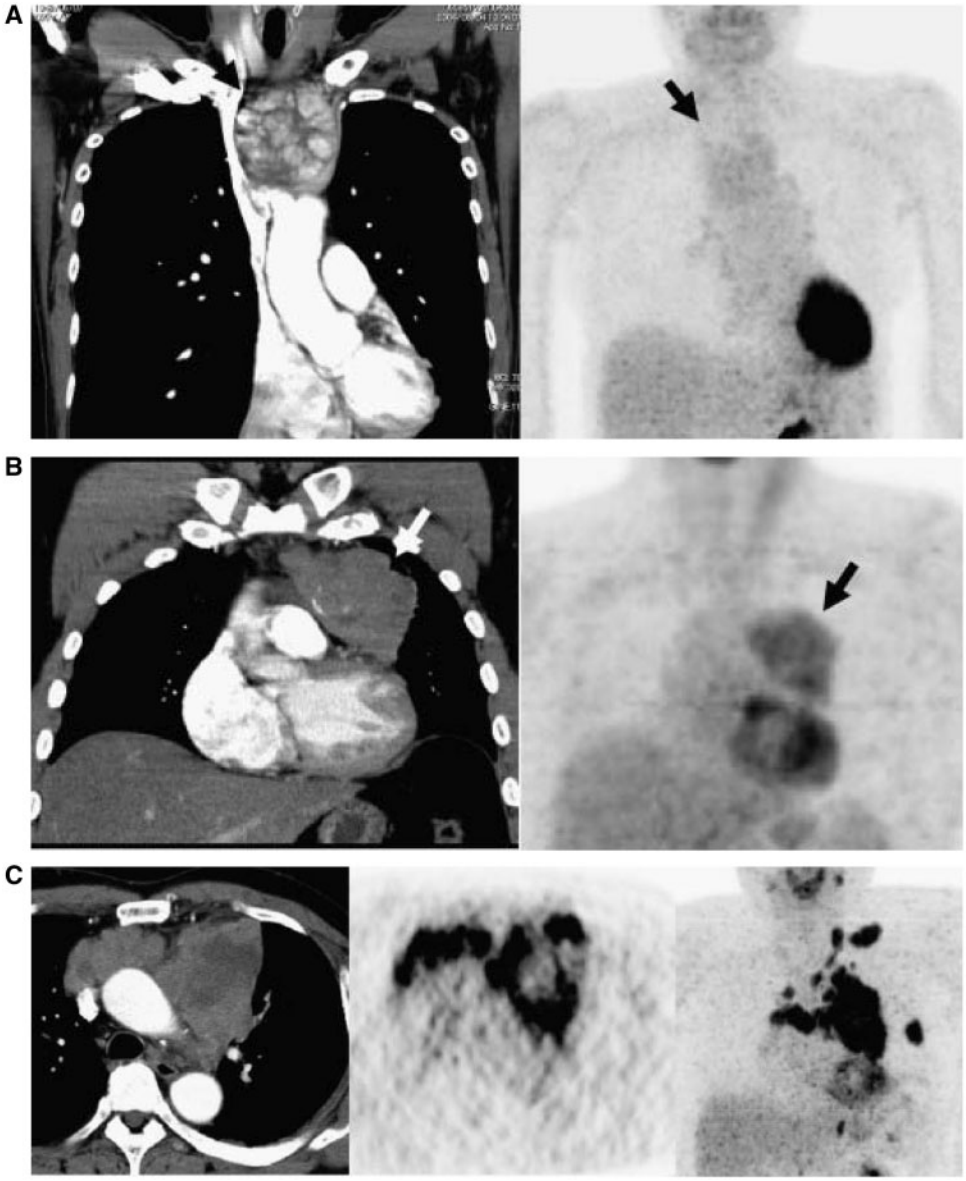

Figure 1 **(a) Low-risk thymoma (type A and Masaoka stage I), (b) high-risk thymoma (type B2 and Masaoka stage II), and (c) thymic carcinoma (Masaoka stage IV).**

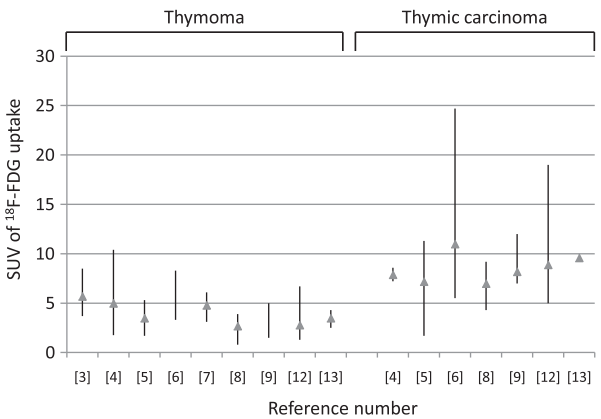

Figure 2 **Distribution of [^{18}F]FDG uptake on PET in patients with thymic epithelial tumors according to each study included in this review.**

92.3% and 5.0 in Ref.[5], 100%, 92% and 6.3 in Ref.[9], and 63.6%, 91.4% and 6.2 in Ref.[11]. The results for SUV values between low-risk thymoma and high-risk thymoma were 78.3% and 91.3%, respectively, when 4.5 was used as a cutoff[11].

The role of therapeutic monitoring and outcome

One study reported that high uptake of [^{18}F]FDG is significantly associated with poor prognosis[12]. This study included 11 thymic carcinomas among 49 thymic epithelial tumors, and the 11 patients with thymic carcinoma had a significantly high [^{18}F]FDG uptake compared with thymomas. However, it remains unclear whether [^{18}F]FDG uptake is associated with outcome in patients with thymoma.

In monitoring treatment by [^{18}F]FDG-PET, one study documented that [^{18}F]FDG-PET was useful for monitoring response after treatment (chemotherapy or radiation) in inoperable thymic epithelial tumors. Of these 11 patients with inoperable thymic epithelial tumors (3 thymomas and 6 thymic carcinomas), 8 patients received [^{18}F]FDG-PET before and after treatment. In patients with any response ($n = 5$), [^{18}F]FDG uptake after treatment was significantly lower than at baseline. In patients without any response ($n = 3$), however, [^{18}F]FDG uptake after treatment was significantly higher than at baseline.

The relationship between [^{18}F]FDG uptake and relevant molecular abnormalities

Two studies investigated the relationship between glucose transporter 1 (Glut1) expression and [^{18}F]FDG uptake in thymic epithelial tumors, and [^{18}F]FDG uptake within tumor cells has been reported to be closely correlated with Glut1 expression[12,13]. These studies demonstrated that the degree of [^{18}F]FDG uptake in thymic epithelial tumors is closely related to the amount of Glut1, hexokinase II and hypoxic markers.

An in vitro study using a thymic cancer cell line[12], the uptake of [^{18}F]FDG was markedly decreased by the inhibition of Glut1 or hypoxic inducible factor-1alpha (HIF-1α), whereas Glut1 upregulation by the induction of HIF-1α increased the [^{18}F]FDG uptake. The results of this study indicate that cellular uptake of [^{18}F]FDG is mediated by Glut1 and that the expression of Glut1 protein is regulated by HIF-1α.

The role of [^{11}C]methionine- or [^{11}C]acetate-PET

One of 12 studies examined the diagnostic significance of [^{11}C]methionine (MET)-PET in thymic epithelial tumors [5] and another study[9] examined [^{11}C]acetate (AC)-PET. MET-PET was not significantly different among thymic carcinoma, invasive thymoma and non-invasive thymoma; MET uptake in thymic tumors correlated with [^{18}F]FDG uptake. Currently, AC-PET can be used to predict the histologic type of thymoma. AC uptake in type A/AB thymomas was significantly higher than in type B1, B2, B3 thymomas and thymic carcinoma. This is contradictory to the results of [^{18}F]FDG uptake in thymic epithelial tumors. However, SUV by AC-PET was not significantly different between thymomas and thymic carcinomas.

Discussion

This is the first review to evaluate the clinical significance of [^{18}F]FDG-PET in patients with thymic epithelial tumors. Our study found that [^{18}F]FDG-PET is useful for differentiating between thymomas and thymic carcinomas. Previous studies reported that thymic carcinoma can be differentiated from thymoma at a diagnostic specificity of more than 90% if thymic tumors indicate an SUV value of 5.0 or more in [^{18}F]FDG-PET[5,9,11]. Moreover, the results in 4 papers confirmed that [^{18}F]FDG-PET is useful for differentiating between high-risk thymoma and thymic carcinoma. One paper documented that the SUV values for low-risk thymoma and high-risk thymoma had a sensitivity of 78.3% and specificity of 91.3% using a cutoff value of 4.5 for SUV[11], but 2 papers found that [^{18}F]FDG-PET could not differentiate high-risk thymoma from low-risk thymoma. Since the SUV value overlaps between low-risk thymoma and high-risk thymoma, [^{18}F]FDG-PET may not be a useful diagnostic modality for differentiating these groups. Because previous studies had small sample size, a large-scale study is warranted for assessing whether [^{18}F]FDG-PET could be useful for distinguishing tumor subgroups in thymomas.

[^{18}F]FDG-PET imaging of response to chemotherapy or radiation has been reported to be useful for patients with thoracic tumors[17,18]. A recent study suggests that [^{18}F]FDG-PET is useful for monitoring response and outcome after treatment in unresectable thymic epithelial tumors[19]. Although this study consists of only 12 patients who received chemotherapy or radiation because of advanced or metastatic disease, [^{18}F]FDG uptake after treatment in 6 patients with any response was significantly lower than at baseline ($P = 0.0017$). Moreover, the overall survival after treatment tended to be longer in patients with partial metabolic response compared with those with non-partial metabolic response. As these are preliminary data, further investigation is warranted.

Determination of malignant lesions with [^{18}F]FDG-PET is based on glucose metabolism[20,21]. The overexpression of Glut1 has been shown to be closely related to [^{18}F]FDG uptake in human cancer[22,23]. Glut1 is thought to be a possible intrinsic marker of hypoxia, and the expression of Glut1 has been found to be regulated by hypoxia in an HIF-1α-dependent way[24,25]. HIF-1α is considered to support tumor growth by the

induction of angiogenesis via the expression of vascular endothelial growth factor (VEGF) and by high and anaerobic metabolic mechanisms[26]. Two papers have reported that the degree of [^{18}F]FDG uptake in thymic epithelial tumors is closely correlated with the amount of Glut1 and hypoxic markers[12,13]. One of these studies demonstrated that upregulation of Glut1 and HIF-1α was closely associated with [^{18}F]FDG uptake into thymic cancer cells[12]. Biologically, the expression of Glut1 plays a crucial role in the accumulation of [^{18}F]FDG within tumor cells.

MET-PET has been used to measure amino acid metabolism in vivo, and therefore a high MET uptake in the tumor cells is thought to reflect an increase in either the transport mechanism of amino acids or protein synthesis[27]. However, MET uptake was not found to differ between thymic carcinoma and thymoma. Recent studies have documented that AC is a useful PET tracer for the detection of slow-growing tumors that cannot be identified using [^{18}F]FDG-PET, such as prostate cancer and well-differentiated adenocarcinoma of the lung[28,29]. The AC uptake in type A/AB thymoma was significantly higher than that in other histological types. Although AC-PET cannot predict the invasiveness of thymomas assessed by tumor stage, AC-PET has been reported to be useful for predicting the histological type of thymomas[9]. However, we cannot differentiate thymoma from thymic carcinoma using AC-PET. Thus, AC-PET may not be appropriate for differentiating the histological type of thymic epithelial tumors. Compared with MET- or AC-PET tracer, nowadays, [^{18}F]FDG is a better PET tracer for differentiating between thymoma and thymic carcinoma.

Conclusion

This review found that [^{18}F]FDG-PET is a useful radiological modality for differentiating between thymomas and thymic carcinoma. Some papers have reported that thymic carcinoma can be differentiated from thymoma at a diagnostic specificity of more than 90% using an SUV cutoff value more than 5.0. However, [^{18}F]FDG-PET may not be useful for distinguishing these groups, because [^{18}F]FDG accumulation overlaps in low-risk thymoma and high-risk thymoma. [^{18}F]FDG-PET may have an important role in predicting response to treatment and prognosis in thymic epithelial tumors. [^{18}F]FDG-PET may have an additional use for radiological differential diagnosis between thymoma and thymic carcinoma.

Conflict of interest

None of the authors has any financial or personal relationships with other people or organizations that could inappropriately influence our work.

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