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[18F]fluoromethylcholine (FCH) positron emission tomography/computed tomography (PET/CT) for lymph node staging of prostate cancer: a prospective study of 210 patients

Mads H. Poulsen*§, Kirsten Bouchelouche†, Poul F. Høilund-Carlsen†§, Henrik Petersen†, Oke Gerke†, Signe Inglev Steffansen†, Niels Marcussen‡§, Niels Svolgaard*, Werner Vach¶, Ulla Geertsen* and Steen Walter*§

*Departments of *Urology, †Nuclear Medicine, and ‡Pathology, Odense University Hospital, §Institute of Clinical Research, University of Southern Denmark, Odense, Denmark, and ¶Clinical Epidemiology, Freiburg University Medical Center, Germany*

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What's known on the subject? and What does the study add?
Staging of patients with prostate cancer is the cornerstone of treatment. However, after curative intended therapy a high portion of patients relapse with local and/or distant recurrence. Therefore, one may question whether surgical lymph node dissection (LND) is sufficiently reliable for staging of these patients.

Several imaging methods for primary LN staging of patients with prostate cancer have been tested. Acceptable detection rates have not been achieved by CT or MRI or for that matter with PET/CT using the most common tracer fluoromethylcholine (FCH). Other more recent metabolic tracers like acetate and choline seem to be more sensitive for assessment of LNs in both primary staging and re-staging. However, previous studies were small. Therefore, we assessed the value of [18F]FCH PET/CT for primary LN staging in a prospective study of a larger sample and with a 'blinded' review. After a study period of 3 years and >200 included patients, we concluded that [18F]FCH PET/CT did not reach an optimal detection rate compared with LND, and, therefore, it cannot replace this procedure. However, we did detect several bone metastases with [18F]FCH PET/CT that the normal bone scans had missed, and this might be worth pursuing.

OBJECTIVES

- To assess the value of [18F]fluoromethylcholine (FCH) positron emission tomography/computed tomography (PET/CT) for lymph node (LN) staging of prostate cancer.
- To evaluate if FCH PET/CT can replace LN dissection (LND) for LN staging of prostate cancer, as about one-third of patients with prostate cancer who receive intended curative therapy will have recurrence, one reason being undetected LN involvement.

PATIENTS AND METHODS

- From January 2008 to December 2010, 210 intermediate- or high-risk patients had a FCH PET/CT scan before regional LND.
- After dissection, the result of histological examination of the LNs (gold standard) was compared with the result of FCH PET/CT obtained by 'blinded review'.
- Sensitivity, specificity, positive (PPV), and negative predictive values (NPV) of FCH PET/CT were measured for detection of LNe metastases.

RESULTS

- Of the 210 patients, 76 (36.2%) were in the intermediate-risk group and 134 (63.8%) were in the high-risk group. A medium (range) of 5 (1–28) LNs were removed per patient.
- Histological examination of removed LNs showed metastases in 41 patients. Sensitivity, specificity, PPV, and NPV of FCH PET/CT for patient-based LN staging were 73.2%, 87.6%, 58.8% and 93.1%, respectively.
- Corresponding values for LN-based analyses were 56.2%, 94.0%, 40.2%, and 96.8%, respectively.
- The mean diameter of the true positive LN metastases was significantly larger than that of the false negative LNs (10.3 vs 4.6 mm; $P < 0.001$).
- In addition, FCH PET/CT detected a high focal bone uptake, consistent with bone metastases, in 18 patients, 12 of which had histologically benign LNs.

CONCLUSIONS

- Due to a relatively low sensitivity and a correspondingly rather low PPV, FCH PET/CT is not ideal for primary LN staging in patients with prostate cancer.
- However, FCH PET/CT does convey important additional information otherwise not recognised, especially for bone metastases.

KEYWORDS

prostate cancer, lymph node staging, [18F]-fluorocholine, choline, FCH, PET, PET/CT

INTRODUCTION

The treatment of patients with prostate cancer relies on the stage of the disease. Patients with localised prostate cancer are offered curative therapy. In contrast, patients with disseminated prostate cancer are incurable and offered life prolonging treatment and palliation. Hence, the stage of prostate cancer is crucial for the choice of treatment, course of the disease, and the life of the patient [1,2].

Today, the standard for lymph node (LN) staging of prostate cancer is pelvic LN dissection (LND) [1]. The extent of the LND is still debated, although the trend is toward extended LND [3]. But, however large the dissection might become, it still may fail to identify LN metastases present outside the region of the LND [4]. Currently 30–40% of patients treated with curative therapy relapse [5–7]. It is estimated that half of these relapses are due to metastatic disease [8], mainly caused by LN metastases that were overlooked at the primary staging [9].

New methods for LN staging of prostate cancer are emerging within the field of imaging, bringing promise of more extensive staging with fewer complications [10]. PET/CT is one such method, combining the anatomy of CT with the cellular function depicted by PET. Prostate cancer cells of the primary cancer and its metastases have an up-regulation of choline kinase. This induces an elevated uptake of choline for the synthesis of phospholipids. Once inside the cell, choline is phosphorylated and thereby trapped within the cell. By radioactive labelling of choline PET/CT imaging enables the differentiation of prostate cancer cells from neighbouring non-malignant tissue [11,12].

The aim of the present study was to prospectively assess the value of [^{18}F]fluoromethylcholine (FCH) PET/CT for LN staging of prostate cancer and to subsequently evaluate if FCH PET/CT could replace LND for LN staging of prostate cancer.

PATIENTS AND METHODS

From January 2008 to December 2010, 210 consecutive patients with newly diagnosed prostate cancer and a metastases-negative γ-camera whole-body bone scan were enrolled; another 32 patients either did not want to participate or discontinued. In cases of doubt an MRI was used to exclude bone metastases. All were scheduled for intended curative therapy, i.e. radical prostatectomy or external beam radiotherapy. All patients met the following inclusion criteria: (i) Gleason score >6 and/or, (ii) a PSA concentration of >10 ng/mL and/or (iii) a T3 cancer. The exclusion criteria were: (i) withdrawal of informed consent, (ii) a TNM stage of T4, (iii) detection of bone metastases, or (iv) prior or active androgen-deprivation therapy. The study was approved by the Regional Ethics Committee and registered at ClinicalTrails.gov. All participants gave oral and written-informed consent to participate, and all accepted 'blinding' of the FCH PET/CT results.

RADIOPHARMACEUTICALS AND IMAGING PROTOCOL

[^{18}F]FCH was produced on the TracerLab MXFDG automated synthesis system via alkylation of dimethylaminoethanol with [^{18}F]fluorobromomethane [13]. The [^{18}F]FCH was obtained in a radiochemical purity >99% as shown by HPLC. The decay-corrected reaction yield was 7.3 ± 2.62% on average.

PET/CT data were acquired by a Discovery VCT PET/CT scanner (GE Healthcare, UK) [14]. A diagnostic CT scan (64-slice helical, 120 kV, 'smart mA' maximum 400 mA), was acquired using *in vivo* contrast medium from the base of the skull to mid-thigh. PET of the same region was obtained with an acquisition time of 2.5 min per bed position. CT, PET and fused PET/CT data were analysed on a GE Healthcare Advantage Workstation v.4.4. FCH PET/CT scans were interpreted considering regional and distant metastases, and were assessed both as CT alone and as PET/CT, but results in the present study were based solely on the FCH PET/CT data, whereas the CT scan was used for clinical purposes. The first 110 scans were interpreted by one nuclear medicine specialist and an onco-radiologist, whereas the remaining 100 scans were interpreted by the same nuclear medicine specialist, who at the same time was a CT specialist. Patients fasted for 6 h before the i.v. administration of radiotracer, each receiving 4 MBq/kg body weight [15]. In all PET/CT-scans, acquisition started ≈60 min after injection of the radio-tracer. The results of the FCH PET/CT scans were not available to the surgeon and the pathologist, and vice versa. The FCH PET/CT scans were obtained up to 2.5 weeks before the LND.

SURGICAL TECHNIQUE

An open retroperitoneal bilateral LND was undertaken through a midline incision, either as part of the radical prostatectomy or as an individual operation. The LND was performed along the medial side of the external iliac vessels from the femoral canal up to the bifurcation of the internal and external iliac vessels, including the obturator fossa. The LND included most of the LNs of the external iliac, obturator, and hypogastric nodes. The specimens were prospectively mapped according to their anatomical location.

HISTOLOGICAL EXAMINATION

The specimens were processed according to standard protocols. The LNs were counted; small LNs were divided in two along the longitudinal axis whereas larger ones were cut into more slices to allow all LN tissue to be embedded and included. The tissue was cut into 3–4 μm thick sections that were stained with haematoxylin and eosin. In unclear cases, the sections were stained immunohistochemically with antibodies against pan-cytokeratin or PSA.

STATISTICAL ANALYSIS

The binary outcome variable 'metastases in the regional lymph nodes' (yes/no) was used to estimate the diagnostic usefulness of FCH PET/CT. Sensitivity, specificity, positive and negative predictive value (PPV and NPV) were calculated in a per patient- and a per LN-based analysis, with two-sided 95% Wilson-score CIs [16]. For LN-based analyses, robust sandwich variance estimators were used to account for the clustered data of LNs within patients. Size of true positive vs false negative LNs was compared by the Wilcoxon rank-sum test.

RESULTS

The characteristics of the 210 patients are presented in Table 1. The median age of the patients was 65 years and about a quarter were stage T1, another quarter were T2 and nearly half were T3. The median PSA

TABLE 1 Characteristics of the patient population

Variable	Value
Total number of patients	210
Age, years:	
Mean (SD)	65.5 (5.4)
Median (range)	65 (50–76)
PSA concentration, ng/mL	
Mean (SD)	20.3 (18.5)
Median (range)	12 (1–108)
N (%):	
Clinical stage (range T1b to T3b):	
T1	59 (28.1)
T2	57 (27.1)
T3	94 (44.8)
Pathological Gleason score (range 5–9):	
<7	19 (9.0)
7	133 (63.3)
>7	58 (27.6)
D'Amico risk group:	
Intermediate	76 (36.2)
High	134 (63.8)

TABLE 2 Patient-bases results for the 210 patients

	Histology		
Metastases	+	–	Total
FCH PET/CT			
+	30	21	51
–	11	148	159
	41	169	210

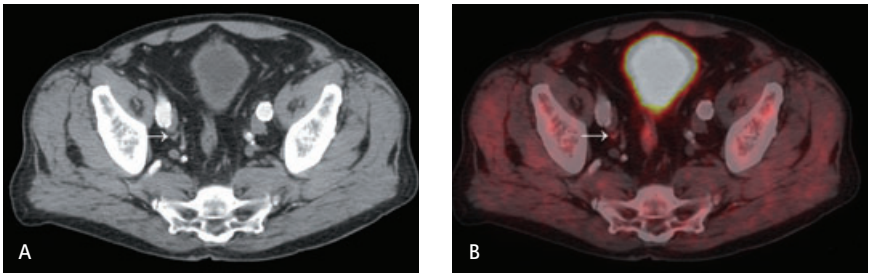
TABLE 3 Sensitivity, specificity, PPV, NPV, and number of correctly recognised cases with FCH PET/CT in the detection of LN metastases (210 patients, 1093 LNs)

%	Patient analysis	LN analysis
Sensitivity (95% CI)	73.2 (58.1–84.3)	56.2 (39.4–73.0)
Specificity (95% CI)	87.6 (81.8–91.7)	94.0 (91.7–96.4)
PPV (95% CI)	58.8 (45.2–71.3)	40.2 (28.0–52.4)
NPV (95% CI)	93.1 (88.0–96.1)	96.8 (95.1–98.5)
No. correctly recognised cases % (95% CI)	84.8 (79.3–89.0)	91.5 (88.9–94.1)

TABLE 4 Characteristics of LNs from the LND

Characteristic	Value
Total no. of LNs removed	1093
LNs without metastatic deposit, n	1020
LNs with metastatic deposit, n	73
No. of LNs removed per patient	
Mean (SD)	5.2 (2.9)
Median (range)	5 (1–28)

*FIG. 1. Images of patient number 28, who had a histopathologically confirmed LN metastasis within the external iliac LNs at the right side. In **A**, a conventional CT, there was an unenlarged LN of 7 mm. In **B**, the corresponding FCH PET/CT scan, there was a pathological high tracer uptake at the same unenlarged LN, which harbored the metastasis.*



concentration was 12 ng/mL and almost three-quarters had a Gleason score of ≤7, while about two-thirds were in the D'Amico high-risk group.

From the 210 patients in the study, 1093 LNs were removed corresponding to a mean of 5.2 LNs/patient. In all, 41 patients (19.5%) had histological confirmed LN metastases. The number of metastases per patient ranged from one to seven, with only one in 24 and two in 11 patients. In all, 73 LNs (6.7%) harboured metastases. In the region of the LND, PET/CT showed high FCH uptake, consistent with metastases in 51 patients from a total of 102 LNs.

In the per patient-based analysis there was agreement between the histological examination of the LNs removed and FCH PET/CT in 30 of the 41 patients who harboured metastases, in other words, FCH PET/CT missed metastases in 11 patients or 26.8% of patients with metastases. At the same time, FCH PET/CT was false positive in another 21 patients. This gives a sensitivity of 73.2%, a specificity of 87.6%, a PPV of 58.8%, and a NPV of 93.1%. Further results are given in Tables 2–4. An example of a FCH PET/CT scan of a patient with a LN metastasis is shown in Fig. 1.

In the per LN-based analysis there was agreement between the histological examination of the LNs removed and FCH PET/CT in 41 of the 73 LNs that harboured metastases, i.e. sensitivity 56.2%, specificity 94.0%, PPV 40.2%, and NPV 96.8%. For further results and comparison with the patient-based analysis see Tables 3–5.

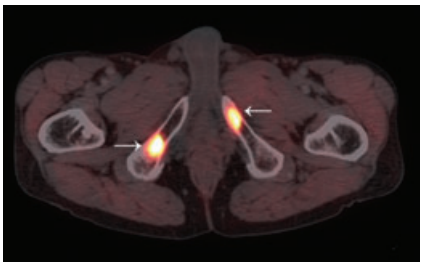
The mean (range) diameter of the metastatic deposits within the LNs removed was 7.8 (0.4–25) mm. The true positive lymph nodes were significantly larger with a mean (SD) diameter of 10.3 (5.5) mm than the size of metastatic deposit of the false negative nodes at 4.6 (3.1) mm ($P < 0.001$).

A fair number of patients had additional findings: 19 patients with benign LNs harvested at LND showed increased FCH uptake, consistent with metastases, in LNs located in adjacent areas in the pelvis or lower abdomen. Furthermore, six patients with histologically confirmed metastases at

TABLE 5 LN-based results (1093 LNs)

	Histology		
Metastases	+	–	Total
FCH PET/CT			
+	41	61	102
–	32	959	991
Total	73	1020	1093

FIG. 2. Images of patient number 30. At the histopathological examination after the LND, we did not detect any metastases, and the bone scan was normal. The FCH PET/CT scan showed normal LNs, but pathologically high tracer uptake in the os pubis bilaterally was consistent with bone metastases.



the LND also had FCH positive LNs in adjacent regions.

Looking beyond LNs, FCH PET/CT detected a high focal bone uptake, consistent with one or more bone metastases, in 18 patients, 12 of which had histologically benign LNs at the LND. An example is seen in Fig. 2.

We did not detect any unknown malignancies, and none of the PET/CT scans were associated with complications.

DISCUSSION

In the present study, there was a rather low sensitivity and a low PPV with FCH PET/CT suggesting that this imaging approach in its present form is not ideal for primary LN staging of prostate cancer, and, therefore, cannot replace LND.

Instead could FCH PET/CT be used as a 'gatekeeper' for LND, meaning that a positive FCH PET/CT should be followed by LND? This indeed would have reduced the number of patients in the present study that needed a LND from 210 to 51. However, in doing this, we would have missed 11 of 41 patients with LN metastases, and, therefore, FCH PET/CT is hardly sufficiently accurate for this purpose either.

Only three other clinical trials on primary LN staging of prostate cancer with FCH PET or PET/CT with choline derivatives in the materials and comprising ≥50 patients have been published [17–19]. Beheshti *et al.* [17] obtained with FCH in a per patient-based analysis of 130 patients, a sensitivity of 45% [95% CI 29–62%] and a specificity of 96% [95% CI 89–99%]. In comparison, Schiavina *et al.* [18] and de Jong *et al.* [19] who used [^{11}C]choline found in 57 and 67 patients, respectively, sensitivities of 60% [95% CI 32–83%] and 80% [95% CI 57–98%] and specificities of 98% [95%CI 87–100%] and 96% [95% CI 84–99%], respectively. Thus, the present results (sensitivity 73.2%, specificity 87.6%) were somewhat in between, but with values not high enough to recommend FCH PET/CT for primary LN staging of prostate cancer.

However, various circumstances should be considered before discarding FCH PET/CT as a staging method in prostate cancer in general. When comparing [^{11}C] and [^{18}F] choline studies, one has to assume that the tracers perform equally, which from a chemical point of view there is no particular reason to believe. These are different isotopes, their presence and location in the molecule and their influence on the final tracer's *in vivo* behaviour, including its specificity and affinity for prostate cancer, has never been fully explored. Whether one uses [^{18}F]FCH or [^{18}F]fluoroethylcholine may also play a role. Direct comparisons of [^{11}C]choline PET/CT and FCH PET/CT for imaging of prostate cancer has never been performed, although *in vitro* studies show that FCH closely mimics the natural processes of both [^{11}C]choline and choline [12,20], suggesting that [^{11}C]choline and FCH may perform uniformly for the detection of prostate cancer cells. The limited spatial resolution of PET of 2–4 mm makes it difficult to detect very small foci [21]. On the other hand, a high specific activity and a very intense local tracer accumulation may to some extent overcome this limitation. Further, the inter- and intra-observer variability in evaluating PET/CT images is widely unknown and objective evaluation approaches based on standardised uptake value measurements may increase the diagnostic accuracy. The ideal time of acquisition after administration of tracer is also unknown [22,23]. Finally, choline is a metabolic tracer that is not specific for prostate cancer, as it may accumulate also in inflammatory tissue [24]. However, the present study suggests that this problem does not cause a clinically unacceptably low specificity.

In the future, several of these factors must be clarified and considered together with other variables, e.g. genetic and histopathological properties, the speed of growth, the aggressiveness and the hormone susceptibility of the tumour and its metastases. All this can be taken into account with molecular imaging as opposed to structural imaging with CT and MRI, and, therefore, we intend to examine this method further and if possible optimise its clinical use in prostate cancer. If one considers also the series of new and potentially more specific prostate cancer tracers that are under investigation, it seems likely the clinical effect of molecular imaging will continue to grow and offer further improvement in the management of prostate cancer [25].

When reviewing the additional findings, we found 25 patients with elevated FCH uptake in LNs in the adjacent areas, 19 of which had benign histology at LND. Because of the close vicinity to the LND zone it seems fair to assume that some of these LNs were in fact malignant. Our PPV of 58.8% with the per patient-based analysis suggests that 11 of the 19 patients would harbour metastases solely outside the zone of the LND. In addition, FCH PET/CT detected a high focal bone uptake, consistent with bone metastases, in 18 patients, 12 of which had histologically benign LNs at LND. In another setting, we found with FCH PET/CT a PPV of 82% for the detection of bone lesions [26]. These additional findings may be clinically noteworthy: the LN findings support the current trend towards a more extensive LND as some of the metastases are solely at more distant locations [3]. The bone findings align with Even-Sapir *et al.* [27] and Schirrmeister *et al.* [28] who found that the bone scan might be suboptimal for M-staging of prostate cancer, and with Langsteger *et al.* [29] who recently reported a sensitivity of 91% and specificity of 83%

for detection of bone metastases in patients with prostate cancer using FCH PET/CT, in a per patient-based analyses.

For LN staging, FCH PET/CT may have failed, so far, in outperforming the traditional LND. However, compared with other imaging methods, e.g. CT, MRI, and ProstaScint (γ-camera imaging with indium-111-labeled monoclonal antibody to prostate-specific membrane antigen) and their respective reported sensitivities of 39%, 42%, and 62%, and specificities of 82%, 82%, and 72%, FCH PET/CT performs remarkably well [30,31].

A limitation of the present study was the relatively few LNs removed per patient. Today, it is recommended that LND should be extended [1], presumably with removal of ≥20 LNs. When we designed the present study back in 2006 the urological and pathological guidelines were different from today, and the trend towards an extended LND was less clear. Therefore, in the present study, we did not perform an extended LND. Still, the present study did provide results of a prospective and 'blinded' direct comparison of 210 patients with 1093 LNs after LND, which included most of the external iliac, obturator, and hypogastric LNs. We find it hard to believe that further LNs in adjacent areas would be easier to detect by PET/CT, so that this in itself could change our data in a decisive way. We see rather a necessity to improve and optimise PET-imaging methods based on the underlying pathology and the patient's individual differences, which molecular imaging have special opportunities to meet.

In conclusion, FCH PET/CT is not ideal for primary LN staging in prostate cancer, due to a relatively low sensitivity and a correspondingly rather low PPV. However, FCH PET/CT does convey important additional information otherwise not recognised, especially for bone metastases.

CONFLICT OF INTEREST

None declared.

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Correspondence: Mads Hvid Poulsen, Department of Urology, Odense University Hospital, DK-5000 Odense C, Denmark.
e-mail: mads.poulsen@webspeed.dk

Abbreviations: **LN(D)**, lymph node (dissection); **FCH**, fluoromethylcholine; **(P)(N)PV**, (positive) (negative) predictive value.