Clinical use of combined positron emission tomography and computed tomography in thymoma recurrence

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Abstract

The aim of this study is to evaluate the efficacy of hybrid fluorine-18 fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) for surveillance and follow-up of thymoma patients to detect recurrent disease. A retrospective chart review was performed on 37 thymoma patients who underwent FDG-PET/CT-scans during postoperative follow-up. The following information was obtained: clinical indication for FDG-PET/CT, the results of the FDG-PET/CT, particularly with regard to the additional diagnostic imaging information, the localization of the disease and subsequent clinical patient management. A total of 51 CT-scans were performed on 37 patients providing sensitivity and specificity for thymoma recurrence of 71% and 85%, respectively. Forty-five FDG-PET/CT-scans were performed on the same group of patients with an overall sensitivity and specificity of 82% and 95%, respectively. Notably, FDG-PET/CT sensitivity when employed for diagnosis of thymoma recurrence in the anterior mediastinum has reached 100% (CT has shown only 55% sensitivity for the detection of anterior mediastinal thymoma recurrence). Our preliminary study demonstrates that during follow-up after thymoma excision, FDG-PET/CT is superior to computed tomography alone in the detection and localization of mediastinal recurrence. In particular, the combined structural and metabolic information of FDG-PET/CT enhances the diagnostic confidence in lesion characterization.

Keywords: Thymoma; Positron emission tomography; Computed tomography; Myasthenia gravis

1. Introduction

Thymomas are a heterogeneous group of tumors encompassing capsulated tumors, benign lesions and highly infiltrative, evidently malignant neoplasms. Thymectomy is an established treatment modality for thymoma.

Although their clinical course is not as rapid as that of other tumors, thymomas are known to have a propensity for late recurrence even after complete resection. Long-term follow-up is required for accurate evaluation of the incidence of relapse [1, 2].

Computed tomography (CT) and magnetic resonance imaging (MRI) are currently used during follow-up to detect recurrent disease; however, differential diagnosis based solely on structural imaging information remains challenging. CT and MRI may not differentiate between residual or recurrent disease from fibrosis and scarring (postoperative and/or post-irradiation), especially in the anterior mediastinum.

Fluorine-18 fluorodeoxyglucose (FDG)-positron emission tomography (PET) has emerged as a strong diagnostic tool for the diagnosis, staging and re-staging of thymic gland tumors [3–5]. FDG-PET provides metabolic information that may facilitate the diagnostic imaging evaluation of thymoma. Moreover, the recently developed hybrid FDG-PET/CT imaging system has improved the diagnostic accuracy and confidence by providing both structural and metabolic diagnostic information [6, 7]. FDG-PET/CT allows for the precise localization of metabolic abnormalities and for metabolic characterization of normal and abnormal anatomical structures.

The aim of this study is to evaluate the diagnostic utility of hybrid FDG-PET/CT in the evaluation of patients with suspected or known thymoma recurrences.

2. Patients and methods

2.1. Patients

From 1998 to 2007, 138 thymoma patients underwent surgery at King Khalid University Hospital, King Saud University and at King Faisal Specialist Hospital and Research Center, Alfaïsaïl University, Riyadh, Saudi Arabia. Between 2003 and 2007, a retrospective analysis of computerized databases and medical records of 37 consecutive patients...
who underwent FDG-PET/CT for suspected thymoma recurrence was undertaken. Use of the data for research was approved by our internal review board, and an exemption was granted for specific patient consent.

Table 1 summarizes the recurrence proportions by surgical-pathological staging. The study included 20 men and 17 women with a mean age at the time of the first operation of 35 years (range 18–60 years). The extent of thymoma recurrence was staged following the classification suggested by Massoka and associates (Table 1). The initial surgical approach was sternotomy in 28 patients, posterolateral thoracotomy in five patients, and video-assisted thoracoscopic (VAT) excision of the thymoma and thymectomy in four patients.

Postoperative radiation therapy was offered to patients with stage II with positive margins and all patients with stages III and IV whom did not receive radiation therapy after first procedure. For those who received radiation previously, chemotherapy was offered.

Recurrence was confirmed via histopathological examination of the surgical specimens in 17 patients. Mediastinal recurrence occurred in 11 patients and pleural dissemination (recurrence) occurred in six patients.

During the follow-up period after initial thymectomy, our protocol was to perform a chest CT six months after the procedure as a baseline for future annual comparisons. Persistence or worsening of myasthenia gravis (MG) symptoms after thymectomy warranted earlier study.

### 2.2. Indications for FDG-PET/CT

The decision to perform FDG-PET/CT was based on one of the following clinical scenarios: (1) persistence of MG symptoms; (2) abnormal CT with indicators of recurrence, in which case FDG-PET/CT was performed to estimate the metabolic activity of the suspicious lesion; (3) indeterminate CT study, and (4) follow-up for an invasive thymoma even with no evidence of recurrence.

### 2.3. Surgical technique

Recurrent thymomas were approached by a median sternotomy in 10 patients. In six patients, when the mediastinal recurrence was accompanied with unilateral pleural dissemination, a posterolateral thoracotomy approach was preferred. In two patients, an additional thoracotomy (one or two intercostal spaces below the first thoracotomy using the same skin incision) was necessary to properly resect recurrent lesions on the diaphragm.

### 2.4. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, ver.12.0, Chicago, IL, USA). Sensitivity, specificity, and positive and negative predictive value (PPV and NPV, respectively) of CT and FDG-PET/CT imaging were determined by correlating their results with the histopathological results and with clinical outcomes in all cases. The likelihood ratio (LR) was also calculated.

To assess the agreement between CT and FDG-PET/CT and final diagnosis more precisely, the Cohen K with its 95% confidence interval (CI) was calculated for the same patients.

### 3. Results

Among 138 patients who had thymoma resections, there were 23 recurrences of thymomas (23/138, 17%). In the group of patients who received FDG-PET/CT, 17 (17/137) were confirmed to have a recurrence (Table 1).

Ten patients (group I) had persistence of symptoms of MG (10/37). CT reported mediastinal recurrence of thymomas in five patients (5/10). FDG-PET/CT reported high uptake in the anterior mediastinum in only three patients (Fig. 1). CT imaging detected pleural dissemination in three patients (3/10). FDG-PET/CT showed uptake in only two patients. One patient with a 1.3-cm right pleural nodule did not show uptake.

In one patient, both CT and FDG-PET/CT were false positive (FP). Both showed a 2-cm nodule that was labeled as recurrence but on follow-up there was reduction in the size of nodule by 50% of its size.

Twenty-seven thymoma patients (group II) without associated symptoms of MG were also given follow-up care. CT studies reported three patients with anterior mediastinal recurrences, two patients with indeterminate studies, and 22 patients negative for recurrence in the anterior mediastinum. CT also detected pleural dissemination in three patients, including a 2-cm pleural nodule (n=1), a 4-cm diaphragmatic mass (n=1), and a 1.2-cm middle lobe nodule (n=1) (Table 2).

FDG-PET/CT confirmed CT results in three patients with anterior mediastinal recurrences. FDG-PET/CT detected abnormally high activity in the anterior mediastinum in two patients whose statuses had been classified as indeterminate by CT. The FDG-PET/CT also detected abnormal uptake in the anterior mediastinum in three patients previously classified by CT studies as negative (Fig. 2).

FDG-PET/CT could detect pleural dissemination in only one patient with a relatively large diaphragmatic mass. As for the other two patients who had a positive result for pleural dissemination by CT, the FDG-PET/CT studies produced false negative (FN) results showing no activity in FDG-PET/CT.

Re-exploration confirmed FDG-PET/CT findings of anterior mediastinal recurrence by histopathological examination of
Fig. 1. Discordant findings between CT and FDG-PET/CT where CT (panel a) shows suspicious mediastinal mass indicating recurrence. FDG-PET/CT (panel b) shows no significant metabolic uptake within the same area favoring postoperative changes. This finding was confirmed by 12 months follow-up.

CT, computed tomography; FDG-PET/CT, fluorine-18 fluorodeoxyglucose-positron emission tomography/computed tomography.

Fig. 2. Discordance between CT and FDG-PET/CT findings. CT examinations (panel a) showed suspicious anterior mediastinal mass with calcification mass (arrow). FDG-PET/CT reported high SUV uptake at the same area (panel b) indicating recurrence of thymoma (arrow). Re-exploration and histopathological examination of the surgical specimen confirmed FDG-PET/CT results.

CT, computed tomography; FDG-PET/CT, fluorine-18 fluorodeoxyglucose-positron emission tomography/computed tomography; SUV, standardized uptake value.

Table 2. Imaging results from the follow-up of the 37 patients: correlation with final diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Myasthenic thymomas (n = 10)</th>
<th>Non-myasthenic thymomas (n = 27)</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>PET/CT</td>
<td>3</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

Ant. med. recu., anterior mediastinal recurrence; Pl. recu., pleural recurrence; TP, true positive; FP, false positive; FN, false negative; TN, true negative; PET/CT, positron emission tomography/computed tomography; CT, computed tomography.
the surgical specimens in 11 patients. The remainder of the patients (n=26) had negative FDG-PET/CT-scans and no signs of recurrent disease in the anterior mediastinum within at least 12 months of follow-up. FDG-PET/CT failed to detect pleural dissemination in three patients. The pleural dissemination was confirmed in those patients after surgical exploration and resection of pleural nodules.

A total of 51 CT and 45 FDG-PET/CT studies were performed altogether for 37 patients. CT overall sensitivity for detecting the mediastinal recurrence and pleural dissemination of thymomas is 71% (95% CI, 50% and 92%). Similarly, CT specificity is 85% (95% CI, 70% and 100%). As for FDG-PET/CT, the overall sensitivity and specificity for thymoma recurrence are 82% (95% CI, 64% and 100%) and 95% (95% CI, 85% and 100%), respectively. The sensitivity of FDG-PET/CT when employed for the diagnosis of thymoma recurrence in the anterior mediastinum has reached 100% (CT showed only 55% sensitivity for detection of anterior mediastinal thymoma recurrence).

LRs are a useful and practical way of expressing the power of diagnostic tests in increasing or decreasing the likelihood of disease [9]. In this study, the LR of CT was five, while that of the FDG-PET/CT was 16. FDG-PET/CT correctly identified thymoma recurrence in 93% of patients (95% CI, 67% and 99%), while the CT post-test probability was 80% (95% CI, 57% and 92%).

Table 3 summarizes the comparative performances of CT and FDG-PET/CT in the detection of recurrent thymoma in the 17 patients. By comparing the K of CT (K=0.56; 95% CI from 29% and 82%) and that of FDG-PET/CT (K=0.78; 95% CI from 58% and 98%), it can be concluded that the agreement between FDG-PET/CT and final diagnosis was better than the agreement between CT and final diagnosis.

4. Discussion

Lifetime surveillance and careful follow-up of patients who undergo thymoma resection (either encapsulated or invasive) is strongly advocated. In our patient population, local recurrence confined to the mediastinum occurred in 30% (11/37) of cases, whereas pleural dissemination was present in 17% (6/37).

From a clinical point of view, it may be difficult to differentiate local recurrence in the mediastinum from post-treatment changes by morphological imaging because both processes may demonstrate similar appearances on a CT-scan [10]. A new non-invasive technique with the ability to clearly diagnose a recurrent tumor would thus be valuable.

FDG-PET is a non-invasive technique that appears to be efficient in the diagnosis of different thymic pathologies (i.e. thymic hyperplasia, thymoma and thymic carcinoma). The mean standardizes uptake value (SUV) in the mediastinum observed in 11 patients in the present series was 4.4±0.8 (with a range from 3.4 to 5.9), which is comparable to a previous report by the authors stating an SUV of three as a cut-off value for diagnosis of thymoma and differentiation between thymoma and thymic hyperplasia [3].

FDG-PET/CT appeared to be more accurate than conventional imaging in distinguishing recurrent tumors in the mediastinum from fibrotic scar tissue in patients who underwent surgical excision of a thymoma. All mediastinal recurrences (n=11) were correctly identified by FDG-PET, whereas CT imaging reported five FN and two FP cases at the time of PET diagnosis. The results of the present study suggest that FDG-PET is more sensitive (82%) than CT (77%) for detection of residual or recurrent thymoma after treatment.

Ito and his colleagues [11] discussed the role of FDG-PET in the accurate assessment of recurrent thymoma and its therapeutic strategy. They stated that primary thymomas are usually large enough to produce correct SUVs, whereas the nodules of recurrent thymoma with pleural dissemination often appear as multiple small nodules, which make it difficult to determine their actual SUVs. The comparatively poor dependency between FDG uptake and lesion size correlates with the observation of Vesselle et al. [12], who defined the influence proliferation markers and tumor differentiation on the intensity of tracer accumulation.

In some situations, such as when disseminated tumors are too small to be seen by PET, CT is also able to increase the sensitivity of the PET/CT examination. Thus, there is a consensus that PET/CT is more accurate in tumor staging than PET or CT alone and even more than PET and CT images viewed side-by-side. The advantage of conjoint image viewing is such that authors of recent studies [13–15] have shown that in approximately two-thirds of patients with lesions seen on PET images, CT data are needed to improve the specificity of the findings. Imperfect specificity of PET may also be due to FDG accumulation in irradiated tissues and postsurgical inflammatory changes.

Although our results showed higher specificity of FDG-PET/CT over CT (95% vs. 85%, respectively), FDG-PET/CT reported three FN results with pleural dissemination. There was no uptake in three pleural nodules measuring 1.3, 2 and 1.2 cm. Those nodules were correctly identified by CT and proven to be pleural disseminations by histopathological examination of surgical specimens.

Our study is limited by the retrospective nature of the data analysis. We did not directly compare the diagnostic performance of FDG-PET/CT to separate FDG-PET and CT-scans, as this was beyond the scope of this study. The interpretation of FDG-PET/CT was performed in a clinical

Table 3. Comparative overall performance of CT and FDG-PET/CT in detection of recurrent thymoma

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity % (n)</th>
<th>Specificity % (n)</th>
<th>PPV % (n)</th>
<th>NPP % (n)</th>
<th>Proportion in agreement</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>71 (12/17)</td>
<td>85 (17/20)</td>
<td>80 (12/15)</td>
<td>77 (17/22)</td>
<td>0.78</td>
<td>0.56</td>
</tr>
<tr>
<td>FDG-PET/CT</td>
<td>82 (14/17)</td>
<td>95 (19/20)</td>
<td>93 (14/15)</td>
<td>86 (19/22)</td>
<td>0.89</td>
<td>0.78</td>
</tr>
</tbody>
</table>

CT, computed tomography; FDG-PET/CT, fluorine-18 fluorodeoxyglucose-positron emission tomography/computed tomography; PPV, positive predictive value; NPP, negative predictive value.
setting with knowledge of the clinical history and findings from other imaging modalities. We have used a standardized 12 month follow-up period to determine the diagnostic performance of FDG-PET/CT, and the duration of follow-up could have biased our results. The FDG uptake in cancer varies, depending, for example, on the histological subtype of thymoma [4]. However, the question about the specific advantage of using FDG-PET/CT over the separate imaging procedures is of crucial importance and requires a thorough analysis in prospective studies to better understand the benefits and potential limitations of FDG-PET/CT imaging in cases of recurrent thymoma.

In conclusion, our preliminary study demonstrates that during follow-up after thymoma excision, FDG-PET/CT is superior to CT alone in the detection and localization of mediastinal recurrence. The combined structural and metabolical information of FDG-PET/CT enhances the diagnostic confidence in lesion characterization differentiating thymoma recurrence from postoperative and/or postirradiation changes especially for those patients with inconclusive CT studies.

References