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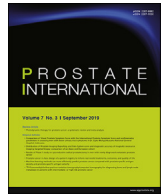
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Original Article

¹⁸F-Fluoromethylcholine-positron emission tomography/computed tomography for diagnosing bone and lymph node metastases in patients with intermediate- or high-risk prostate cancer

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ABSTRACT

Background: The use of molecular imaging in staging of prostate cancer (PC) is debated. In patients with newly diagnosed PC we investigated the diagnostic value of ¹⁸F-fluoromethylcholine positron emission tomography/computed tomography (¹⁸F-FCH-PET/CT) for the detection of bone and lymph node metastases compared to whole-body bone scintigraphy (WBS) with technetium-99-methylene diphosphonate (^{99m}Tc-MDP) and results of extended pelvic lymph node dissection, respectively.

Materials and methods: Between January 2013 and April 2016, 143 patients, aged 49–83, mean 69, years with newly diagnosed PC and disease characteristics necessitating WBS underwent both WBS and ¹⁸F-FCH-PET/CT using magnetic resonance imaging as standard. Eighty of these patients underwent pelvic lymph node dissection as part of radical prostatectomy or prior to external beam radiation and in these results of ¹⁸F-FCH-PET/CT were compared to histologic findings.

Results: Bone metastases were detected in 8/143 patients and sensitivity and specificity of WBS were 37.5% and 85.2% versus 100.0% and 96.3% with ¹⁸F-FCH-PET/CT, $P=0.63$ and 0.002 , respectively. Histologically confirmed metastases to regional lymph nodes were found in 25/80 patients. Suspicious choline uptake on PET/CT in pelvic lymph nodes was found in 35 patients. Sensitivity, specificity, PPV, NPV and accuracy of ¹⁸F-FCH-PET/CT in detection of lymph node metastases were 62.5%, 69.6%, 46.9%, 81.3% and 67.5%, respectively.

Conclusions: Findings in this study suggested that ¹⁸F-FCH-PET/CT is a more sensitive and specific method for detection of bone metastases from PC than WBS and could potentially reduce the need for confirmatory imaging if used instead of WBS. However, ¹⁸F-FCH-PET/CT performs sub-optimally in pre-operative staging of lymph node metastases in patients undergoing extended pelvic lymph node dissection.

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1. Introduction

As the incidence of prostate cancer (PC) is high and still rising in several Western countries, the number of patients receiving treatment for their PC is also increasing.¹ The therapeutic approach is highly dependent on the stage of the disease, and definitive staging at the time of diagnosis is therefore crucial.

Despite limitations, the method of choice for detecting bone metastases is still whole-body bone scintigraphy (WBS), with its relatively low cost and high availability.^{2,3} In regard to lymph node staging, other current imaging modalities have proven to be sub-optimal. Pathological studies have shown that there is no clear-cut correlation between lymph node size and malignancy,⁴ and imaging modalities solely relying on morphology often do not detect small metastatic deposits.⁵ As of now, the use of any sort of imaging in lymph node staging is discouraged by European guidelines, with pelvic lymph node dissection being the only reliable tool for definitive staging of lymph node status.⁶

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With the improved availability of positron emission tomography/computed tomography (PET/CT), there might be better options in the future for staging of PC. PET/CT already plays a role in staging and diagnosis of several other cancers, with radiolabeled fluorodeoxyglucose (FDG) being the most widely used tracer. Early studies on FDG-PET/CT in PC showed that FDG was not suitable for bone or lymph node staging in patients with relatively well-differentiated tumors.^{7,8} Only in cases with highly dedifferentiated tumors or neuroendocrine tumors, FDG-PET/CT might play a role in staging and management.^{9,10}

Radiolabeled choline is the most commonly used PET tracer in PC management. Choline is a precursor for phosphatidylcholine, a phospholipid that is integrated in the cell membrane, making it a marker for cell membrane turnover and metabolism.¹¹ With the use of radiolabeled choline, it should, therefore, be possible to detect metastases to bone earlier as they are actually bone marrow and not bone matrix metastasis¹²—as only structural changes in the bone substance is detectable with WBS and other indirect imaging modalities.

The purpose of this study was to prospectively compare the diagnostic value of ¹⁸F-fluoromethylcholine-PET/CT (¹⁸F-FCH-PET/CT) and WBS in patients with newly diagnosed PC necessitating WBS and to evaluate the ability of ¹⁸F-FCH-PET/CT to detect lymph node metastases in patients undergoing extended pelvic lymph node dissection.

2. Patients and methods

Between January 2013 and April 2016, we identified 163 eligible patients with newly diagnosed PC and disease characteristics necessitating WBS according to European guidelines.¹³ All patients were scheduled for ¹⁸F-FCH-PET/CT in addition to the conventional WBS. Patients referred from other clinics in the region were included knowing that their locally performed WBS was negative because this was a prerequisite for referral to our university clinic serving the entire region with surgical treatment of PC. In cases of conflicting results, magnetic resonance imaging (MRI) of the suspicious region was performed as reference standard. The study was approved by the local ethics committee (S-20120047) and the Danish Data Protection Agency and was registered at clinicaltrials.gov (NCT02232685). Written informed consent was obtained from all participants.

2.1. PET/CT imaging

¹⁸F-FCH-choline was produced on automated synthesis systems via alkylation of dimethylaminoethanol with ¹⁸F-fluorobromomethane. The ¹⁸F-FCH was obtained in a radiochemical purity >99% as shown by high-performance liquid chromatography. The decay-corrected reaction yield was $7.3 \pm 2.62\%$ on average. PET/CT data were acquired on Discovery VCT, Discovery STE, Discovery RX, or Discovery 690 scanner (GE Healthcare, UK).^{14,15} A helical diagnostic CT scan was acquired with *in vivo* contrast (Ultravist 370 I/ml) using a standard CT protocol with a scan field of view of 70 cm. Data were reconstructed with a standard filter into transaxial slices with a field of view of 50 cm, matrix size of 512×512 (pixel size 0.98 mm), and a slice thickness of 3.75 mm. CT scan was followed immediately by a PET scan performed using a standard whole-body acquisition protocol, with 6–7 bed positions, a slice overlap of 7 (STE, VCT, and RX) or 11 (690), and an acquisition time of 2.5 min per bed position. The scan field of view was 70 cm. Attenuation correction was based on the CT scan. PET data were reconstructed into transaxial slices with a matrix size of 128×128 , with the pixel size of 5.47 mm (STE, VCT, and RX), or 256×256 , with the pixel size of 2.74 mm (690), and a slice thickness of 3.75 mm using iterative 3D ordered subset

expectation maximisation (2 iterations, 28 subsets). Corrections for attenuation, randoms, dead time, and normalization were carried out inside the iterative loop. Analysis of CT, PET, and fused PET/CT data was carried out on a GE Advantage Workstation, version 4.4 (GE Healthcare, UK). Patients fasted for 6 hours before administration of tracer, and each patient received a dose of 4 MBq per kg body weight of tracer.

2.2. Whole-body bone scan

Whole-body planar imaging in anterior and posterior positions was acquired 3 hours after injection of 600 MBq ^{99m}Tc-hydroxymethylene diphosphonate using a dual head gamma camera (PRISM XP2000 or Skylight; Philips Medical, UK; with a low-energy high-resolution (LEHR) collimator, energy window of 140 keV \pm 20%, matrix of 256×1024 , and scan speed of 14 cm/min).

2.3. Magnetic resonance imaging

MRI was performed according to department standard for evaluation of bone metastatic disease. All patients were scanned using sagittal T1 and T2 STIR or T2m Dixon sequences supplemented by axial T1 and T2 when clinically indicated.

2.4. Image interpretation

All WBS were analyzed according to normal procedure at our institution or at other local departments in patients referred from other parts of the country. All ¹⁸F-FCH-PET/CT scans were analyzed visually by an experienced nuclear medicine specialist and an oncoradiologist. In patients with conflicting results on WBS and ¹⁸F-FCH-PET/CT, the MRI was analyzed by an experienced oncoradiologist with special knowledge on MRI.

2.5. Lymph node dissection

In patients in whom lymph node dissection was indicated, an extended pelvic lymph node dissection was performed covering the obturator, internal iliac, and external iliac nodes along the iliac vessels to the ureteric crossing, as recommended by current guidelines.⁶ This was performed either during robot-assisted radical prostatectomy or laparoscopically before radiotherapy.

2.6. Histological examination

Removed lymph nodes were examined according to standard procedures. All lymph nodes from each sample were counted. All removed lymphatic tissue was cut into 3- to 4- μ m-thick segments and stained with hematoxylin and eosin stain.

2.7. Statistical tests

Patient demographics were analyzed using descriptive statistics. The target variables “metastases to bone” (yes/no) and “metastases to regional lymph nodes” (yes/no) were used to evaluate the diagnostic performance of WBS and ¹⁸F-FCH-PET/CT for diagnosis of bone metastases and ¹⁸F-FCH-PET/CT alone for the diagnosis of regional lymph node metastases. Sensitivity and specificity were calculated with two-sided 95% Wilson score confidence intervals (CIs) in both settings. Positive predictive value, negative predictive value, and accuracy were calculated only with respect to lymph node data. Equality between the imaging modalities with respect to sensitivity and specificity was tested by using exact McNemar significance probabilities. Only per-patient analysis was performed. Intergroup comparison of lymph node sizes was performed by two-

Table 1
Patient characteristics.

Age, years	69 (49–83)
PSA, ng/mL	18 (1.4–327)
Gleason score	7 (6–10)
Clinical stage	
cT1 (%)	20 (14)
cT2 (%)	37 (26)
cT3 (%)	85 (59)
cT4 (%)	1 (1)

Median (range) for age, PSA, and Gleason score. PSA, prostate-specific antigen.

sample Wilcoxon rank-sum test. All analyses were performed by using Stata/IC 15.0 (StataCorp, College Station, Texas, USA).

3. Results

A total of 163 men were recruited. Twelve were excluded due to withdrawal of consent ($N = 8$), choline production failure ($N = 3$), or forwarded date of surgery ($N = 1$). In addition, another eight patients, included in the early phase of the study with low-risk PC, were excluded from data analysis to better reflect the population necessitating WBS. Characteristics of the thus included 143 patients are given in Table 1.

Bone metastases were detected in 8 of the 143 patients (6%). All metastatic lesions were detected by ^{18}F -FCH-PET/CT, whereas WBS only showed metastatic disease in 3 of the 8 patients. Fig. 1 demonstrates an example of metastases seen by ^{18}F -FCH-PET/CT but not WBS.

In 20 patients (14%), WBS raised suspicion of malignancy that was not confirmed by MRI. The corresponding number with ^{18}F -FCH-PET/CT was 5 patients (3%).

Sensitivity and specificity (with 95% CI) for WBS and ^{18}F -FCH-PET/CT in detection of bone metastases were 37.5% (13.7–69.4) vs 100.0% (67.6–100) and 85.2 (78.2–90.2) vs 96.3 (91.6–98.4), respectively, with corresponding P -values of 0.63 and 0.002.

Eighty patients underwent pelvic lymph node dissection either as part of radical prostatectomy or before external beam radiation. Median time between ^{18}F -FCH-PET/CT and surgery was 33 days (range, 4–84). A total of 1336 lymph nodes were removed, with a median of 16 (range, 2–39) removed lymph nodes per operated patient. Histologically confirmed metastases to regional lymph nodes were found in 24 patients (30%). Suspicious choline uptake on PET/CT in pelvic lymph nodes was found in 32 patients (40%). ^{18}F -FCH-PET/CT visualizing pelvic metastases can be seen in Fig. 2. Patient-based diagnostic performance of ^{18}F -FCH-PET/CT in detection of lymph node metastases can be seen in Table 2.

The largest histologically detected lymph node metastasis did not differ significantly ($P = 0.22$) between patients with suspicious lesions on ^{18}F -FCH-PET/CT with a mean size of 10.1 mm (range, 0.8–40.0) and patients with no suspicious lesions on ^{18}F -FCH-PET/CT with a mean size of 4.3 mm (range, 2.0–10.0).

4. Discussion

The present study is one of the largest prospective studies to date on the use of ^{18}F -FCH-PET/CT in patients with newly diagnosed intermediate- or high-risk PC. The use of radiolabeled choline has been studied intensively since its introduction 20 years ago¹⁶—first in brain cancer and later in PC. ^{18}F -FCH-PET/CT is now well established in PC recurrence after definitive therapy.¹⁷ The usefulness of ^{18}F -FCH-PET/CT in other settings of PC management is still debated. Under normal conditions, these patients would undergo planar WBS and possibly conventional CT scan. Our study suggests that ^{18}F -FCH-PET/CT outperforms WBS in diagnostic

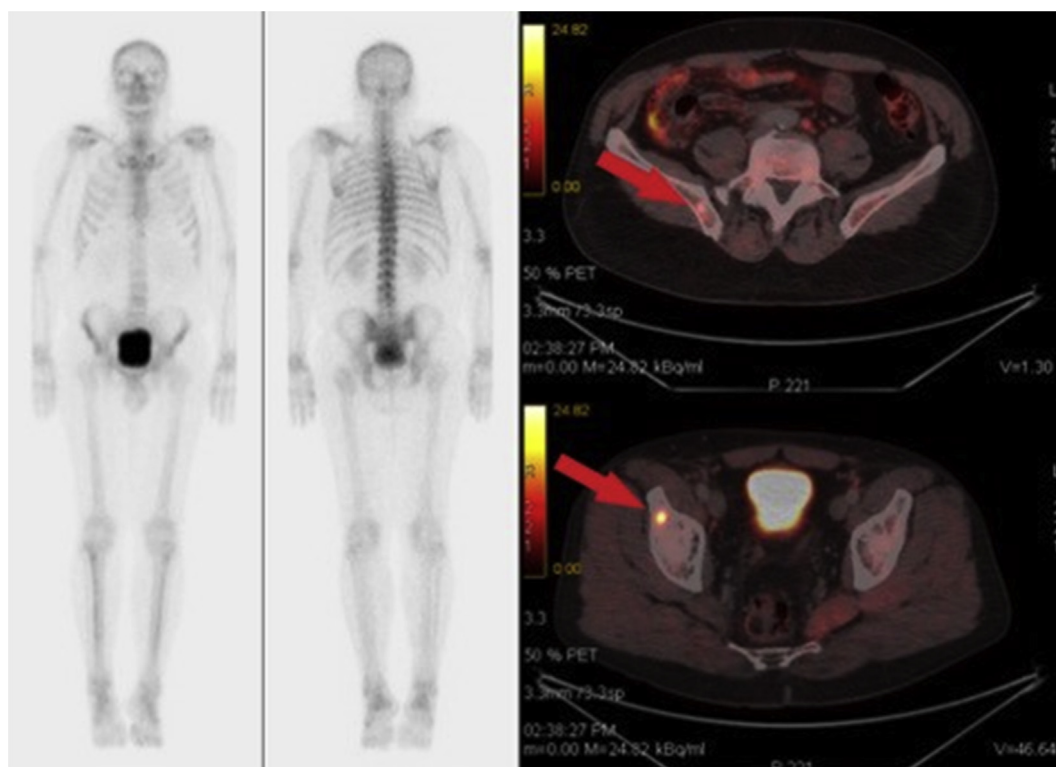


Fig. 1. Comparison of WBS and ^{18}F -FCH-PET/CT in a patient with confirmed metastases to the right iliac bone (arrows). No sign of bone dissemination is seen on WBS.

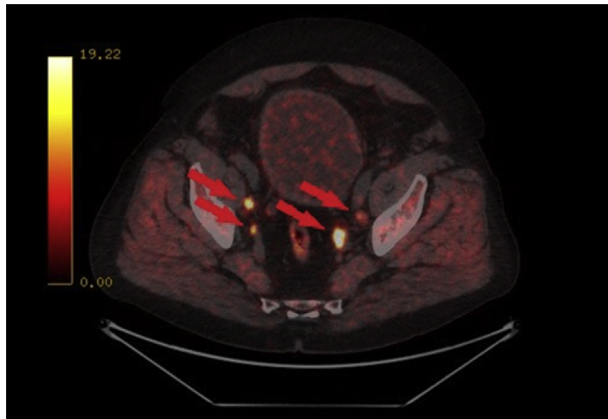


Fig. 2. ^{18}F -FCH-PET/CT of patient with histologically confirmed pelvic lymph metastases (arrows).

performance, particularly with regard to significantly better specificity. With the shortcomings of WBS, it has been shown that PET/CT using radiolabeled fluoride outperformed planar WBS in patients with high-risk PC.² Previous studies from our own institution also suggest that ^{18}F -FCH-PET/CT detects significantly more bone lesions in patients with well-known metastases.¹⁸ Owing to the low bone metastatic burden in patients included in our study, only patient-based analysis was performed—no lesion-based analysis was performed. Sensitivity of WBS reported in other studies ranges from around 40% in lesion-based analysis to around 70% in patient-based analysis.^{2,19} As some patients in our study were included with knowledge of a negative bone scan, the reported sensitivity of 37.5% might very well be underestimated as suggested by aforementioned studies. It must also be noted that patients with bone metastatic disease on WBS performed at other clinics never reached our institution, thereby causing a low overall metastatic burden in the study population. Generally, ^{18}F -FCH-PET/CT has shown high specificity in the detection of bone metastases. Initial studies reported a specificity of 97% in a mixed population of patients undergoing preoperative evaluation and patients with suspected recurrence²⁰—results very similar to the findings in our study. Similarly, high specificity (96%) has since been reported in patients with castration-resistant disease.²¹ In our study, the use of ^{18}F -FCH-PET/CT changed treatment strategy for 3% of the patients due to the finding of bone metastases that would have been missed by conventional standard imaging. Moreover, if ^{18}F -FCH-PET/CT alone had been used instead of WBS alone, the need for further confirmatory imaging would have been reduced by 75% (from 20 to 5 cases).

One thing to be noted is that patients with no sign of metastatic lesions on either WBS or ^{18}F -FCH-PET/CT were considered having no metastasis with no confirmatory imaging performed and therefore might have been misclassified as having no metastases. On the other hand, as there is no infallible reference for skeletal metastases, this issue remains unsolved.¹²

Previously published results regarding performance of choline-based PET/CT in lymph node staging are diverse. Early studies

suggested that ^{11}C -choline-PET/CT detected lymph node metastases with high sensitivity, specificity, and accuracy in patients with very high risk of dissemination.²² More recent studies, including studies from our own institution, have not been as encouraging as those. The largest meta-analysis on lymph node staging with choline PET/CT revealed a discouraging pooled sensitivity of 49%, with studies reporting a sensitivity as low as 10%.²³ In this meta-analysis, pooled specificity for choline PET/CT was 95%, ranging from 80% to 100%. Findings of our study suggest a slightly higher sensitivity but considerably lower specificity just below 70%. This could very well be due to different interpretation of when a lymph node is malignant or not on PET/CT, but other factors need to be considered as well. Patients undergoing lymph node dissection in this study were all planned for extended lymph node dissection as described previously. In some patients, very few lymph nodes were removed leading to the question if the dissection truly can be described as being extended. Also, various degrees of mapping were performed during lymph node removal, ranging from only indication of which side the nodes had been removed from to more exact location.

One of the caveats in lymph node evaluation is the size of the lymph node versus the spatial resolution of the imaging device in question. Lymph node metastases under 5 mm are not readily detected by ^{18}F -FCH-PET/CT.^{24,25} As seen in our results, metastases not detected by ^{18}F -FCH-PET/CT were around this exact size on average, whereas lymph nodes detected by ^{18}F -FCH-PET/CT tended to be slightly, although not significantly, bigger. Also, to be noted is that ^{18}F -FCH-PET/CT in this study overlooked malignant lymph nodes as large as 10 mm. A meta-analysis from 2007 concluded that CT and MRI were equally poor in detecting lymph node metastases from PC.⁵

Choline is, with a large margin, the most intensively investigated PET tracer in PC diagnostics. Despite years of studies, the only place where ^{18}F -FCH-PET/CT has an established role is in detection of recurrent disease. Initial studies hypothesized that imaging with radiolabeled choline could be the one-step solution to definite diagnosis and staging of PC. This has since been proven to be not only the case based on both the previously described limitations but also due to extra cost and lesser availability than traditionally used modalities.

More recently, new tracers targeting the prostate-specific membrane antigen (PSMA) have been developed.^{26,27} Initial investigations suggested that PSMA-PET/CT was superior to ^{18}F -FCH-PET/CT primarily due to a markedly higher tumor-to-background ratio.²⁸ Larger prospective studies on PSMA-PET/CT are still missing but are well underway.²⁹ The data that exist point to PSMA-PET/CT being superior to ^{18}F -FCH-PET/CT in every aspect of PC staging and management.^{30,31}

In conclusion, ^{18}F -FCH-PET/CT is a sensitive and specific method for detection of bone metastases from PC and could potentially reduce the need for confirmatory imaging if used instead of WBS. ^{18}F -FCH-PET/CT performs suboptimally in preoperative staging of lymph node metastases. However, with the introduction of PSMA-PET/CT, it seems apparent that an even better imaging modality might exist. More prospective studies are warranted to determine the true role of PSMA-PET/CT in PC management.

Table 2

Diagnostic performance of ^{18}F -FCH-PET/CT in detection of lymph node metastases.

Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, % (95% CI)
62.5 (42.7–78.8)	69.6 (56.7–80.1)	46.9 (30.9–63.6)	81.3 (68.1–89.8)	67.5 (56.6–76.8)

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

Conflicts of interest

Mike A. Mortensen received funding from the Danish Cancer Society and the Region of Southern Denmark. Other authors of this study declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pnrl.2019.01.002>.

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