Review Article

Practical value of fluorodeoxyglucose positron emission tomography in treatment strategies for thymic epithelial tumors: implications for more specific use in routine clinical practice

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Abstract: Many studies have demonstrated that 18-fluorine fluorodeoxyglucose positron emission tomography (FDG-PET) is useful for predicting the grade of malignancy of thymic epithelial tumors (TETs), and there is a close relationship between the maximum standardized uptake value (SUVmax) and tumor stage. However, more specific usage of FDG-PET for TETs has not been proposed, and the actual value of FDG-PET in routine clinical practice should be firmly clarified. In this review, following three cutoff values of SUVmax that may be helpful in determining treatment strategies in cases of anterior mediastinal masses, particularly presented as discrete and resectable lesions, are identified: (I) SUVmax of 7.5 as an indicator for pretreatment biopsy: differential diagnosis between TETs and mediastinal lymphoma (ML); (II) SUVmax of 4.2 as an indicator for a minimally invasive approach (MIA): differentiation of noninvasive TETs and invasive TETs; and (III) SUVmax of 5.9 as a reference value for the necessity of lymph node dissection (LND). There are still several challenges in using FDG-PET for routine clinical practice that need to be addressed, such as variations between instruments and institutions, leading to lower reproducibility. Harmonization methods should be applied to make clinical practice more uniform. Due to the rarity of these diseases, multi-institutional studies are warranted.

Keywords: Thymic epithelial tumor (TET); fluorodeoxyglucose positron emission tomography (FDG-PET); mediastinal lymphoma (ML); minimally invasive approach (MIA); lymph node dissection (LND)

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Introduction

18-fluorine fluorodeoxyglucose positron emission tomography (FDG-PET) is crucial for evaluating malignant tumors before determining treatment strategies. For thymic epithelial tumors (TETs), numerous studies have examined the importance of FDG-PET (1-5). To date, they have demonstrated that FDG-PET is useful for predicting the grade of malignancy in TETs, and in particular, that there is a significant difference in FDG uptake between thymoma and thymic carcinoma (TC) (3-5). In addition, several studies have investigated the relationship between tumor stage and the maximum standardized uptake value (SUVmax) and demonstrated that SUVmax increases in more advanced-stage tumors (5,6). On the other hand, in the initial management of anterior mediastinal lesions, for a tumor that is considered to be resectable, surgical resection is recommended without a biopsy to confirm the histological diagnosis before surgery (7). In this situation, the role of FDG-PET before treatment remains unclear. However, in routine clinical practice, even with such simplified strategies, there are several important points that thoracic surgeons should keep in mind. First, even in resectable tumors, particularly tumors that manifest as a well-defined anterior mediastinal mass in the thymic bed, mediastinal lymphoma (ML) should be ruled out (8,9). Second, surgical approaches are an essential part of surgical procedures (10).

To date, median sternotomy has been considered to be the standard approach. On the other hand, in the National Comprehensive Cancer Network (NCCN) guidelines, minimally invasive procedures may be considered for clinical stages I–II if all oncologic goals can be met as in standard procedures (7). Hence, accurate prediction of invasion is the most important issue in determining surgical approaches. Third, FDG-PET is essential for evaluating lymph node (LN) status when establishing treatment strategies. In TETs, the clinical significance of LN metastasis has not been fully investigated, and the necessity of LN dissection during surgery is still controversial (11).

Thus, simplified strategies contain some important points, and FDG-PET can be a potentially useful tool for this situation. This review investigates the significance of FDG-PET in terms of these three issues.

Articles written in English were researched on PubMed. The retrieval terms used were "thymic epithelial tumors" combined with "FDG-PET" and "malignant lymphoma" OR "stage" OR "lymph node metastasis". The inclusion criteria were clinical studies with comprehensive pathological results detailing histological subtype and stage, emphasizing the differences in SUVmax between TETs and MLs, as well as between early-stage TETs and advanced-stage TETs.

Necessity of differentiation of TETs from MLs, particularly in discrete and resectable masses

Thymic tumors are the most common primary tumors of the anterior mediastinum, mainly including TETs, lymphomas, and germ cell tumors (GCTs) (12,13). TETs and MLs can account for more than 50% of all anterior mediastinal tumors, and are the two most common anterior mediastinal tumors (14,15). For different types of anterior mediastinal tumors, the treatment options are also totally different. Most TETs are usually treated with surgery, while surgery should be avoided for MLs, and the systemic treatments for advanced TETs and MLs are also different. Since resection is recommended without confirmation of the histological diagnosis before surgery for a resectable tumor (7), a few total thymectomies are inevitably performed for patients with a tumor other than TETs. Indeed, Kent *et al.* reported the prevalence of a "nontherapeutic" thymectomy in the Nationwide Inpatient Sample. They demonstrated that 363 (27.8%) of 1,306 total thymectomies were nontherapeutic. Among them, 46 (3.76%) were performed for patients with MLs (16). In another report, among 160 thymectomies, 38 (23.8%) were performed for patients with MLs (17). Thus, to avoid futile thymectomies, even for a resectable anterior mass, it is important to differentiate TETs from MLs. However, the differential diagnosis between TETs and MLs using FDG-PET has still not yet been fully evaluated. To date, several studies have investigated the significance of FDG-PET for differentiating TETs from MLs (8,18-22).

Zhu *et al.* retrospectively investigated primary thymic neoplasms that had been pathologically diagnosed as TETs or MLs on the basis of surgical findings or core needle biopsy specimens, and immunohistochemistry testing to assess whether FDG-PET image features combined with clinical information can distinguish TETs from MLs for the first time. The cutoff value of SUVmax with the best diagnostic performance was 12.3 with an area under the curve (AUC) of 0.764 (sensitivity: 70.4%, specificity: 70.8%) (18). At present, five studies have investigated the differences in SUVmax between TETs and MLs (8,18-21). The details are shown in *Table 1*. Patients with ML were significantly younger than patients with TET. Regarding histological subtypes of MLs, diffuse large B-cell lymphoma and classic Hodgkin lymphoma are common. SUVmax in MLs tended to be higher than that in TETs. The cutoff values of SUVmax to differentiate TETs form MLs are around 10. Most of the studies included both resectable and unresectable tumors. For an unresectable lesion, in routine clinical practice, histological confirmation should always be performed. In this situation, differentiation between TETs and MLs with FDG-PET seems to be less valuable. Of these five studies, only one study by Byrd *et al.* examined a total of 48 patients with resectable thymoma and 29 of those with ML that manifested as a discrete and resectable lesion. The median SUVmax values of thymoma and ML differed dramatically: 4.35 versus 18.00 ($P<0.001$). SUVmax values less than 7.50 and 12.85 were associated with thymoma with 85.4% sensitivity and 100.0% specificity, and 100.0% sensitivity and 79.3% specificity, respectively. MLs are likely with an SUVmax value greater than 12.85. They concluded that tumors with an SUVmax value greater than 7.50 should be biopsied to rule out MLs (8).

Thus, although several optimal cutoff values of SUVmax in the tumor for differentiating TETs from MLs have been reported, many factors contribute to the range of a cutoff value including tumor size, histological subtypes of TETs and MLs, and the extent of the tumor. The threshold SUVmax value that separates TETs from MLs needs to be further evaluated, particularly for a discrete and resectable

Table 1 Studies on SUVmax and cutoff value between thymic epithelial tumors with mediastinal lymphomas

Authors	Inclusion criteria	No. of patients	Gender	Age (years, mean ± SD)	Histologic subtype	SUVmax	Cutoff value of SUVmax	AUC, sensitivity, specificity
Zhu *et al.* [2020] (18)	TETs and MLs	TETs: n=65	TETs: male, 61.5%; female, 38.5%	TETs: 54.2±15.2	TETs: thymoma, n=26; TC, n=31; NET, n=8	TETs: 10.6±6.2	12.3	0.764, 70.4%, 70.8%
		MLs: n=71	MLs: male, 31.0%; female, 69.0%	MLs: 30.3±14.4	MLs: DLBL, n=30; HL, n=26; TLL, n=9; others, n=9	MLs: 16.6±6.4		
Wang *et al.* [2022] (19)	TETs (surgery: n=28, biopsy alone: n=52) and MLs (biopsy alone: n=93)	TETs: n=80	TETs: male, 61.0%; female, 39.0%	TETs: 50.8±14.8	TETs: thymoma, n=28; TC, n=44; NET: n=8	TETs: 7.2±4.3	10.5	0.845, 74.2%, 85.0%
		MLs: n=93	MLs: male, 56.0%; female, 44.0%	MLs: 30.3±14.6	MLs: DLBL, n=37; HL, n=31; TLL, n=23; others, n=2	MLs: 15.5±7.6		
Byrd *et al.* [2023] (8)	Thymomas and MLs that manifested as a discrete, resectable lesion	TETs: n=48	TETs: male, 35.4%; female, 64.6%	55.0	TETs: thymoma, n=48	TETs: 4.4	7.50[a] or 12.85[b]	[†]NR, 85.4%, 100.0% or [‡]NR, 100.0%, 79.3%
		MLs: n=29	MLs: male, 44.8%; female, 55.2%		MLs: DLBL, n=20; HL, n=7; others, n=2	MLs: 18.0		
Zhou *et al.* [2024] (20)	Invasive TETs and MLs	TETs: n=61	TETs: male, 54.1%; female, 45.9%	TETs: 55.8±11.4	TETs: thymoma, n=33; TC, n=28	TETs: 7.6±4.6	9.7	0.841, 77.8%, 81.9%
		MLs: n=72	MLs: male, 55.5%; female, 44.5%	MLs: 28.9±10.4	MLs: DLBL, n=28; HL, n=16; TLL, n=11; others, n=10	MLs: 15.7±8.2		
Yan *et al.* [2024] (21)	TETs and MLs (surgery: n=125, biopsy alone: n=105)	TETs: n=186	TETs: male, 53.8%; female, 46.2%	TETs: 50.4±15.6	TETs: thymoma, n=82; TC, n=84; NET, n=20	Low-risk thymoma: 5.6±2.3, high-risk thymoma: 7.2±2.7, TC: 12.4±5.5, NET: 12.8±7.4	12.0	0.890, NR, NR (accuracy: 78.3%)
		MLs: n=44	MLs: male, 52.3%; female, 47.7%	MLs: 32.0±12.7	MLs: DLBL, n=25; HL, n=10; TLL: n=9	MLs: 21.6±8.6		

Values are presented as the median value for the study by Byrd *et al.*, or as the mean ± SD for other studies. The superscripts [†] and [‡] indicate the AUC, sensitivity, and specificity for each cutoff value of SUVmax for [a] and [b], respectively. AUC, area under the curve; DLBL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; MLs, mediastinal lymphomas; NET, neuroendocrine tumor; NR, not reported; SD, standard deviation; SUVmax, maximum standardized uptake value; TC, thymic carcinoma; TETs, thymic epithelial tumors; TLL, T-lymphoblastic lymphoma.

lesion. A multi-institutional study should be considered.

Usefulness for determining a surgical approach: standard approach or minimally invasive approach (MIA)

Surgical approaches for TET include a trans-sternal approach and MIAs, such as video-assisted thoracic surgery (VATS) and robot-assisted thoracic surgery (RATS) (10). The choice of approach is important for achieving an appropriate surgical view for complete tumor resection. As mentioned above, in the NCCN guidelines, minimally invasive procedures may be considered for clinical stages I–II if all oncologic goals can be met as in standard procedures (7). Accordingly, in preoperative evaluations, predicting the presence or absence of invasion to the neighboring structures in patients with TETs is important. Several studies have investigated the relationship between tumor stage and SUVmax, and have demonstrated that SUVmax is higher in more advanced-stage tumors. Matsumoto *et al.* reported a significantly higher SUVmax for Masaoka-Koga stage IV compared to stages I–II as well as for larger tumors (≥60 mm) (23). Conversely, in the study by Fukumoto *et al.*, the SUVmax of stages III–IV thymomas showed a higher trend toward stages I–II thymomas (24). However, the optimal cutoff values between noninvasive tumors and invasive tumors have not been fully investigated. To date, only a few studies have investigated the difference in SUVmax between noninvasive disease (stages I–II) and invasive disease (stages III–IV). Ito *et al.* analyzed the association between FDG uptake and Masaoka-Koga stage or tumour-node-metastasis (TNM) stage. They found a significant difference in SUVmax between Masaoka-Koga stages III–IV and stages I–II, and identified an optimal cutoff value of 5.4 (sensitivity: 85.0%, specificity: 80.0%). The SUVmax in TETs according to T factors of the TNM classification was 4.45±2.06 in T1a, 4.9±0 in T1b, 7.12±2.69 in T2, 8.31±2.57 in T3, and 9.79±7.48 in T4, and T3 TETs had significantly higher SUVmax than T1a TETs (P<0.01). They also reported a significant difference in SUVmax between TNM stages III–IV and TNM stages I–II, and identified an optimal cut-off value of 5.6 (sensitivity: 89.0%, specificity: 78.0%) (25). Akamine *et al.* retrospectively analyzed patients who exhibited TNM clinical stage I TETs with lesion size <5 cm as determined by computed tomography (MIA-candidate TETs). FDG-uptake in the tumor tended to gradually increase from TNM pathological stage I to IV. The ROC analysis demonstrated that the AUC was 0.820 [95% confidence interval (CI): 0.646–0.919], and the best cutoff value of SUVmax to differentiate the diagnosis of upstaged and pathological stage I patients was 4.2 (sensitivity: 88.9%, specificity: 72.5%) (26).

Thus, preoperative FDG-PET could be useful for the differentiation of invasive TETs and noninvasive TETs. These findings provide valuable information for thoracic surgeons to help them select the appropriate approach for patients with TETs. In routine clinical practice, regardless of FDG-PET findings, MIA is usually adopted for such tumors. However, information on the possibility of invasion to surrounding structures could help thoracic surgeons to determine the surgical approach and prepare for conversion to an open approach before surgery. In addition, it is also important that some information on the possibility of conversion from MIA to an open approach or combined resection of neighboring structures can be provided to patients before surgery. Thoracic surgeons should keep in mind the possibility of more aggressive tumors with the necessity of combined resections of neighboring structures, particularly in high FDG-uptake tumors.

Role of FDG-PET in the decision-making regarding the necessity of LN dissection

One of the most critical roles of FDG-PET when dealing with malignant tumors is evaluating the presence or absence of LN metastasis. In particular, FDG-PET is essential in assessing LN status in several cancers. Regarding the status of LN metastasis in TETs, a study by Fang *et al.* demonstrated that LN involvement rates were 1.5% in thymomas, 17.6% in TCs, and 27.7% in neuroendocrine thymic tumors (27). These findings are identical to those of several other studies (28,29). Since thymoma is the most common entity among TETs, an LN involvement is rare in TETs. Due to this rarity, the usefulness of FDG-PET for evaluating LN status and the necessity of LN dissection in TETs has not been thoroughly investigated. On the other hand, several studies have demonstrated the risk factors for LN metastasis in TETs, and these findings can give valuable suggestions on the role of FDG-PET for LN evaluation in TETs (29,30).

A previous prospective landmark study by Fang *et al.* found three independent risk factors for LN metastasis in TETs, including histology (type B3 thymoma, TC, and thymic neuroendocrine tumor), pathological T category (T3 and T4), and dissection of N2 lesion (29). Another study by Wang *et al.* on the factors that predicted LN metastasis

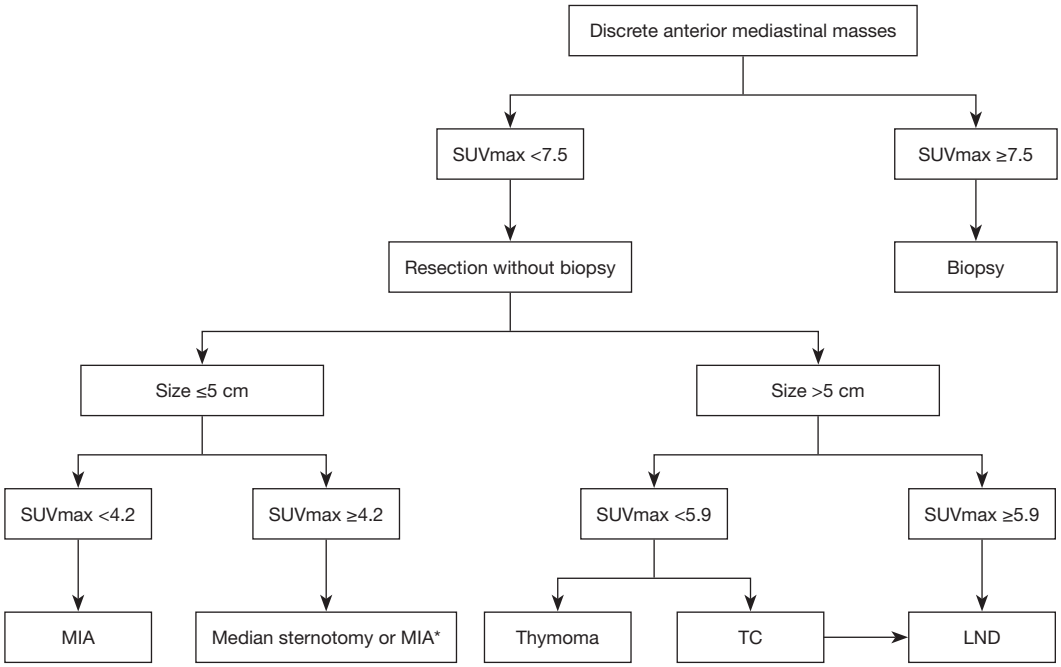

Figure 1 Treatment strategies for discrete anterior mediastinal masses in non-myasthenic patients based on the NCCN guidelines combined with SUVmax in the tumor. *, if performed in specialized centers by surgeons with experience in MIA techniques. LND, lymph node dissection; MIA, minimally invasive approach; NCCN, National Comprehensive Cancer Network; SUVmax, maximum standardized uptake value; TC, thymic carcinoma.

found that pathological T category (T3 and T4) and histology (TC) were significant factors (30). Their model showed good accuracy for predicting LN metastasis with a C-statistic of 0.807 (95% CI: 0.773–0.841), indicating that the nomogram had a good discrimination ability for estimating the status of LN in TETs. Furthermore, the prediction model (AUC =0.807) performed better than predictors of the T category (AUC =0.597, P<0.001) or histology (AUC =0.790, P=0.047) alone. Thus, the risk factors for LN metastasis in TETs include pathological T factors and high-grade histology, particularly TC. Accordingly, FDG-PET might become an important modality in determining the necessity of LN dissection, since it can accurately predict these factors to some extent.

To date, only one study by Akamine *et al.* has addressed the potential use of FDG-PET for the determination of LN dissection for TETs (31). They revealed that LN metastasis was found only in patients with a tumor SUVmax of more than 5.9. Furthermore, none of the patients with SUVmax <5.9 had LN metastasis, LN recurrence, but they had a good prognosis, even in a pathologically advanced stage. They suggested that LN dissection could be omitted in patients with cN0 tumors with low FDG-uptake, even if the tumor is TC. Furthermore, in their previous study, after thymomectomy (resection of tumor without total thymectomy) without extensive LN dissection, no LN recurrence was observed in c-stage I TC <5 cm in size with PET-negative LN, suggesting that LN dissection can be omitted in limited patients (26).

At present, although the necessity of LN dissection in TETs remains controversial, based on the International Thymic Malignancy Interest Group recommendation (32), Hwang *et al.* demonstrated that necessity of LN dissection including paratracheal node for stage II or higher thymic malignancies (28). More reasonable strategies for LN dissection in patients with TET could be established by combining several clinicopathological factors and SUVmax.

Treatment strategies for discrete anterior mediastinal masses

Figure 1 shows a flowchart for treatment strategies based on the NCCN guidelines combined with three cutoff values of SUVmax reported in several articles. First, an SUVmax

of 4.2 is used as a cutoff value between pathological stage I TETs and more advanced-stage TETs in patients with clinical stage I TETs smaller than 5 cm (26). Second, use of an SUVmax cutoff of 5.9 is based on the findings by Akamine *et al.* (31) that none of the patients with SUVmax <5.9 had LN metastasis, LN recurrence, but had a good prognosis, even in a pathologically advanced stage. Finally, an SUVmax of less than 7.5 identified thymoma with 100% specificity; this suggests that tumors with SUVmax less than 7.5 may be resected without biopsy (8). These strategies are merely a proposal to apply existing FDG-PET findings to routine clinical practice, and cannot be generalized to every institution. For example, regarding approaches, if performed in specialized centers by surgeons with experience in MIA techniques, MIA can be selected even for patients with a tumor that is appropriate for a standard procedure in the NCCN guidelines. Furthermore, as mentioned in the NCCN guidelines, biopsy of a possible thymoma should avoid a transpleural approach because of the substantial risk of converting a stage I thymoma to a stage IV thymoma by spreading tumor within the pleural space (7). Accordingly, the cutoff value of SUVmax for biopsy of discrete lesions may need to be set to a higher value, as recommended by Giles and Cassivi (9). To apply an optimal cutoff value of SUVmax widely in routine clinical practice, there are still many issues with FDG-PET for TETs. One of the most critical issues is the reproducibility and predictive performance of radiomic features derived from different centers and scanners. Quantitative values in FDG-PET depend on technical, biological, and physical factors. In addition, such variability may have a significant impact on clinical outcomes. Harmonization methods should be adapted for FDG-PET in TETs in the future (33).

Conclusions

Anterior mediastinal tumors consist of various tumors, and treatment strategies vary even in resectable lesions. In addition, surgical procedures also include many components. For establishing more precise treatment strategies and performing surgery more safely and effectively, FDG-PET could play an essential role in patients with an anterior mediastinal mass, particularly those that present as a discrete and resectable lesion.

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Footnote

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