18F-Fluoroethylcholine PET/CT Identifies Lymph Node Metastasis in Patients with Prostate-Specific Antigen Failure After Radical Prostatectomy but Underestimates Its Extent

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Abstract

Background: The detection of lymph node metastases (LNMs) is one of the biggest challenges in imaging in urology.

Objective: To evaluate the accuracy of combined 18F–fluoroethylcholine (FEC) positron emission tomography (PET)/computed tomography (CT) in the detection of LNMs in prostate cancer (PCa) patients with rising prostate-specific antigen (PSA) level after radical prostatectomy.

Design, settings, and participants: From June 2005 until November 2011, 56 PCa patients with biochemical recurrence after radical prostatectomy underwent bilateral pelvic and/or retroperitoneal lymphadenectomy based on a positive 18F-FEC PET/CT scan.

Outcome measurements and statistical analysis: The findings of PET/CT were compared with the histologic results.

Results and limitations: Median PSA value at the time of 18F-FEC PET/CT analysis was 6.0 ng/ml (interquartile range: 1.7–9.4 ng/ml). In 48 of 56 (85.7%) patients with positive 18F-FEC PET/CT findings, histologic examination confirmed the presence of PCa LNMs. Of 1149 lymph nodes that were removed and histologically evaluated, 282 (24.5%) harbored metastasis. The mean number of lymph nodes removed per surgical procedure was 21 (standard deviation: ±18.3). A lesion-based analysis yielded 18F-FEC PET/CT sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 39.7%, 95.8%, 75.7%, and 83.0%, respectively.

A site-based analysis yielded sensitivity, specificity, PPV, and NPV of 68.4%, 73.3%, 81.3%, and 57.9%, respectively. Patients with negative PET/CT did not undergo surgery, thus sensitivity, specificity, and negative predictive value on a patient basis could not be calculated.

Conclusions: A positive 18F-FEC PET/CT result correctly predicted the presence of LNM in the majority of PCa patients with biochemical failure after radical prostatectomy but did not allow for localization of all metastatic lymph nodes and therefore was not adequately accurate for the precise estimation of extent of nodal recurrence in these patients.

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1. Introduction

Radical prostatectomy (RP) provides excellent long-term outcomes for clinically localized prostate cancer (PCa) [1–3]. However, prostate-specific antigen (PSA) failure after RP occurs in about 40% of patients and is a clinical dilemma [1–3]. Undetected lymph node involvement at the time of first diagnosis of PCa is one reason for recurrence [4].

At present, no imaging modality can reliably detect lymph node metastasis (LNM). Generally, computed tomography (CT) shows disappointing results in the identification of metastatic lymph nodes [5,6]. Hybrid positron emission tomography (PET)/CT enables the visualization of metabolic to anatomic abnormalities and may help improve detection of LNMs. 11C-Choline PET/CT has shown promise in detection of positive lymph nodes in patients with PSA failure [7–9]; however, it does not allow accurate detection of metastatic spread to small lymph nodes or micrometastases to normal size nodes. 11C-Choline has a short half-life of only 20 min, which limits its availability, and it needs to be synthesized onsite using a cyclotron [10]. Poulsen et al. studied the value of 18F–fluoroethylcholine (FEC) PET/CT for lymph node staging of PCa patients before curative treatment and reported superior results [11]. To our knowledge, the value of 18F–FEC PET/CT in detection of positive lymph nodes in radically treated PCa patients with PSA relapse has not been systematically assessed.

The aim of our study was to evaluate the accuracy of 18F–FEC PET/CT in detection of LNMs in these patients. To address this question, we compared the results from 18F–FEC PET/CT with the histologic data from secondary lymphadenectomy in 56 patients with a positive 18F–FEC PET/CT result.

2. Patients and methods

2.1. Patient selection and data collection

This study was approved by our institutional review board. The records of 56 patients with biochemical recurrence after RP and positive 18F–FEC PET/CT scan and who were treated with secondary, extended-field, bilateral pelvic lymphadenectomy or both pelvic and retroperitoneal lymphadenectomy between June 2005 and November 2011 were reviewed retrospectively. All patients were initially treated for localized PCa by RP and pelvic lymphadenectomy with curative intent. PSA failure after RP was defined as an increase in PSA level to >0.2 ng/ml. Included patients discontinued androgen deprivation therapy at least 4 wk before PET/CT scan. Salvage surgery was not offered as first-choice therapy but was regarded only as an experimental option for patients who refused medication treatment. Selection for salvage lymphadenectomy was based on fitness for surgery, biological age, and desire of the patient. None of the patients had bone metastases (verified by bone scan) or local recurrence.

2.2. Surgical procedure and histologic evaluation

The surgical field for pelvic lymphadenectomy included lymph nodes along the internal and external iliac vessels, the common iliac vessels, the presacral region, the aortocaval region up to the inferior mesenteric artery, and, if positive in PET/CT scan, the pararectal region. The lateral border of lymphadenectomy was the genitofemoral nerve. Retroperitoneal lymphadenectomy included removal of all lymphatic tissue along the abdominal great vessels from the origin of the iliac vessels to the cranial border of the upper renal pole. After lymphadenectomy, surgical specimens were processed according to standard pathology protocols. Lymph node analysis was performed by step sections (200-μm-thick slices) to detect micrometastases. Sections were stained with hematoxylin and eosin for histologic evaluation.

2.3. Integrated 18F-FEC PET/CT imaging

Whole-body PET scans extending from the base of the skull to the proximal femurs were acquired in three-dimensional mode (3 min per bed position) using a state-of-the-art PET/CT scanner (Philips Gemini; Koninklijke Philips Electronics N.V., Hamburg, Germany; and Biograph 64 TruePoint PET/CT; Siemens AG, Forchheim, Germany). Prior to the CT scan, 1.5 ml/kg body weight of iodinated contrast agent (Iopromide, Imeron 300; Bracco Diagnostics Inc, Milan, Italy) was intravenously administered at a flow rate of 2.5 ml/s. The acquisition of the CT scan (200–250 mA, 120 kV, 64 × 0.6 mm collimation, pitch 0.6) was initiated 50 s after the intravenous injection of contrast in the portal venous phase. The emission sequence was initiated 60 min after intravenous injection of 18F-FEC. The mean radiochemical dose was 300 MBq, normalized to the patient’s body weight. Directly prior to the PET/CT scan, patients were asked to empty their bladder to minimize tracer accumulation. Emission data were reconstructed with attenuation correction derived from the CT scan. Two board-certified nuclear medicine physicians and one board-certified radiologist trained in PET/CT interpretation, working side by side, evaluated the PET/CT images together using a dedicated software package (Syngo TrueD; Siemens AG, Forchheim, Germany). Significant choline uptake was not noted in nodes <5 mm in our patient population. The number of positive nodes on PET/CT was determined by reinterpretation of the PET/CT examinations, focusing on lymph nodes that were either >10 mm along the short axis or positive on PET. The number of nodes fulfilling one or both of these criteria was recorded and correlated with the number of lymph nodes resected in each individual patient, as well as in the entire patient cohort.

2.4. Statistical analysis

Means, medians, ranges, and frequencies were recorded as descriptive statistical parameters. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and number of correctly recognized cases of PET/CT in the detection of PCa LNMs were calculated in a patient-, lesion-, and site-based analysis. All statistical analyses were performed with SPSS v.17.0 (IBM Corp., Armonk, NY, USA).

3. Results

Patient characteristics are summarized in Table 1. Median PSA value at 18F–FEC PET/CT was 6.0 ng/ml (interquartile range [IQR]: 1.7–9.4 ng/ml). All 56 patients had a positive 18F–FEC PET/CT analysis after a history of RP for PCa and subsequently underwent secondary lymphadenectomy.

3.1. Patient-based analysis

In 48 of 56 (85.7%) patients with positive 18F–FEC PET/CT findings, histologic examination confirmed the presence of LNMs of PCa (Table 2). Six of the eight patients with
false-positive results had a PSA value <2 ng/ml at the time of the PET/CT examination. For patients with a PSA value >2 ng/ml, the PPV of PET/CT analysis in the detection of LNMs was 95.5% (Table 3).

### 3.2. Lesion-based analysis

A total of 1149 lymph nodes were removed and evaluated histologically. Of these, 282 (24.5%) harbored metastasis at histopathologic analysis. The mean number of lymph nodes removed during each surgical procedure was 21 (standard deviation: ±18.3) (Table 1).

18F-FEC PET/CT correctly detected 112 of 282 (39.7%) metastatic lymph nodes (Table 2). 18F-FEC PET/CT results were falsely positive in 36 lymph nodes; 28 of the 36 (77.8%) false-positive lymph nodes were detected in patients with a PSA value >2 ng/ml at time of PET/CT. 18F-FEC PET/CT results were falsely negative in 170 lymph nodes.

18F-FEC PET/CT sensitivity, specificity, PPV, NPV, and accuracy on a per-patient and per-lesion basis stratified by PSA value at time of PET/CT are reported in Table 3.

### 3.3. Site-based analysis

Of 121 lymph node sites evaluated histologically (48 left pelvic, 45 right pelvic, 28 retroperitoneal), 18F-FEC PET/CT results were positive in 64: 50 in the pelvis and 14 in the retroperitoneum (Table 4). Of the 76 histologically positive lymph node sites, 52 were correctly identified by 18F-FEC PET/CT (68.4%). 18F-FEC PET/CT results were falsely negative in 24 sites.

18F-FEC PET/CT sensitivity, specificity, PPV, NPV, and accuracy on a per-lymph node site basis are reported in Table 4.

### 4. Discussion

Despite the good long-term outcomes after RP for localized PCa, a significant proportion of patients show long-term postprostatectomy PSA failure.

One reason for an increasing PSA level is lymph node involvement. The detection of LNMs is one of the biggest

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**Table 3 – Results according to prostate-specific antigen level at positron emission tomography/computed tomography analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Per patient (n = 56)</th>
<th>Per lesion (n = 1149 LNs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>PSA &lt;2 ng/ml (n = 12)</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PPV, %</td>
<td>85.7 (48/56)</td>
<td>50.0 (6/12)</td>
</tr>
<tr>
<td>NPV, %</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Accuracy, %</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen; LN = lymph node; PPV = positive predictive value; NPV = negative predictive value.
challenges in urologic imaging. Lymphadenectomy remains the most accurate staging modality for the evaluation of lymph node status [12]. However, not all patients harbor the same risk of LNMs. Therefore, different imaging modalities have been evaluated for the accuracy of lymph node staging.

For the detection of LNMs, conventional CT and magnetic resonance imaging (MRI) have shown similar results in the literature [12]. In a meta-analysis for both imaging modalities, sensitivity was 35% and 42%, respectively, while the reported specificity was 82% [5]. Multimodal MRI (spectroscopy, diffusion, perfusion) has shown superior performance with respect to conventional imaging, it is a valid exam for restaging of PCa patients, with better accuracy of the data analysis.

Table 4 – Results according to lymph node site

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall (n = 121)</th>
<th>Left pelvic (n = 48)</th>
<th>Right pelvic (n = 45)</th>
<th>Retroperitoneum (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, %</td>
<td>68.4 (52/76)</td>
<td>74.2 (23/31)</td>
<td>63.0 (17/27)</td>
<td>66.7 (12/18)</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>73.3 (33/45)</td>
<td>58.8 (10/17)</td>
<td>83.3 (15/18)</td>
<td>80.0 (8/10)</td>
</tr>
<tr>
<td>PPV, %</td>
<td>81.3 (52/64)</td>
<td>76.7 (23/30)</td>
<td>85.0 (17/20)</td>
<td>85.7 (12/14)</td>
</tr>
<tr>
<td>NPV, %</td>
<td>57.9 (33/57)</td>
<td>55.6 (10/18)</td>
<td>60.0 (15/25)</td>
<td>57.1 (8/14)</td>
</tr>
<tr>
<td>Accuracy, %</td>
<td>70.2 (85/121)</td>
<td>68.8 (33/48)</td>
<td>71.1 (32/45)</td>
<td>71.4 (20/28)</td>
</tr>
</tbody>
</table>

LN = lymph node; PPV = positive predictive value; NPV = negative predictive value.

5. Conclusions

A positive 18F-FEC PET/CT result correctly predicted the presence of LNM in the majority of patients, but it did not aid in localization of a large proportion of positive lymph nodes. Therefore, although 18F-FEC PET/CT can be considered as valid exam for restaging of PCa patients, with better performance with respect to conventional imaging, it is not adequately accurate for the precise estimation of extent of nodal recurrence in PCa patients with biochemical failure after RP.

Author contributions: Derya Tilki had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Tilki, Seitz.

Acquisition of data: Tilki, Reich, Hacker, Graser, Silchinger, Becker, Khoder, Bartenstein, Stief, Loidl, Seitz.

Analysis and interpretation of data: Tilki, Reich, Loidl, Seitz.

Drafting of the manuscript: Tilki, Reich, Loidl, Seitz.

Critical revision of the manuscript for important intellectual content: Tilki, Reich, Hacker, Graser, Silchinger, Becker, Khoder, Bartenstein, Stief, Loidl, Seitz.

Khoder, Bartenstein, Stief, Loidl, Seitz.

References


