

Detection of Lymph Node Metastases in Patients With Prostate Cancer: Comparing Conventional and Digital [18F]-fluorocholine PET-CT Using Histopathology as Reference

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Abstract

Background: Positron emission tomography-computed tomography (PET-CT) can be used to detect and stage metastatic lymph nodes in intermediate to high-risk prostate cancer. Improvements to hardware, such as digital technology, and to software, such as reconstruction algorithms, have recently been made. We compared the capability of detecting regional lymph node metastases using conventional and digital silicon photomultiplier (SiPM)-based PET-CT technology for [^{18}F]-fluorocholine (FCH). Extended pelvic lymph node dissection (ePLND) histopathology was used as the reference method.

Methods: Retrospectively, a consecutive series of patients with prostate cancer who had undergone staging with FCH PET-CT before ePLND were included. Images were obtained with either a conventional or a SiPM-based PET-CT and compared. FCH uptake in pelvic lymph nodes beyond the uptake in the mediastinal blood pool was considered to be abnormal.

Results: One hundred eighty patients with intermediate or high-risk prostate cancer were examined using a conventional Philips Gemini PET-CT ($n = 93$) between 2015 and 2017 or a digital GE Discovery MI PET-CT ($n = 87$) from 2017 to 2018. Images that were obtained using the Philips Gemini PET-CT system showed 19 patients (20%) with suspected lymph node metastases compared with 40 patients (46%) using the GE Discovery MI PET-CT. Sensitivity, specificity, and positive and negative predictive value (PPV and NPV) were 0.30, 0.84, 0.47, and 0.72, respectively, for the Philips Gemini and 0.60, 0.58, 0.30, and 0.83, respectively for GE Discovery MI. Area under the curve (AUC) in a receiver operating characteristics (ROC) analysis was similar between the two PET-CT systems (0.58 and 0.58, $P = 0.8$).

Conclusions: A marked difference in sensitivity and specificity was found for the different PET-CT systems, although similar overall diagnostic performance. This is probably due to differences in both hard- and software, including reconstruction algorithms, and should be considered when new technology is introduced.

Background

Recently, positron emission tomography – computed tomography (PET-CT) scanners with digital silicon (Si)-photomultiplier (PM) -based technology has been introduced with the potential to increase the sensitivity to detect pathological lesions (1). New reconstruction algorithms have also been developed such as the block-sequential regularisation expectation maximisation algorithm (BSREM), which has the commercial name Q.Clear (1, 2) (GE Healthcare). This method allows for fully convergent iterative reconstruction, which results in a higher image contrast compared to conventional reconstruction methods, while also minimising the noise level. Together, the new hard- and software developments are hoped to improve the detection capabilities of particularly small metastases, such as lymph nodes (3).

Prostate cancer is one of the most common cancers among men worldwide (4). Prostatectomy with extended pelvic lymph node dissection (ePLND) is considered to be the best available procedure to provide information about loco-regional staging and prognosis in patients with intermediate to high-risk

prostate cancer (4-7). PET-CT is often used for staging of high-risk prostate cancer. Nowadays, prostate-specific membrane antigen (PSMA) based radiopharmaceuticals are recommended. Before the introduction of PSMA PET-CT, [^{18}F]-fluorocholine (FCH) was often used. In previous studies, FCH with conventional PM-based PET technology has shown a high specificity but a low sensitivity for the detection of lymph node metastases (8-11). To the best of our knowledge, not studies exist which compare the performance conventional and digital PET-CT in patients with prostate cancer. Although FCH PET-CT is not a superior method for detection of lymph node metastases in high-risk prostate cancer, it has been used in a standardized way in our county for staging of high-risk prostate cancer before prostatectomy with ePLND. It is thus a suitable setting to compare the real-world performance of conventional and digital PET-CT systems in large cohorts of patients where histopathology is available as reference method.

In this study, we compared the ability to detect pelvic lymph node metastases on images that were obtained using a conventional PM-based PET-CT system (Gemini Time of Flight; Philips Healthcare) with a line-of-response row-action maximum-likelihood (BLOB-OS-TOF) reconstruction algorithm to those obtained from a digital SiPM-based PET-CT system (Discovery MI; GE Healthcare) using BSREM in patients who were undergoing clinical FCH PET-CT scanning. Histopathology from ePLND was used as the reference method.

Methods

Patients and surgery

Two hundred ninety-one patients were referred for clinical FCH PET-CT followed by prostatectomy with ePLND at Skåne University Hospital in Malmö and Lund, Sweden, from January 2015 to November 2018. One hundred eleven patients were excluded due to incomplete data within their medical records, denied participation or examination on a third PET-CT system, as shown in Figure 1. After exclusions, 180 patients with biopsy-verified intermediate or high-risk prostate cancer were enrolled into the study.

EPLND was performed using a standard template including the area of the iliac bifurcation, along the external and internal iliac vessels, and the obturator fossa. All surgical procedures and histopathological examinations were performed in the Department of Urology at Skåne University Hospital, Malmö, Sweden.

The PET-CT examination clinical reports were compared with the histopathology reports after ePLND for the presence of lymph node metastases on a per-patient and per-side basis.

This study was approved by the regional review board in Lund (#2016/417 and 2018/753) and performed according to the Declaration of Helsinki. All patients provided written informed consent.

PET-CT systems

Examination images were acquired on one of the following PET-CT systems; Philips Gemini TF PET-CT (Gemini Time of Flight; Philips Healthcare, Cleveland, OH, USA) or GE Discovery MI PET-CT (Discovery MI; GE Healthcare, Milwaukee, WI, USA).

The Philips Gemini TF PET-CT systems were installed in 2006 and discontinued in 2017 in the Department of Medical Imaging and Physiology, Skåne University Hospital in Malmö, and Lund. The system used lutetium–yttrium oxyorthosilicate crystals (crystal size, $4.0 \times 4.0 \times 22 \text{ mm}^3$) coupled to an array of PM tubes. The PET-detector had an axial field of view of 17.6 cm and the bed positions had an overlap of 50%. According to the National Electrical Manufacturers Association standards, the sensitivity was 7 cps/kBq. The system had a 16-slice CT.

For reconstruction, the BLOB-OS-TOF algorithm was used, with three iterations, 33 subsets, and a 5-mm Gaussian post filter. The matrix size was 144×144 (voxel size, $4 \times 4 \times 4 \text{ mm}$) and time-of-flight and CT attenuation corrections were included. The CT scans were acquired with diagnostic quality, using a 5-mm reconstructed slice thickness, a pitch factor of 0.938, rotation speed of 0.75 s, 120 kV, and high-beam tube current modulation (120–300 mA) based on the patient's total body mass. For the CT, a filtered back projection reconstruction was used.

The GE Discovery MI PET-CT systems were installed in 2017 in the Department of Medical Imaging and Physiology, Skåne University Hospital in Malmö, and Lund. The system uses lutetium–yttrium oxyorthosilicate crystals (crystal size, $4.0 \times 5.3 \times 25 \text{ mm}^3$) coupled to an array of SiPM. The PET-detector has an axial field of view of 20 cm and the bed position has an overlap of 24%. According to the National Electrical Manufacturers Association standards, the sensitivity is 13 cps/kBq. The system has a 128-slice CT.

PET image reconstruction was performed using BSREM including time-of-flight, the point-spread function, and CT-based attenuation correction with a 256×256 matrix (pixel size, $2.7 \times 2.7 \text{ mm}^2$; slice thickness, 2.8 mm) and a β value of 500 (12). The diagnostic CT was performed with the tube current modulation applied and the tube current was adjusted for each patient, with a noise index of 42.25. A 100-kV tube voltage was used for a body mass index (BMI) that was less than 30 kg/m^2 , and 120 kV was used when the BMI was greater than 30 kg/m^2 . An adaptive statistical iterative reconstruction technique was used for the CT images.

PET-CT imaging and interpretation

FCH was administrated intravenously at a dose of 4 MBq/kg after a minimum fasting time of 4 hours. A whole-body PET-CT was acquired after an accumulation time of 60 minutes on either one of the PET-CT systems. The images on both PET-CT systems were acquired from the upper thigh to the base of the skull with 2.0 minutes per bed position.

Each PET-CT examination was interpreted by one nuclear medicine physician and one radiologist who jointly wrote a clinical report. Lymph node FCH uptake that exceeded that of the mediastinal blood pool were generally considered to be abnormal. Eight experienced nuclear medicine physicians have worked and interpreted FCH PET images in our department from 2015 to 2018. Among these eight physicians, seven interpreted images on both PET-CT systems. For this study, one of the nuclear medicine physicians (ET, with 7 years of experience in reading FCH images), reviewed the clinical reports and sorted the patients into the following two groups: suspected/possible lymph node metastases and without lymph node metastases. When the clinical report was ambiguous (for example possible but not certain metastases), the patient was considered to have abnormal lymph nodes in the subsequent analysis.

Statistical analysis

Clinical and pathological information was retrospectively obtained from medical records. Comparison of baseline variables for patients who were examined using the Discovery MI and Gemini TF was performed using a Chi-square test and a Mann–Whitney U-test. The overall diagnostic performance was analysed using the receiver operating characteristics (ROC) analyses. Per-patient and per-side (left and right) sensitivity, specificity, PPV, and NPV were calculated on the different PET-CTs within the ePLND template using histology results from the ePLND as the reference method. Confidence intervals for the respective groups were 95%. Statistical significance was considered for *P* less than 0.05. Statistical analyses were performed using IBM SPSS version 26 (IBM Corp., Armonk, NY, USA) and Stata 16.0 (StataCorp LLC, College Station, TX, USA).

Results

Patients

Clinical and pathological characteristics of the 180 patients who were included in this study are presented in Table 1. Ninety-three patients were imaged using a Philips Gemini PET-CT system and 87 patients were imaged using a GE Discovery MI PET-CT. There were no significant differences between the two groups regarding the Gleason score, prostate-specific antigen (PSA), pathological local tumour stage, risk group classification, and number of days between biopsy and PET-CT examination.

PET findings

For the Philips Gemini system, 19 patients (20%) were considered to have suspected lymph node metastases within the ePLND template (along internal and external iliac arteries). Based on histology results, 30 patients (32%) had positive lymph nodes. For the GE Discovery MI system, 40 patients (46%) were considered to have lymph node metastases and 20 patients (23%) had positive lymph nodes based on histopathology.

The sensitivity was markedly higher for images that were obtained using the GE Discovery MI system, 0.60 (95% CI 0.39-0.78), compared with the Philips Gemini system 0.30 (95% CI 0.17-0.48). The specificity was lower for images that were obtained with the GE Discovery MI, 0.58 (95% CI 0.46-0.69), compared with the Philips Gemini system, 0.83 (95% CI 0.70-0.91). The positive and negative predictive value for images obtained on the GE Discovery system was 0.30 (95% CI 0.18-0.45) and 0.83 (95% CI 0.70-0.91). For images obtained on the Philips Gemini system was the positive and negative predictive value 0.47 (95% CI 0.27-0.69) and 0.72 (95% CI 0.61-0.81). Sensitivity, specificity, and the positive and negative predictive values per-patient and per-side are shown in Table 2.

Area under the curve (AUC) in the ROC analysis for correctly predicting lymph node metastases was similar between the systems (0.58 for Philips Gemini and 0.58 for GE Discovery MI; $P = 0.8$).

Discussion

This study showed high specificity and low sensitivity for detecting of lymph node metastases in patients who were examined using a conventional PET-CT system and a relatively low sensitivity and low specificity for patients who were examined using a digital PET-CT system using FCH. Overall diagnostic performance, however, which was measured as the AUC in the ROC analysis, was similar ($P = 0.8$) between the two PET-CT systems.

The combination of new detector technology and new reconstruction algorithms have been found to increase image quality, increase the lesion-to-blood-pool SUV ratios in smaller lesions, increase the maximum SUV in lesions and increase the number of detected lesions compared to the previous generation of scanners (13-17). This does not, however, necessarily lead to improved diagnosis, as seen in the present study. When introducing new technology, such as digital PET-CT systems and new reconstruction algorithms, it is of uttermost importance to validate the technology in different settings. In this study we used FCH, which is generally no longer recommended for patients with prostate cancer, but the results illustrate the need for repeated accuracy studies, both when tracers are widely used in clinical practice and when new technology is introduced. The results from the present study suggest that the same criteria for interpreting an uptake as abnormal cannot necessarily be used for images that are obtained using different PET-CT systems or reconstruction methods.

During the installation of the GE Discovery MI PET-CT systems in our department, a small number of patients were examined on both the Philips Gemini TF and the digital GE Discovery MI. Unfortunately, none of these patients underwent prostatectomy with ePLND after the PET-CT, and they were not included in this study. The results of the dual imaging can, however, be used to explain the results that were obtained in the present study. Representative images of two patients who were imaged on both systems are shown in Figure 2. The SUV in small objects, such as lymph nodes, was higher using the Discovery MI system compared with the Philips Gemini system due to differences in reconstruction methods and technology such as spatial resolution within the PET-CT system (18), which result in a higher recovery coefficient for the digital system for small objects. We do not know whether the lymph nodes in Figure 2

are malignant, but is suggested that more lymph nodes may be interpreted as malignant when reviewing images that were obtained using the Discovery MI (19).

Similar to our results on the accuracy of FCH for detecting lymph node metastases with conventional PET-CT systems, previous studies have also showed a low sensitivity and high specificity. Beheshti et al. reported a sensitivity of 0.45, specificity of 0.96, PPV of 0.82 and NPV of 0.83 for FCH PET-CT (8), which is similar to the results that were obtained by Kjolhede et al. (10) who reported a sensitivity, specificity, PPV, and NPV of 0.33, 0.92, 0.76, and 0.65, respectively. We have recently published a study of a large FCH cohort (11), partly included in the present study. In that study, a low sensitivity of 0.43 was found, with a relatively low specificity of 0.70. 252 patients were included over 4 years, and scanned with three different generations of PET-CT systems. Previous studies for detecting lymph node metastases on SiPM-based PET-CT systems have also been published, but these studies used [^{18}F]-fludeoxyglucose rather than FCH (1, 19). Similar to our study, the sensitivity was higher for SiPM-based PET-CT compared with conventional PET-CT systems.

Limitations

There were some limitations in our study. First, the study design was retrospective. Only patients who were clinically selected as suitable for prostatectomy using ePLND, based on clinical factors and findings on the PET-CT, were included in this study. For example, patients with a high risk of having metastases outside the ePLND template based on PET-CT were excluded from surgery with curative intent. Second, only a patient- and a side-based analysis but not a lesion-based analysis was performed because these data were not available from the histopathological reports. Although all nuclear medicine physicians were experienced, there is a possibility of inconsistent image interpretation over time.

Conclusions

Conventional and digital FCH PET-CT, including reconstruction algorithms as per the vendor recommendations, had similar overall diagnostic performances when measured using the AUC in the ROC analysis and for detecting lymph node metastases in patients with intermediate or high-risk prostate cancer. Marked differences in sensitivity and specificity were found. This is probably due to differences in both hard- and software, including reconstruction algorithms, and should be considered when new technology is introduced. Regardless of the PET-CT system used, the overall diagnostic performance was poor, and FCH PET-CT cannot be recommended for initial staging of patients with prostate cancer.

Abbreviations

AUC, area under the curve

BLOB-OS-TOF, line-of-response raw-action maximum-likelihood

BSREM, block-sequential regularized expectation maximization algorithm

CT, computed tomography

ePLND, extended pelvic lymph node dissection

FCH, [^{18}F]-fluorocholine

GE Discovery MI, General Electric Discovery molecular imaging

NPV, negative predictive value

PET-CT, positron emission tomography-computed tomography

Philips Gemini TF, Philips Gemini Time-of-Flight

PM, photomultiplier

PPV, positive predictive value

PSA, prostate-specific antigen

ROC, receiver operating characteristic

SiPM, silicon photomultiplier

SUV, standardised uptake value

Declarations

Ethics approval and consent to participate

This study was approved by the regional review board in Lund (#2016/417 and 2018/750 and performed according to the Declaration of Helsinki.

Consent for publication

All patients provided written informed consent.

Availability of data and material

The datasets that were used and analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors participated in the design of the study. MB, CP, JA, AB, and ET participated in data analysis. MB wrote the manuscript, and the other authors revised the manuscript. All authors read and approved the final manuscript.

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Tables

Tables 1 and 2 are not available with this version.

Figures

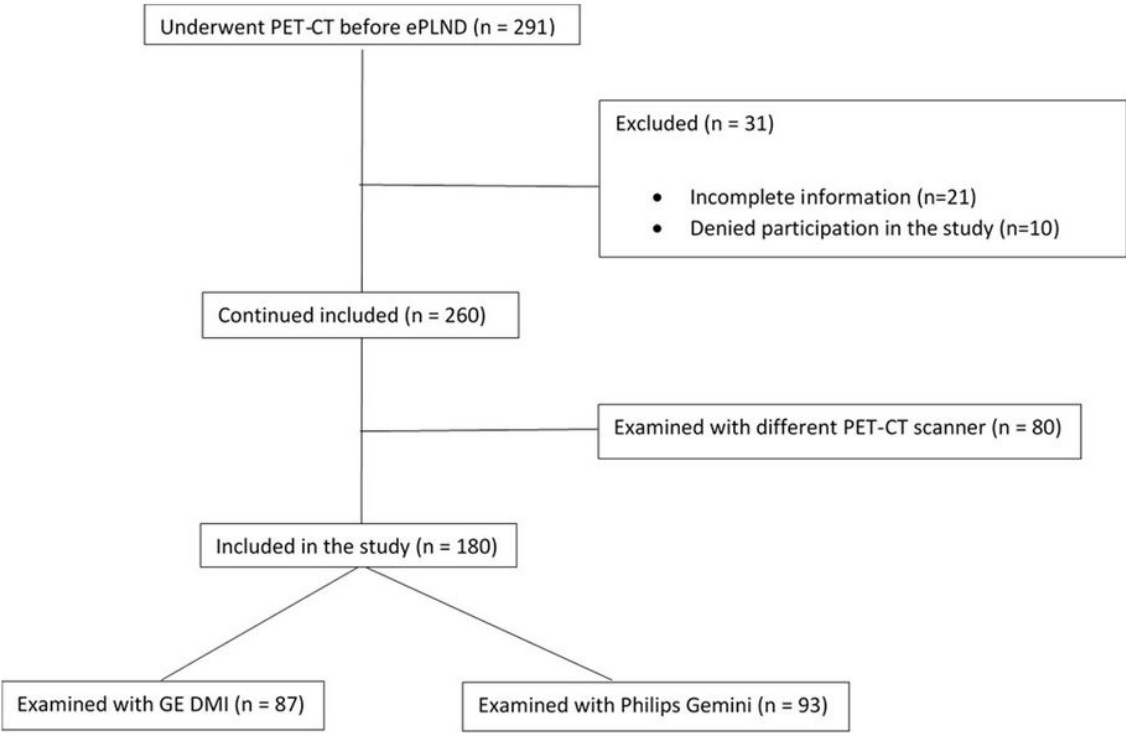


Figure 1

Flow chart of all patients in the study. PET-CT, positron emission tomography-computed tomography; ePLND, extended pelvic lymph node dissection; GE D690, General Electric Discovery 690; Philips Gemini TF, Philips Gemini Time-of-Flight; GE Discovery MI, General Electric Discovery molecular imaging.

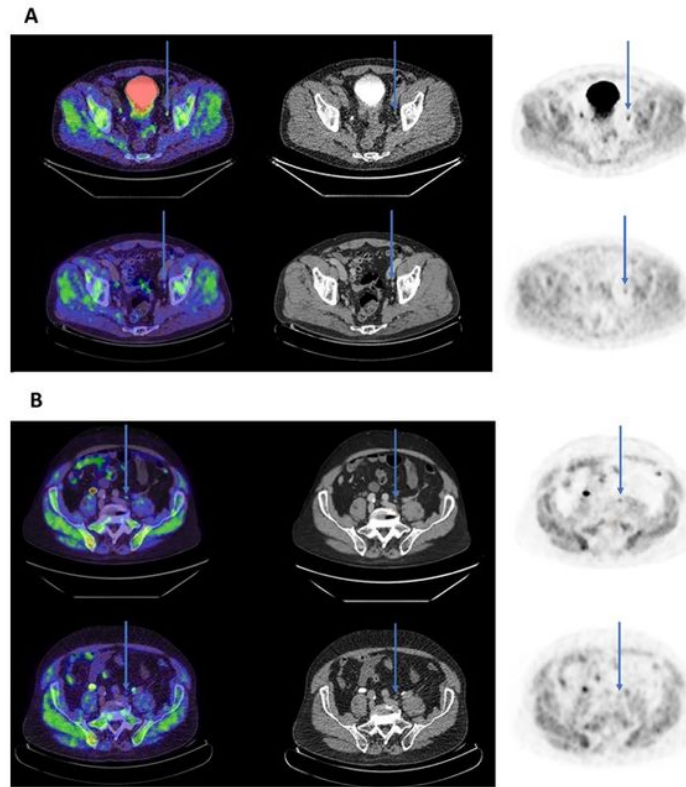


Figure 2

The patient in image (A) was first imaged on a Gemini TF (lower row) and then on a Discovery MI (upper row). The patient in image (B) was first imaged on a Discovery MI (upper row) and then on a Gemini TF (lower row). The left column shows fused PET-CT images, the middle column shows the CT image, and the right column shows the PET image. Arrows indicate a lymph node, which is better visualised in the Discovery MI images compared with the Gemini TF images.