The nonspecific lymph node uptake of $^{18}$F-choline in patients with prostate cancer — a prospective observational study

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Abstract

BACKGROUND: The aim of this study was to observe and characterize the nonspecific $^{18}$F-choline lymph node uptake in patients with prostate cancer.

MATERIAL AND METHODS: In this single center, prospective observational study which was done in University Hospital Center Zagreb between December 2012 and October 2014, 69 patients (median age 71 years; range 50–92) with prostate cancer were included. Patients underwent $^{18}$F-choline PET/CT for staging or restaging of prostate cancer. The mean follow-up period was 11.5 months. Kruskal-Wallis test was used to find out if the differences between SUV values of specific and nonspecific accumulation of the tracer are statistically significant.

RESULTS: Nonspecific accumulation of $^{18}$F-choline in lymph nodes was found in 36 patients (52.7%). Most of these findings (n = 24) were nonspecific accumulation of the tracer in mediastinal lymph nodes. Other sites of nonspecific tracer uptake were pulmonary hila (n = 20), inguinal lymph nodes (n = 15), and axillary lymph nodes (n = 10). Mean SUV values for mediastinal lymph nodes, pulmonary hila, axillary and inguinal lymph nodes were 4.8, 4.3, 3.1 and 4.1, respectively. Mean SUV value of nonspecific sites of tracer accumulation was lower (not significantly; p = 0.2) than tracer uptake values measured in metastases sites (bone metastases mean SUVmax value — 13.2, metastatic lymph nodes mean SUVmax value — 9.2).

CONCLUSIONS: $^{18}$F-choline PET/CT is a valuable and an established functional diagnostic imaging method for staging and restaging prostate cancer. However, nonspecific uptake of the tracer can often be seen in lymph nodes not related to primary disease. Patient history, clinical examination, laboratory tests and correlation with other imaging methods, must be taken into consideration when interpreting $^{18}$F-choline PET/CT findings.

KEY words: $^{18}$F-choline, prostate cancer, false positive uptake, pitfalls

Background

Prostate cancer is the most common malignancy in men in Europe and the US [1, 2]. Diagnostic procedure from clinical suspicion to diagnosis includes determination of PSA serum value, transrectal ultrasound (TRUS) with or without biopsy, magnetic resonance imaging (MRI), computerized tomography (CT) and bone scintigraphy in patients with highly elevated PSA values [3–5].
tissue, increased lipid synthesis is found, as well as the increased activity of choline kinase enzyme activity which increases choline uptake. On the cell level imported choline becomes part of the cell membrane, as phosphatidylcholine [8]. Physiological tracer uptake is found in the liver and pancreas, spleen, salivary and lachrymal glands. Variable uptake can be present in the bone marrow, the small and large intestines kidneys, urinary bladder and ureters [9]. 18F-choline has been recognized as a valuable imaging method for prostate cancer evaluation, notably after primary treatment has been done [10–12]. As with each diagnostic tool, apart from all the benefits and relevant data it provides, some drawbacks have been noticed. Nonspecific uptake of 18F-choline is seen in lymph nodes, whether a low-grade lymphoma or, more often, inflammatory altered inguinal, axillary or mediastinal lymph nodes, as has been reported by some scientific groups [9, 13].

The purpose of this study was to observe and characterize nonspecific lymph node uptake of 18F-choline in order to expand the awareness of broader physiological 18F-choline uptake.

Material and methods

Design and setting

This prospective observational study was done in University Hospital Center Zagreb from December 2012 till October 2014.

Participants

Sixty nine patients underwent 18F-choline PET/CT for staging or restaging of their disease. The patients have been referred from their oncologists mostly because of increased PSA values observed after primary therapy.

Their median age was 71 years, range 50–92 years. The median PSA value was 5.3 ng/ml (doubling time less than 6 months in 9 patients). PSA values exceeding 0.2 ng/ml for patients with radical prostatectomy and 2 ng/ml higher than the lowest known PSA value for patients with only radiotherapy treatment were considered as biochemical relapse. PSA values that doubled in less than 6 months without any disease progression observed, was at least 6 months without any disease progression observed.

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18F-choline PET/CT examination

All patients fasted 6 hours before the examination. Mean administered activity was 183 MBq (4.9 mCi) of 18F-choline (2 MBq/kg. IASOcholine was purchased from IASON GmbH A-8054 Graz-Seiersberg, Austria). The whole-body PET/CT was acquired 20 minutes after the intravenous F-choline administration (Siemens Biograph mCT, Siemens Medical Solutions USA, Inc., USA PET/CT; 3 minutes per bed position).

The follow-up was at least 6 months, median 11, range 6–22 months.

Interpretation of 18F-FDG PET/CT scans

All PET/CT scans were interpreted by two board-certified nuclear medicine physicians (DH, AM). An increased uptake was defined as focal activity higher than that of surrounding background tissue not located in areas of physiological 18F-choline uptake, without similar activity seen on the contralateral side. SUV value was calculated for each lesion. A normal uptake was defined as no abnormal 18F-choline uptake.

As true positive were considered patients with clearly visible increased uptake in the lymph nodes or bone structures in the regions where prostatic cancer metastases can be often found (pelvis, central skeleton). Those patients received further treatment (most often radiotherapy or hormonal therapy) suggested by their referring physicians.

Reference standard

In patients with increased tracer uptake in easily reachable lymph nodes a fine needle aspiration cytology (FNAC) or biopsy was performed. A true negative finding was noted if the FNAC or biopsy analysis reported a benign lesion or the follow-up period was at least 6 months without any disease progression observed.

Ethics

Signed informed consent was obtained from all patients for imaging and using patient data for further research.

Statistical analyses

Kruskal-Wallis test was used to determine differences between SUV values of specific and nonspecific accumulation of the tracer.

Results

Specific accumulation of the tracer

True positive focal uptake in prostate bed (local recurrence) was found in 6 (9%) patients, with a mean SUVmax value of 10.2. Bone metastases were found in 15 patients (21.7%; SUVmax mean value 13.2, range 4.7–21.3). True positive findings in the abdominal, retroperitoneal (Figure 1) and iliac lymph nodes were noted in 27 patients (39.1%, SUVmax mean value 9.2, range 3.9–16.1) (Table 2). Pulmonary metastases have been observed in two patients with the SUVmax values of 6.8 and 2.3. All of our patients with positive findings and tracer uptake in abdominal lymph nodes, bone and lung metastases were scheduled for subsequent treatment, mostly radiotherapy.

Nonspecific accumulation of the tracer

Nonspecific tracer uptake to the lymph nodes was observed in 36 patients (52.7%). Most of the false-positive lymph nodes were identified in the mediastinum (24 patients; mean SUVmax value of 4.8) (Figure 2), and pulmonary hila (20 patients, mean SUVmax of 3.8) (Figure 2), and pulmonary hila (20 patients, mean SUVmax...
values of 4.3). The uptake in axillary lymph nodes was found in 10 patients with a mean SUVmax value of 3 and in inguinal lymph nodes in 15 patients (Figure 3), with mean SUVmax value of 4.1 (Table 3).

Median PSA value in patients with nonspecific tracer uptake was 5.8, while it was found to be 8.8 in patients with 18F-choline true positive lesion (not statistically significant, p = 0.2).

Table 2. 18F-choline true positive focal lesions

<table>
<thead>
<tr>
<th>Location</th>
<th>Patients (n = 35)</th>
<th>Mean SUVmax value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate bed (local recurrence)</td>
<td>6 (8.7%)</td>
<td>10.2</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>15 (21.8)</td>
<td>13.2</td>
</tr>
<tr>
<td>Abdominal lymph node metastases</td>
<td>27 (39.1%)</td>
<td>9.2</td>
</tr>
</tbody>
</table>

SUV — standardized uptake value

Discussion

Results of this study showed that in over half of our patient population, nonspecific sites of tracer uptake have been observed in lymph nodes out of the pelvis, not suggestive for prostate cancer metastases. The obtained SUV values in those uptake sites were lower than in metastatic sites, but not enough to be statistically significant. In most cases, we have observed accumulation of 18F-choline in the mediastinal lymph nodes (35% of patients). The main limitation of our study is that pathohistological confirmation has not been performed, but during patient follow-up there have been no evidence of disease progression, rise in PSA levels or patient deaths due to prostate cancer. Additional ultrasound exami-
nation with fine needle aspiration cytology of axillary and inguinal lymph nodes with low tracer uptake has shown fatty infiltration in four patients and a relapse of low grade lymphoma in one patient. No similar false positive, nonspecific radiotracer uptake was found in abdominal or pelvic lymph nodes, making the interpretation easier. In the minimal 6 month follow-up (median of 11.5 months), no clinically apparent sign of disease progression was found, pertaining to patients with nonspecific lymph node uptake. Other limitations of this study were relatively small sample size and clustering patients with variable disease stages and treatment options. Also, in patients with very suggestive findings for prostate cancer metastases (local recurrence in pelvis, central skeleton) we didn’t obtained final pathology confirmation since referring physicians ordered a further therapy without any delay.

Variability in physiological distribution, pitfalls and image artifacts of F-18-FDG has been the topic of numerous articles [14, 15], and the same considerations should be made when imaging with 18F-choline. Up to date only one study (Rietbergen et al [13]) reported similar percentage of patients with nonspecific choline uptake, not pertaining to prostate cancer disease extent. Liu et al [16] have shown increased choline uptake in various thoracic diseases, such as sarcoidosis, noncaseating granuloma, tuberculosis and lymphomas. 18F-choline accumulation is found to be specific in true positive lesions with a prevailing morphological and statistical correlate. Nonspecific tracer uptake will follow an increased cell membrane production not connected to prostate cancer, but rather due to acute or chronic inflammatory process or low grade immunoproliferative diseases.

18F-choline PET/CT is considered a particularly useful diagnostic tool in several stages of patient care, with the added information gained from revealing multiple pathophysiological processes. It has found its role especially in restaging prostate cancer patients, with the recommended use in patients with PSA levels > 1 ng/ml following radical disease treatment [6]. Increasing demands of imaging modalities have been observed in recent years because of aging population, screening methods and growing incidence of prostate cancer.

The need for unequivocal disease extent estimation has introduced functional imaging methods, such as 18F-choline PET/CT, in regular clinical practice [17], and the future of prostate cancer imaging will lie in the more specific radiotracers, such as the PSMA tracer [18–20].

### Conclusions

Although 18F-choline PET/CT has demonstrated valuable information in staging and restaging of prostate cancer, moderate tracer accumulation in lymph nodes out of the pelvis should be carefully evaluated since in many cases it is false positive. Variability in physiological uptake, as well as benign causes of accumulation, such as inflammation, should be kept in mind when interpreting unusual sites of increased uptake, with no association with the primary disease. Recognizing the importance of patient follow-up is crucial.

### References