The utility of $[^{18}F]$-fluorodeoxyglucose positron emission tomography-computed tomography in thymic epithelial tumours

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Received 5 June 2012; received in revised form 11 August 2012; accepted 23 August 2012

Abstract

OBJECTIVES: Positron emission tomography using $[^{18}F]$-fluoro-2-deoxy-D-glucose ($[^{18}F$-FDG-PET) plays an important role in many oncological settings. In this study, we assessed the utility of $[^{18}F$-FDG PET-CT for predicting the histologic type and stage of thymic epithelial tumours.

METHODS: We retrospectively analyzed 58 patients with thymic epithelial tumours who underwent PET–CT before treatment and investigated the relationship between the histologic type based on the World Health Organization classiﬁcation and the maximum standardized uptake value (SUVmax) of each tumour. We also analyzed the relationship between the Masaoka tumour stage and the SUVmax.

RESULTS: The study included 31 males and 27 females, ranging in age from 25 to 80 years (median: 62 years). The tumour histology of 44 tumours was thymoma and that of the remaining tumours was thymic carcinoma, including 11 squamous cell carcinomas and 3 carcinoids. The Masaoka tumour stage was as follows: Stage I in 8, Stage II in 24, Stage III in 18 and Stage IV in 8 patients. The patients were divided into three groups according to a simpliﬁed histologic classiﬁcation: low-risk thymomas (types A, AB and B1, n = 23), high-risk thymomas (types B2 and B3, n = 21) and thymic carcinomas (n = 14). The SUVmax of the thymic carcinoma group was signiﬁcantly higher than those of the low-risk thymoma and high-risk thymoma groups (P < 0.001, respectively). No signiﬁcant differences between the low-risk thymoma and high-risk thymoma groups were observed (P = 0.204). The SUVmax of Stages III and IV thymomas showed a higher trend toward Stages I and II thymomas (P = 0.060).

CONCLUSIONS: PET–CT is a useful modality for predicting the histologic type and tumour stage of thymic epithelial tumours.

Keywords: $[^{18}F$-FDG PET–CT • Thymic epithelial tumours • Histologic type • Stage

INTRODUCTION

Thymic epithelial tumours, including thymomas and thymic carcinomas, are the most common tumours in the anterior mediastinum. In the latest classiﬁcation updated in 2004, thymic epithelial tumours were classiﬁed into two major categories: ﬁve types of thymomas, including types A, AB, B1, B2 and B3; and thymic carcinomas, including neuroendocrine carcinomas [1]. It has been reported that the World Health Organization (WHO) histologic classiﬁcation reﬂects the clinical features and prognostic factors of thymic epithelial tumours [2–4]. Therefore, predicting histologic type and tumour stage is considered to be very important for planning treatment strategies.

Positron emission tomography using $[^{18}F$-fluoro-2-deoxy-D-glucose ($[^{18}F$-FDG-PET) plays an important role in many oncological settings. The maximum standardized uptake value (SUVmax) of a tumour determined using FDG-PET provides a semi-quantitative estimate of tumour metabolism and therefore serves as an index of tumour malignancy. A few reports have indicated that FDG-PET is useful for predicting the histologic type of thymic epithelial tumours. Inoue and Luzzi and et al. [5, 6] reported that the SUVmax of low-risk thymomas containing types A, AB and B1 tumours is signiﬁcantly lower than those of high-risk thymic tumours consisting of types B2 and B3 thymomas and thymic carcinomas. However, there exist few reports regarding the role of FDG-PET in the differential diagnosis of thymomas and thymic carcinomas.

In this study, we retrospectively analyzed 58 patients with thymic epithelial tumours who underwent FDG PET–CT examination before treatment and investigated the relationship
between histologic type of the WHO classification and SUV$_{\text{max}}$. We also analyzed the relationship between tumour stage determined according to the Masaoka staging system [7] and SUV$_{\text{max}}$.

**MATERIALS AND METHODS**

From December 2006 to March 2012, 58 patients with thymic epithelial tumours underwent FDG PET-CT during the pretreatment period in Nagoya University Hospital. In one patient with double thymomas, the larger tumour was evaluated. In patients who underwent initial surgery ($n=45$), definitive diagnoses of the tumours were obtained by examining the resected specimens. In patients who received induction chemotherapy or radiation therapy ($n=12$), the diagnoses of the tumours were confirmed by examining the needle biopsy specimens. In one patient who received chemoradiation therapy alone, the diagnosis of the tumour was confirmed by examining the needle biopsy specimen. These specimens were reviewed by an experienced pathologist, and the tumours were classified by the WHO classification as follows: types A, AB, B1, B2, B3 and thymic carcinoma. All tumours were staged using the Masaoka staging system.

All patients fasted for at least 6 hours before undergoing 18F-FDG PET examination. The patients received an intravenous injection of 3.7–4.07 MBq/kg of FDG and then rested for $\sim$50 min before undergoing imaging. Image acquisition was performed using a PET-CT scanner (Biograph16; Siemens Medical Solutions, Erlangen, Germany). Three-dimensional emission scanning was performed from the groin to the top of the skull. The emission time per bed position was two minutes (12–16 min per whole-body scan), which is in line with standard clinical protocols. Emission PET images were reconstructed using iterative ordered subset expectation maximization with non-contrast CT. To evaluate 18F-FDG accumulation, the tumours were first examined visually by two experienced radiologists. For the semi-quantitative assessment, regions of interest (ROIs) were overlaid on FDG-avid mediastinal tumours, and the SUV$_{\text{max}}$ [the maximum ROI activity (MBq/g)/injected dose (MBq)/body weight (g)] of each tumour was measured.

The Mann–Whitney U-test for unpaired observations was used for comparing the levels of SUV$_{\text{max}}$ in each group. $P$ values <0.05 were considered to indicate significant differences for comparisons between two groups. $P$ values <0.016 were considered to indicate significant differences for comparisons between three groups, according to the Bonferroni method. The Spearman rank correlation coefficient was calculated to clarify the correlation between tumour size and the SUV$_{\text{max}}$ on PET–CT. The statistical evaluations were performed using computer software STATA Ver.11 (College Station, TX, USA). The Institutional Review Board of Nagoya University Hospital approved this retrospective study.

**RESULTS**

This study included 31 males and 27 females, ranging in age from 25 to 80 years (median: 62 years). The median of tumour size was 52 mm (range: 25–80 mm). At pathologic examination of the resected or biopsied specimens, 44 tumours were diagnosed as thymomas, including 14 type AB tumours, 9 type B1 tumours, 16 type B2 tumours and 5 type B3 tumours. Fourteen tumours were determined to be thymic carcinomas, including 11 squamous cell carcinomas and 3 carcinoids (Fig. 1). Eight Stage I, 24 Stage II, 18 Stage III and 8 Stage IV tumours were observed (Table 1). There were no patients with distant metastases. Eight Stage IV patients had pleural dissemination or lymph node metastases. Most of metastatic lymph nodes were positive

![Figure 1](attachment:image.png)  
**Figure 1:** CT and PET–CT findings of patients with thymoma and thymic carcinoma. (a and b) A 61-year-old female with type AB thymoma, Masaoka Stage II. (c and d) A 64-year-old male with squamous cell carcinoma, Masaoka Stage III. The SUV$_{\text{max}}$ were 4.6 and 9.6, respectively.
in PET–CT, while pleural disseminations had no or extremely weak FDG accumulation.

The SUV_{max} determined according to the WHO histologic classification is shown in Table 2. The patients were divided into three groups according to a simplified histologic classification: low-risk thymomas (types A, AB and B1, n = 23), high-risk thymomas (types B2 and B3, n = 21) and thymic carcinomas (n = 14). The SUV_{max} of the tumours in each group was shown in Fig. 2. The SUV_{max} of the thymic carcinomas was significantly higher than those of the low-risk thymomas (median, range: 3.6, 1.1–5.8) and high-risk thymomas (median, range: 4.1, 2.2–6.4) (P < 0.001). No significant differences were found between the low-risk thymomas and the high-risk thymomas (P = 0.204).

The SUV_{max} according to the Masaoka stage of thymomas was shown in Table 3. As shown in Fig. 3, the SUV_{max} of the Stages III and IV (advanced stage) thymomas showed a higher trend toward the Stages I and II (early stage) thymomas (P = 0.060). In the patients with thymoma, a suggestive correlation between tumour size and the SUV_{max} on PET–CT was observed (r = 0.432). However, no obvious correlations between tumour size and the SUV_{max} on PET–CT were observed in patients with thymic carcinoma (r = 0.084).

Of 12 patients who received induction therapies, SUV_{max} of main tumours before and after induction therapies were available in 10 patients. Six patients showed partial response (PR) and four patients showed stable disease (SD) in the evaluation with CT. All of the SUV_{max} in patients who showed PR have

**Table 2:** SUV_{max} according to the WHO histologic classification of thymic epithelial tumours

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>N</th>
<th>SUV_{max} Median</th>
<th>Range</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>14</td>
<td>3.2</td>
<td>1.9–5.4</td>
<td>1.9</td>
</tr>
<tr>
<td>B1</td>
<td>9</td>
<td>4.4</td>
<td>1.1–5.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Low-risk thymoma (AB + B1)</td>
<td>23</td>
<td>3.6</td>
<td>1.1–5.8</td>
<td>1.9</td>
</tr>
<tr>
<td>B2</td>
<td>16</td>
<td>4.1</td>
<td>2.7–6.4</td>
<td>1.2</td>
</tr>
<tr>
<td>B3</td>
<td>5</td>
<td>4.3</td>
<td>2.2–4.9</td>
<td>0.5</td>
</tr>
<tr>
<td>High-risk thymoma (B2 + B3)</td>
<td>21</td>
<td>4.1</td>
<td>2.2–6.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>14</td>
<td>7.2</td>
<td>4.9–12.6</td>
<td>3.0</td>
</tr>
</tbody>
</table>

WHO: World Health Organization; SUV_{max} maximum standardized uptake value; IQR: interquartile range.

**Table 3:** SUV_{max} according to the Masaoka stage of thymomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>SUV_{max} Median</th>
<th>Range</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8</td>
<td>3.5</td>
<td>1.1–5.4</td>
<td>2.4</td>
</tr>
<tr>
<td>II</td>
<td>22</td>
<td>3.8</td>
<td>1.9–5.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Early stage (Stage I + II)</td>
<td>30</td>
<td>3.7</td>
<td>1.1–5.8</td>
<td>1.9</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>4.3</td>
<td>3.1–6.4</td>
<td>3.2</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>4.1</td>
<td>3.0–5.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Advanced stage (Stage III + IV)</td>
<td>14</td>
<td>4.3</td>
<td>3.0–6.4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

SUV_{max}: maximum standardized uptake value; IQR: interquartile range.

**Figure 2:** The SUV_{max} in subgroups according to a simplified WHO histologic classification. The SUV_{max} of the thymic carcinomas (median, range: 7.2, 4.9–12.6) was significantly higher than those of the low-risk thymomas (median, range: 3.6, 1.1–5.8) and high-risk thymomas (median, range: 4.1, 2.2–6.4) (P < 0.001). No significant differences were found between the low-risk thymomas and the high-risk thymomas (P = 0.204).

**Figure 3:** The SUV_{max} of the Stages III and IV thymomas (median, range: 4.3, 3–6.4) showed a higher trend toward the Stages I and II thymomas (median, range: 3.7, 1.1–5.8) (P = 0.060).
decreased. There was no obvious change of the $\text{SUV}_{\text{max}}$ in patients who showed SD.

**DISCUSSION**

Thymomas and thymic carcinomas are quite different with respect to oncological behaviour. Surgical resection is the mainstay of treatment for thymomas and multidisciplinary treatment with induction chemotherapy is advocated for patients with Stage III disease with great vessel invasion or Stage IV disease. [8, 9] Thymic carcinomas are much more aggressive tumours, and the incidence of lymph node and distant metastasis is higher than that observed in thymomas. Because of the higher incidence of nodal metastasis, lymph node dissection around the tumour may be performed during surgery. When considering induction therapies for advanced staged patients, it should be noted that chemotherapy regimens differ according to histologic type. Predicting the histologic type and stage of thymic epithelial tumours is extremely important for planning treatment strategies.

During the past few decades, PET–CT imaging has been increasingly studied and used in clinical practice. This imaging technique offers a holistic approach for malignant tumour diagnosis because it integrates structural, functional and metabolic information about tumours. In patients with lung cancer, PET–CT is widely used for preoperative staging [10]. A few reports have indicated that $^{18}$F-FDG PET is useful for making differential diagnoses of thymic epithelial tumours. Travaini and co-workers [11] reported the role of FDG-PET-CT and CT for differential diagnosis between thymic malignancies and benign lesions. Iagi et al. [12] reported that the SUV$_{\text{max}}$ of thymic carcinomas ($n=5$) was significantly higher than that of thymomas ($n=8$). Endo et al. classified thymic epithelial tumours into three groups: low-risk thymomas containing types A, AB and B1 tumours ($n=15$), high-risk thymomas containing types B2 and B3 tumours ($n=10$) and thymic carcinomas ($n=11$). They showed that the SUV$_{\text{max}}$ of low-risk and high-risk thymomas was significantly lower than that of thymic carcinomas and the SUV$_{\text{max}}$ of low-risk thymomas was significantly lower than that of high-risk thymomas [13]. Similarly, Sung et al. classified thymic epithelial tumours into the same three groups and showed that the SUV$_{\text{max}}$ of low-risk ($n=8$) and high-risk thymomas ($n=9$) was significantly lower than that of thymic carcinomas ($n=16$), whereas no differences between low-risk thymomas and high-risk thymomas are observed [14]. These results are consistent with our observations.

A few reports also document a relationship between tumour stage and SUV$_{\text{max}}$. Luzzi and Terzi et al. showed a direct correlation between tumour stage and SUV$_{\text{max}}$ [6, 15]. However, both thymoma and thymic cancer are included in these studies. We have analyzed thymoma group separately from thymic cancer group. In our study, the SUV$_{\text{max}}$ in patients with Stages III and IV thymomas showed a higher trend toward patients with Stages I and II disease; however, no significant differences were observed ($P = 0.060$). As for thymic cancer, there was no obvious correlation between tumour size and SUV$_{\text{max}}$. The SUV$_{\text{max}}$ of thymic cancer would be high regardless of tumour stage, because tumour size is generally correlated with tumour stage.

Our retrospective analysis revealed the following implications: high SUV$_{\text{max}}$ on PET–CT images indicate a higher possibility for thymic carcinomas and advanced stage thymic epithelial tumours. In such cases, pathologic diagnosis should be obtained before treatment in order to consider induction therapy. Although needle biopsy is not necessary for early stage, additional lymph node dissection around the tumour might be needed because of high incidence of lymph node metastases in thymic cancer cases. In addition, PET–CT might have a potential power to predict the response to induction therapies.

There are some limitations in our retrospective analysis. First, the number of study cohorts is not large; however, to our knowledge, the number is the largest of any report. Second, the method of determining SUV$_{\text{max}}$ varies at individual institutions according to the blood glucose level [16] and the reconstruction algorithms and methods for drawing the regions of interest employed. One method of ensuring the universality of SUV$_{\text{max}}$ to be universal is to calculate the ratio of SUV$_{\text{max}}$ of tumours and the mean SUV of the mediastinum [13]. Correcting SUV$_{\text{max}}$ by mean liver SUV is another method [17]. However, some additional steps are required to calculate these adjusted SUV$_{\text{max}}$. Non-adjusted SUV$_{\text{max}}$ can be used as a parameter for estimating the histologic type and extent of disease because it is easily available in clinical practice at each institution.

**CONCLUSIONS**

$^{18}$F-FDG PET–CT is a useful modality for differential diagnosis between thymoma and thymic carcinoma, and might be helpful for predicting stage of thymoma. Treatment strategies for thymic epithelial tumours can be made more precise with PET–CT because information regarding the tumours can be predicted before the treatment is initiated.

**ACKNOWLEDGEMENTS**

The authors thank Hisashi Tateyama, MD, at the Department of Pathology, Clinical Laboratory, Kasugai Municipal Hospital, Kasugai, Japan, for providing the pathologic data.

Conflict of interest: none declared.

**REFERENCES**


APPENDIX: CONFERENCE DISCUSSION

Dr E. Ruffini (Torino, Italy): We know that for neuroendocrine tumours in general, PET-CT has a low sensitivity. So what was the SUVmax of the three carcinoid tumours in your series?

Dr Fukumoto: All three carcinoid tumours were positive, and the SUVmax of those tumours was very high, more than 7 or 8.

Dr Ruffini: Probably because neuroendocrine thymic tumours behave very aggressively, contrary to other neuroendocrine tumours in the human body.

Dr Fukumoto: I think so.

Dr W. Hanna (Toronto, ON, Canada): I was just wondering whether you have seen a difference in the SUVmax of thymic carcinomas before and after induction therapy, if you did induction therapy? That was the first question. SUVmax is a very non-uniform reading between institutions. It depends on the dose and radionucleotide that is given, the machine, the model of the machine, the radiologist reading it. My second question is, how can you comment on the uniformity of your results?

Dr Fukumoto: In response to your first question, in advanced thymoma patients the chemotherapy response was very good: PR was obtained in more than half of the patients and then the SUVmax decreased in such cases. But in thymic carcinoma cases, there were only a few responders, so the SUVmax was almost the same as before chemotherapy. As to your second question, it is the limitation of my study. It would be very difficult to set up the points to calculate the universal level of cut-off, for example, to differentiate thymoma and thymic carcinoma, so it would be better to confirm at each institution.