

Adequate Diagnostic Performance of Combined [¹⁸F]-Fluormethylcholine PET-CT with Diffusion-Weighted MRI in Primary Staging of High Risk Prostate Cancer

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Received 26 March 2016; accepted 25 April 2016; published 28 April 2016

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Abstract

Introduction: [¹⁸F]-fluoro-methylcholine (FCH) PET/CT and MRI with diffusion-weighted MRI (DW-MRI) have insufficient performance in lymph node staging of primary prostate cancer by themselves, but the combination may perform better. We aim to prospectively determine the diagnostic performance of combined FCH PET and MRI for lymph node staging. **Methods:** This was a single site study of diagnostic accuracy in a well-defined group of 21 consecutive high-risk primary prostate cancer patients (>30% chance of lymph node metastases) in a large community hospital. We performed FCH PET/CT and MRI with DW-MRI prior to endoscopic extended pelvic lymph node dissection (EPLND). PET was fused and interpreted together with various MRI image sets (T1, T2, DWIBS) and was only scored positive when a lymph node seen on MRI coincided with increased focal FCH uptake on PET. Findings were compared with detailed histological evaluation, on a per-patient and per-region level. We calculated sensitivity, specificity, positive and negative predictive value of combined PET-MRI. **Results:** 14 out of 21 patients had metastatic lymph nodes with 37 out of 164 evaluable regions harboring metastases. On a per-patient analysis, PET-MRI had a sensitivity/specificity of 79/100% with a PPV/NPV of 100/77%. On a per-region analysis (n = 164) these figure were 65/99% and 96/91%, respectively. **Conclusions:** Combined DW-MRI and FCH PET/CT has a very high positive predictive value in high risk prostate cancer patients. If confirmed in larger series a positive combined scan may safely allow cancellation of surgical staging

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in selected patients, depending on local protocols in N1 M0 patients.

Keywords

Positron Emission Tomography, Diffusion-Weighted Imaging, Fluor-Methyl-Choline, Prostate Cancer, Primary Staging

1. Introduction

In higher stages of prostate cancer detection of lymph node metastases remains important, although there is controversy around the choice of therapy depending on the volume of N1 disease [1]-[5]. Despite all developments in imaging, the detection of locoregional lymph node metastases remains in its infancy as conventional CT and standard MRI have poor diagnostic sensitivity and specificity [6] [7]. Therefore, the standard method for lymph node staging currently is extended pelvic lymph node dissection (EPLND) with its associated invasive nature, difficulty and complications [8]-[11].

Recently, both choline positron emission tomography (PET) and newer magnetic resonance imaging (MRI) techniques have been proposed for improved non-invasive staging of pelvic lymph nodes [12]-[16]. Multiple studies have demonstrated that carbon-11-choline or fluor-18-methyl-choline PET/CT scans may visualize metastatic pelvic lymph nodes, but sensitivity/specificity values are currently insufficient to allow widespread use in primary staging. In restaging, however, PET is more and more used [12]-[14] [17]. Similar moderate performance in primary staging has been reported for newer MRI techniques including diffusion-weighted imaging (DW-MRI) [15] [16]. This technique enables the delineation of pelvic lymph nodes, even when small, but is less feasible to separate benign from malignant nodes [16].

Therefore, as both PET and MRI by themselves seem insufficient for adequate lymph node staging, there may be added value in the combined approach. MRI will then show the node and PET can determine its benign or malignant nature. Although many studies have compared PET with MRI, this combined approach has hardly been studied [18]. Visualization of the exact location of a lymph node may allow more sensitive local reading of choline PET. In addition, areas of doubtfully increased choline uptake without the local presence of a lymph node can be considered normal image noise or otherwise benign. Combining MRI and choline PET therefore may increase both sensitivity and specificity, possibly to levels where clinical application may become feasible.

Based on these ideas, the aim of this study is to obtain an initial impression of the clinical performance of combined MRI including DW-MRI with fluor-18-methyl-choline PET in a newly diagnosed, homogeneous and well-defined group of high risk prostate cancer patients selected for EPLND using detailed histology as a golden standard.

2. Patients and Methods

2.1. Patients

Between January 2012 and August 2014 we performed a prospective diagnostic accuracy study and selected patients with newly diagnosed biopsy-proven high-risk prostate cancer being considered for EPLND at the Isala hospital Zwolle, which serves as a large regional referral center in the north-east of the Netherlands. Patients were eligible for inclusion when prior bone scanning was negative for bone metastases, WHO performance status was 0, 1 or 2 and the chance of having lymph node metastases according to the Memorial Sloan Kettering Cancer-Center pre-treatment PC nomogram was 30% or more [19]. No imaging tests focused on lymph node staging had been performed before inclusion. Patients with prior prostate cancer treatments, chance of lymph node mets <30%, patients on hormonal therapy, with severe claustrophobia or prosthesis interfering with MRI were excluded. Patients were scheduled to undergo FCH PET and MRI within a 1 - 2 week interval in the 1 - 3 weeks preceding EPLND. The study was approved by the Isala local ethics review board and all patients gave their informed consent in writing. This report follows the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines.

2.2. FCH PET

Patients were injected intravenously with 200 - 250 MBq FCH. PET/CT acquisition was carried out at 60 min post-injection covering the lower neck to mid femur. Low-dose CT was applied for localization and attenuation-correction (120 kV, 30 mA). PET acquisitions were performed using dedicated PET-CT scanners (GE Discovery LS or Philips Ingenuity TF PET/CT) for 3 - 5 min per bedposition, 6 - 10 beds.

2.3. MRI

MRI scans from just above the aortic bifurcation to the pubic symphysis were obtained using a Philips Infinion 1.5 Tesla MRI scanner with torso XL coil. We acquired T1-turbo spin echo (TSE) transversal (FOV $300 \times 300 \times 100$ mm, voxel 1 mm, slices 4 mm, reconstructed voxel size 0.8 mm), T2-TSE transversal, T2-TSE sagittal, T2-TSE coronal, Diffusion-Weighted Whole Body Imaging with Background Body Signal Suppression (DWIBS)-coronal, single-shot (SSH)-DW transversal, T1-TSE Dynamic and 3D-PRESS/SPECTRO transversal (FOV $375 \times 296 \times 199$ mm, voxel size 2.5 mm, slice thickness 7 mm and reconstruction slice thickness 1.46 mm).

2.4. PET-CT Image Registration

After loading PET and MRI data series onto a workstation rigid image registration was performed automatically with manual corrections, using the CT component of the PET/CT study which easily aligns with MRI. In this way also the PET dataset was reliably fused with all other MRI sequence studies. Mean absolute registration (in 3D) errors were <5 mm for all patients.

2.5. Image Analysis

MRI studies were separately read by 2 experienced radiologists (MFB, MtVtK) blinded for any PET information. T1, T2 and DWI sequences were the basis of interpretation. DWIBS series served as a locator for lymph nodes that were verified on corresponding T1 or T2 slices. Although size is a rather nonspecific parameter in MRI assessment of lymph nodes, for the current study a lymph node on MRI was scored positive when the short-axis diameter was greater or equal to 5 mm (as determined on T1 slices). MRI was not further interpreted for the prostate itself or for malignant aspects of nodes (such as spheric shape), as the purpose of this study was to study combined PET/MR focused on lymph node staging. PET/CT images were interpreted by experienced nuclear medicine specialists in direct conjunction with MRI. All readers were blinded to the results of surgery and pathology.

Choline uptake was visually determined for each lymph node with a maximum short-axis diameter of 5 mm or more on MRI. *Vice-versa*, all PET local hotspots (defined as spots showing FCT uptake clearly over the background) were visually verified for the presence of a lymph node on MRI, in order to separate local image noise, intestinal uptake, the ureter or bones from real uptake in metastases. All image analysis sessions were done twice by a team of an experienced investigator (PLJ, JB) and discordant findings were discussed with the whole team. PET was only scored as positive when a focus of clearly increased choline uptake coincided with the location of a lymph node, avoiding calling accidental hotspots induced by image noise positive uptake. This interpretation process was carried out for 8 body regions per patient, including the left-and right common iliac artery nodes, internal iliac artery nodes, external iliac nodes and obturator nodes regions.

2.6. Surgery and Pathology

To minimize inter-surgeon variability the laparoscopic extended lymph node dissection was always carried out by one well-experienced urologists (TdH) and included a systematic assessment and maximum tissue removal at the same lymph node stations as described above. Borders of the dissection were the common iliac artery at the level of the crossing ureter, the genito-femoral nerve on the psoas muscle, the external iliac vein crossing the pubic arch and the dorsal border of the obturator nerve. Surgeons were blinded to image data. The removed tissue was accurately pinned onto a plasticised paper template of the pelvis and transported to the pathology department and evaluated using standard methods (Figure 1).

Individual lymph nodes locations were grouped into the 8 regions described above. The same regional evalua-

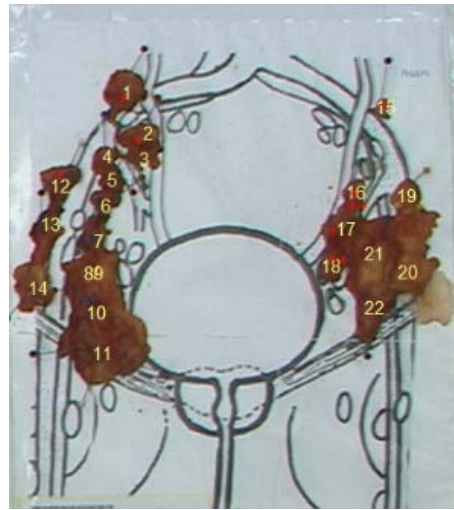


Figure 1. Example of the template used for the assessment of PET, MRI and for the pathological evaluation. Tissue removed at surgery is accurately positioned on the template depending on its origin, and is transported to pathology for evaluation. The template is photographed and numbered. Each numbered node is evaluated separately by the pathologists allowing detailed comparison of both imaging tests with PA evaluation. For assessment nodes are grouped into 8 regions. For example number 1: common iliac region, 2 and 3: internal iliac, 4-11 obturator region, 12 - 14 external iliac.

tion was also used for PET/MRI assessments. Despite these rather extensive efforts it proved quite difficult to reach a perfect match between body regions because of the complex anatomy seen in 3D at surgery and difficult assessment of anatomical boundaries between regions on MRI/PET/CT and the conversion to a 2D template.

2.7. Data Analysis and Statistics

We calculated sensitivity, specificity, positive and negative predictive value of MRI alone (with the constraints described above) as well as of the PET/MRI joint assessment, using the pathology result as a gold standard in all cases. False negative regions were those where PET-MR was negative while pathology was positive, false positive regions were defined as harbouring positive PET-MR findings with normal pathology. This was done on a per-patient and per-region basis.

3. Results

3.1. Patients and Surgery

We included 21 patients who all underwent PET, MRI and surgery yielding complete data for 21 patients and 164 regions. Originally 29 patients had been eligible for inclusion, but 8 patients were not studied due to claustrophobia in 1, unwilling to consent in 2, treatment performed in a different hospital in 2, choline tracer not delivered in 2 patients. One patient was excluded because a bone metastasis, previously read as non-metastatic on the bone scan was detected on the PET scan. The criterion of pre-test chance $> 30\%$ significantly limited the inclusion but guaranteed an uniform high risk patient group. Mean age of the patients was 67 years (range 56 - 77), mean PSA was 41 ± 22 (range 9 - 95), 18 had a T3 tumor, 3 had a T2 tumor, all Gleason sum scores were between 7 and 10 (mean 8.2 ± 1.0).

Although surgery was performed by a single, skilled and experienced urologist who aimed to remove all lymph nodes, the surgeon retrospectively concluded that in 3 patients (4 regions) sampling had been incomplete due to technical difficulty. In these cases a clear PET hotspot coinciding with a clearly enlarged lymph node with malignant aspect on MRI remained unremoved. The 4 regions in which this occurred had to be excluded from the analysis yielding 164 evaluable regions. Patient based and patient-side based analysis, however, was not affected.

Histopathological findings revealed 14 patients with lymph node metastases (67%). This frequency was considerably higher than anticipated from the MSK nomogram which yielded a mean of 45% (30% - 69%). In these 14 patients 37 regions were positive for metastatic disease. Seven patients and 127 regions did not contain metastases. In total 333 lymph nodes were removed, a mean of 16 per patient (range 9 - 27). Fifty-eight of these were metastatic (17%). Mean size of the metastatic lymph nodes was 9.6 mm (range 4 - 30 mm).

3.2. MRI Only Findings

Imaging results are presented in **Table 1** and examples of scans are presented in **Figure 2** and **Figure 3**. MRI (using the 5 mm cutoff definition—with its known limitations) was positive in all 21 patients of the study. This includes all 14 patients with metastatic disease as well as the 7 patients without disease. In the latter 7 the MRI therefore was false positive. This amounts to 100% sensitivity at a low specificity of 14% on a per patient level. On the regional level sensitivity of MRI was 92% at a specificity of 73%, positive predictive value 50%, negative predictive value 97%.

3.3. Combined PET-MRI Findings

PET-MR was positive in 11/14 patients and negative in 7/7 patients, yielding a sensitivity of 79% at a perfect specificity of 100% in this small group. Positive predictive value was 100%, negative predictive value was 70%.

Table 1. MRI, PET + MRI and Surgical Findings.

| Pat | MRI | PET-MR | PA | Pos/tot | Remarks |
|-----|------------------|------------------|------------------|---------|--------------------------|
| | pos | pos | pos | nodes | |
| 1 | 1, 2, 4, 5, 7, 8 | 2, 4 | 1, 2, 4, 5, 6, 7 | 10/27 | |
| 2 | 2, 4, 5, 8 | 8 | 2, 4, 8 | 3/14 | |
| 3 | 3, 4, 7 | neg | 6 | 1/24 | |
| 4 | 4, 8 | neg | neg | 0/26 | |
| 5 | 4, 8 | 4, 8 | 4, 8 | 7/16 | |
| 6 | 3, 6, 8 | 6, 8 | 6, 8 | 2/15 | region 4 excluded |
| 7 | 2, 4, 8 | 4 | 2, 4 | 2/14 | region 3 excluded |
| 8 | 3, 8 | 3, 8 | 2, 3, 8 | 4/17 | |
| 9 | 1 | 8 | 1, 2, 4, 8 | 7/17 | |
| 10 | 6 | neg | neg | 0/15 | |
| 11 | 3, 4, 6, 8 | neg | neg | 0/15 | 0/15 |
| 12 | 3, 4, 7, 8 | 4 | 4, 7, 8 | 3/17 | 3/17 |
| 13 | 1, 3, 4, 5, 7, 8 | neg | neg | 0/10 | |
| 14 | 3, 4, 8 | neg | neg | 0/9 | |
| 15 | 1, 6 | 6 | 6 | 2/9 | |
| 16 | 3, 6, 8 | neg | 6 | 1/17 | |
| 17 | 3, 4, 8 | neg | neg | 0/14 | |
| 18 | 4, 7 | neg | 4 | 1/17 | |
| 19 | 4, 6, 8 | 4, 8 | 4, 8 | 3/21 | |
| 20 | 4, 8 | neg | neg | 0/16 | |
| 21 | 2, 3, 4, 6, 7, 8 | 2, 3, 4, 6, 7, 8 | 2, 3, 4, 6, 7, 8 | 12/18 | regions 1 and 5 excluded |

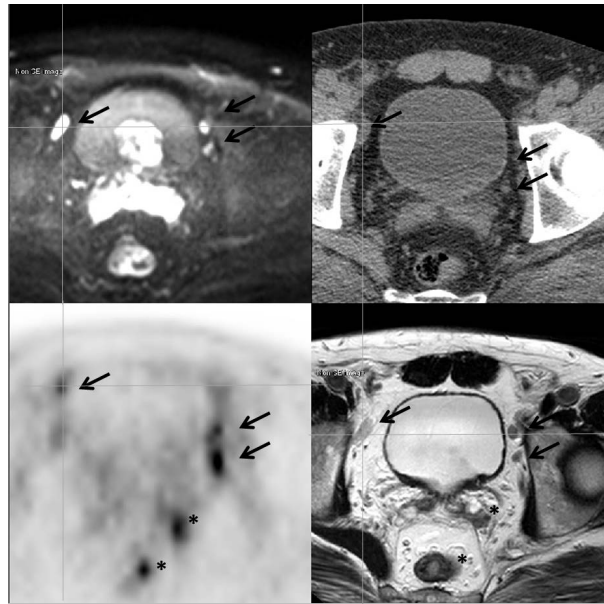


Figure 2. Fusion PET-MR images in a patient with bilateral obturator lymph node metastases confirmed on pathology. Upper left axial MRI DWIBS, upper right low-dose CT (part of PET/CT), lower left FCH PET image, lower right MRI T2 slice. Metastases (arrows) are seen clearly on DWIBS corresponding with increased FCH uptake and location of a node on MRI (and on low dose CT). Choline uptake at the * positions does not align with a substrate on MRI DWIBS and likely represents non-specific bowel uptake. This figure illustrates how information obtained from PET and MRI complements each other.

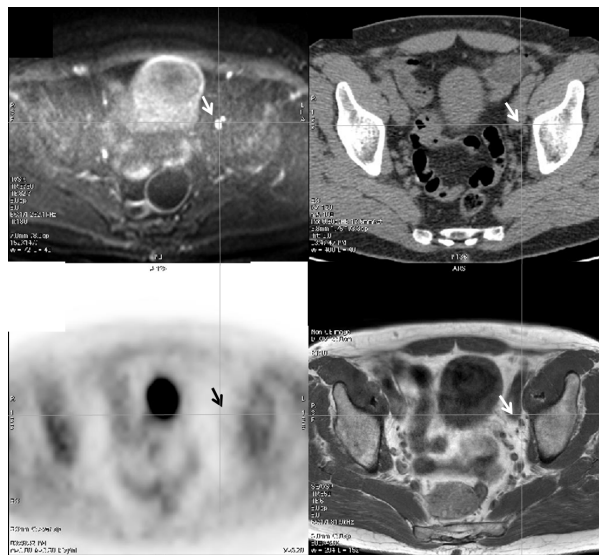


Figure 3. Fusion PET-MR axial images in a patient without lymph node metastases demonstrating complementary information of PET and MR. Upper left MRI DWIBS, upper right low-dose CT, lower left FCH PET, lower right MRI T2. Although MRI DWIBS and MRI T1 both show a 7 mm lymph node in the right external iliac region (arrow) there is no choline uptake in this area, which proved to be correct at pathological evaluation of tissue sampled in this area.

In other words, three metastatic patients were missed, but there were no false positives. These 3 patients only had a single regional metastasis of 4, 5 and 5 mm size.

On the regional level sensitivity/specificity was 65/99% with positive/negative predictive values of 96/91%.

There was one region ultimately considered false positive. Based on PET/CT/MR the lymph node seen in this area was assigned to the internal iliac region, which was a possible assignment error and should have been the obturator region in a patient with multiple positive lymph nodes in the obturator region.

As expected PET/MR true positive metastatic lymph nodes were larger than false negative nodes: 11.6 ± 6.4 mm (range 4 - 30 mm). False negative nodes measured 6.4 ± 3.3 mm (range 2 - 14 mm).

4. Discussion

This study shows a clear added value of combined FCH PET and MRI in primary staging in a small but well-defined and homogeneous group of high risk prostate cancer patients eligible for EPLND. Combining PET and MRI yields a good sensitivity and specificity and nearly perfect positive predictive value in comparison with a detailed histological gold standard in all patients. In every patient, where PET/MRI is positive metastatic disease is confirmed. These results are superior to existing reports where the performance of choline PET and MRI has been separately assessed or compared although we realize that this is just a small study [12]-[14] [17] [20]-[23].

Although not all metastatic nodes are detected, the key finding in our results is the absence of false positive findings. We believe this to be the result of the combined reading of MRI and FCT PET, because possibly positive PET locations are only counted when coinciding with a lymph node seen on MRI, in this way avoiding over-interpretation and increasing specificity. Conversely, the approach allows sensitive focal reading at the site of a confirmed lymph on MRI, improving sensitivity. Balancing this way of analysis we reach potentially clinically meaningful performance levels in this study. In our practice convincing evidence of N1 disease, as potentially provided by choline PET/MRI generally leads to the omission of surgery. However, there is some controversy around this topic as low volume N1 disease (in the absence of M1 disease) may justify intensive local treatment in addition to surgery [4]. The PET/MR findings, however, also give an impression as to the amount of N1 disease.

Our results differ from other studies focusing on choline PET for initial staging. Poulsen described 210 patients and found sensitivity/specificity/PPV/NPV values of 73/88/59/93%, considerably lower values than in our study [17]. Their prevalence of metastatic disease of 20% was much lower than the 65% in our study. They concluded that FCH PET was not valuable for lymph node staging. No explanation was given for false positive findings, but the number of removed lymph nodes per patient [5.6] was much lower than in our study, leaving the possibility that some choline findings might still have been true positive, both within and without the dissection zone, because they were not validated [16]. In addition, that study relied on CT to detect nodes, whereas we used MRI including DW-MRI. However, the number of patients in our study remained much lower weakening our conclusions.

Another recent study that focused on staging was published by Vag *et al.* who found moderate and similar performance of both dwMRI and C11-choline PET, but relied heavily on measurements (ADC vs. SUV) rather than visual interpretation and, importantly, did not combine both data sets [24]. In the study by Budiharto *et al.*, performance was also modest with PPV/NPV of 75/91 for PET and 46/92% for DW-MRI [20]. Regions with macrometastases remained undetected by C11-choline PET (with very early acquisition only) and sensitivity was surprisingly low. The number of false positives, however, appeared limited. It appeared that also in this study PET and MRI were compared but not combined [20]. Another study by Eschmann also compared both modalities and found sensitivity/specificity values of 97/77% for PET and 79/94% for whole body MRI [21]. The authors concluded that PET and MRI were complementary but again the study had not been designed to assess the value of the combined tests. Finally, de Jong *et al.* described a sensitivity/specificity of C11-choline PET of 80/96%, but this study was done before the era of PET/CT, DWMRI and EPLND [22].

Limitations of our study include its small size and the use of software to fuse MRI with PET images obtained on 2 separate occasions. Recently combined PET/MRI scanners are being developed where a combined scan can be done with a single machine in a single session with perfect matching, possibly also with promising new radiotracers such as Gallium-68-PSMA [25]. Another limitation is the still poorly understood phenomenon of nonspecific choline uptake in hilar, mediastinal and sometimes inguinal lymph nodes that should not be confused with metastatic disease. Finally, correct assignment of a metastasis to the correct anatomical region was difficult, and this may interfere with regional sensitivity and specificity values, although it does not affect overall patient-based performance.

In conclusion, in this pilot study combined (DW) MRI and choline PET yielded good results in primary stag-

ing of high risk prostate cancer patients. We believe this should be pursued further as it may save patients unnecessary lymph node dissections.

Acknowledgements

The authors thank Mrs. Vera ten Hag for her valuable assistance in patient planning and organization. We thank Joep Dille in assistance at the time of the design of the study. Supported by a local innovation grant from the Isala hospital.

Conflict of Interest and Source of Funding

No author has any disclosure.

Funding was obtained through a local hospital innovation project grant.

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