Detection of lymph node metastases in patients with prostate cancer: Comparing conventional and digital \[^{18}\text{F}\]-fluorocholine PET-CT using histopathology as a reference

Mimmi Bjöersdorff\(^1\) | Christopher Puterman\(^2\) | Jenny Oddstig\(^3\) | Jennifer Amidi\(^2\) | Sophia Zackrisson\(^4\) | Henrik Kjölhede\(^5,6\) | Anders Bjartell\(^2\) | Per Wollmer\(^1\) | Elin Trägårdh\(^1,7\)

\(^1\)Department of Clinical Physiology and Nuclear Medicine, Skåne University Hospital, Lund University, Malmö, Sweden
\(^2\)Department of Urology, Skåne University Hospital, Lund University, Malmö, Sweden
\(^3\)Department of Clinical Physiology, Radiation Physics, Skåne University Hospital, Lund University, Lund, Sweden
\(^4\)Department of Translational Medicine, Diagnostic Radiology, Lund University and Skåne University Hospital, Malmö, Sweden
\(^5\)Department of Urology, Institute of Clinical Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
\(^6\)Department of Urology, Region Västra Götaland, Sahlgrenska University Hospital, Göteborg, Sweden
\(^7\)Wallenberg Centre for Molecular Medicine, Lund University, Lund, Sweden

**Abstract**

**Background:** Positron emission tomography-computed tomography (PET-CT) with \[^{18}\text{F}\]-fluorocholine (FCH) is used to detect and stage metastatic lymph nodes in patients with prostate cancer. Improvements to hardware and software 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 FCH. Extended pelvic lymph node dissection (ePLND) histopathology was used as a reference method.

**Methods:** The study retrospectively examined 177 patients with intermediate or high-risk prostate cancer who had undergone staging with FCH PET-CT before ePLND. Images were obtained with either the conventional Philips Gemini PET-CT (\(n = 93\)) or the digital SiPM-based GE Discovery MI PET-CT (\(n = 84\)) and compared.

**Results:** Images that were obtained using the Philips Gemini PET-CT system showed 19 patients (20%) with suspected lymph node metastases, whereas the GE Discovery MI PET-CT revealed 36 such patients (43%). The sensitivity, specificity, and positive and negative predictive values were 0.3, 0.84, 0.47, and 0.72 for the Philips Gemini, while they were 0.58, 0.62, 0.31, and 0.83 for the GE Discovery MI, respectively. The areas under the curves in a receiver operating characteristic curve analysis were similar between the two PET-CT systems (0.57 for Philips Gemini and 0.58 for GE Discovery MI, \(p = 0.89\)).

**Conclusions:** Marked differences in sensitivity and specificity were found for the different PET-CT systems, although the overall diagnostic performance was similar. These differences are probably due to differences in both hardware and software, including reconstruction algorithms, and should be considered when new technology is introduced.
1 | INTRODUCTION

Recently, positron emission tomography-computed tomography (PET-CT) scanners with digital silicon (Si)-photomultiplier (PM)-based technology have been introduced and have the potential to increase the sensitivity to detect pathological lesions (Hsu et al., 2017). New reconstruction algorithms have also been developed, such as the block-sequential regularization expectation maximization algorithm (BSREM), which is known commercially as Q.Clear (GE Healthcare) (Hsu et al., 2017; Ross, 2014). This method allows for fully convergent iterative reconstruction, which results in higher image contrast compared to conventional reconstruction methods while also minimizing the noise level. Together, the new hardware and software developments are hoped to improve the detection capabilities of particularly small metastases, such as lymph nodes (Teoh et al., 2015).

Prostate cancer is one of the most common cancers among men worldwide (Mottet et al., 2017). Prostatectomy with extended pelvic lymph node dissection (ePLND) is considered to be the best available procedure to obtain information about loco-regional staging and prognosis in patients with intermediate to high-risk prostate cancer (Fossati et al., 2017; Heidenreich et al., 2014, 2007; Mottet et al., 2017). PET-CT is often used for staging high-risk prostate cancer. Nowadays, prostate-specific membrane antigen (PSMA)-based radiopharmaceuticals are recommended (Giesel et al., 2017). 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 high specificity but low sensitivity for the detection of lymph node metastases (Beheshti et al., 2010; Budiharto et al., 2011; Kjolhede et al., 2014; Puterman et al., 2021).

To the best of our knowledge, no studies have compared the performance of conventional and digital PET-CT in patients with prostate cancer. Although FCH PET-CT is not a superior method for the detection of lymph node metastases in high-risk prostate cancer, it has been used in a standardized manner in a southern county in Sweden for staging high-risk prostate cancer before prostatectomy with ePLND. Thus, this setting is suitable for comparing the real-world performance of conventional and digital PET-CT systems in large cohorts of patients where histopathology is available as a reference method.

In this study, we compared the ability to detect pelvic lymph node metastases in 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 silicon photomultiplier (SiPM)-based PET-CT system (Discovery MI; GE Healthcare) using BSREM. The images were obtained from patients who were undergoing clinical FCH PET-CT scanning. Histopathology from ePLND was used as a reference method.

2 | METHODS

2.1 | Patients and surgery

From January 2015 to November 2018, 291 patients were referred for clinical FCH PET-CT followed by prostatectomy with ePLND at Skåne University Hospital in Malmö and Lund, Sweden. Of these, 114 patients were excluded due to incomplete data in their medical records, declining to participate, or examination on a third PET-CT system, as shown in Figure 1. After exclusions, 177 patients with biopsy-verified intermediate or high-risk prostate cancer were enrolled in the study. The clinical and pathological characteristics of the patients included in the study are presented in Table 1.

The patients underwent examination on one of two PET-CT systems before they underwent prostatectomy with ePLND. 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 clinical reports of the PET-CT examination 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.

2.2 | PET-CT systems

Examination images were acquired on one of the following PET-CT systems: a Philips Gemini TF PET-CT (Gemini Time of Flight; Philips Healthcare) or a GE Discovery MI PET-CT (Discovery MI; GE Healthcare). 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 × 4.0 × 22 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 (NEMA) standards, the sensitivity was 7 cps/kBq. The system had a 16-slice CT (Oddstig et al., 2019). 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 $144 \times 144$ (voxel size, $4 \times 4 \times 4$ mm), and TF and CT attenuation corrections were included.

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, $4.0 \times 5.3 \times 25$ 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 NEMA standards, the sensitivity is 13 cps/kBq. The system has a 128-slice CT (Oddstig et al., 2019). PET image reconstruction was performed using BSREM including TF, the point-spread function, and CT-based attenuation correction with a 256 × 256 matrix (pixel size, $2.7 \times 2.7$ mm$^2$; slice thickness, 2.8 mm) and a $\beta$ value of 500 (Bjoersdorff et al., 2019).

2.3 | PET-CT imaging and interpretation

FCH was administrated intravenously at a dose of 4 MBq/kg after a minimum fasting time of 4 h. Whole-body PET-CT was performed after an accumulation time of 60 min 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 min per bed position.

The CT scans on the Philips Gemini TF were acquired with diagnostic quality using a 5-mm reconstructed slice thickness, a pitch factor of 0.938, a 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. On the GE Discovery MI, the diagnostic CT was performed with 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 when the body mass index (BMI) 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.

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 was 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: those with suspected/possible lymph node metastases and those without lymph node metastases. When the clinical report was ambiguous (e.g., possible but not certain metastases), the patient was considered to have abnormal lymph nodes in the subsequent analysis.

2.4 | Statistical analysis

Clinical and pathological information was retrospectively obtained from medical records. A $\chi^2$ test and a Mann–Whitney U-test were used to compare baseline variables for patients who were examined using the Discovery MI and Gemini TF. The overall diagnostic performance was analysed using receiver operating characteristic...
ROC curve analysis. Per-patient and per-side (left and right) sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the different PET-CTs using histology results from the ePLND as a reference method. The 95% confidence intervals were calculated for the groups. \( p < 0.05 \) was considered to indicate statistical significance. Statistical analysis were performed using IBM SPSS version 26 (IBM Corp.) and Stata 16.0 (StataCorp LLC).

### 3 RESULTS

#### 3.1 Patients

There were 93 patients who were imaged using a Philips Gemini PET-CT system and 84 patients who were imaged using a GE Discovery MI PET-CT. There were significant differences between the two groups regarding prostate-specific antigen (PSA) and pathological local tumor stage. There were no significant differences between the two groups regarding the Gleason score, clinical tumor stage, risk-group classification (Table 1), and the number of days between the biopsy and PET-CT examination.

#### 3.2 PET findings

According to the Philips Gemini system, 19 patients (20%) were considered to have suspected lymph node metastases. Based on the histology results, 30 patients (32%) had positive lymph nodes. According to the GE Discovery MI system, 36 patients (43%) were considered to have lymph node metastases, and 19 patients (23%) had positive lymph nodes based on histopathology (Table 2). The sensitivity was markedly higher for images that were obtained using the GE Discovery MI system compared with the Philips Gemini system. The specificity was lower for images that were obtained with the GE Discovery MI compared with the Philips Gemini system.

### Table 1 Characteristics of the patients

|                      | All patients \( n = 177 \) | Imaged on Philips Gemini \( n = 93 \) | Imaged on GE Discovery MI \( n = 84 \) | \( p \) values |
|----------------------|-----------------------------|--------------------------------------|--------------------------------------|----------------|
| Age mean (standard deviation) | 66 (7)                     | 64 (8)                               | 67 (6)                               | 0.1            |
| Gleason score at prostatectomy, n (%) |                          |                                      |                                      | 0.2            |
| 5–6                  | 22 (12)                     | 15 (16)                              | 7 (11)                               |                |
| 3 + 4                | 35 (20)                     | 21 (23)                              | 14 (17)                              |                |
| 4 + 3                | 31 (18)                     | 13 (14)                              | 18 (21)                              |                |
| 8–10                 | 89 (50)                     | 44 (47)                              | 45 (54)                              |                |
| PSA at diagnosis (ng/ml), n (%) |                          |                                      |                                      | 0.04           |
| <10                  | 90 (51)                     | 46 (50)                              | 44 (52)                              |                |
| Clinical tumour stage n (%) |                          |                                      |                                      | 0.7            |
| Tx, T0, T1           | 70 (40)                     | 34 (37)                              | 36 (43)                              |                |
| T2                   | 82 (46)                     | 44 (47)                              | 38 (45)                              |                |
| T3, T4               | 24 (14)                     | 14 (15)                              | 10 (12)                              |                |
| Missing              | 1 (0)                       | 1 (1)                                | 0 (0)                                |                |
| Pathological tumour stage, n (%) |                          |                                      |                                      | 0.009          |
| Tx, T0, T1           | 1 (1)                       | 1 (1)                                | 0 (0)                                |                |
| T2                   | 56 (32)                     | 21 (23)                              | 35 (42)                              |                |
| T3, T4               | 120 (68)                    | 71 (76)                              | 49 (58)                              |                |
| Risk group classification, n (%) |                          |                                      |                                      | 0.9            |
| High risk prostate cancer | 153 (86)                   | 80 (86)                              | 73 (87)                              |                |
| Intermediate risk prostate cancer | 24 (14)                    | 13 (14)                              | 11 (13)                              |                |

Note: The patients were imaged on either of two PET-CT systems, the Philips Gemini or GE Discovery MI. One patient had no clinical tumor stage since the rectum was amputated. The value in brackets is the standard deviation for the age mean and % for the rest patient characteristics. There were significant differences between the two groups regarding the PSA and pathological local tumor stage. High-risk prostate cancer = T2c–T3 and/or Gleason sum 8–10 or Gleason score 4 + 3 = 7 and/or PSA ≥ 20 µg/L. Intermediate risk prostate cancer = T2b–T2c and/or Gleason sum 7 and/or PSA 10–19 µg/L.

Abbreviations: PET-CT, positron emission tomography-computed tomography; PSA, prostate-specific antigen.
sensitivity, specificity, and positive and negative predictive values per patient and per side are shown in Table 3. The areas under the curves in the ROC curve analysis for correctly predicting lymph node metastases were similar between the systems (0.57 for Philips Gemini and 0.58 for GE Discovery MI; \( p = 0.89 \)).

4 | DISCUSSION

These results showed high specificity and low sensitivity for detecting lymph node metastases in patients who were examined using a conventional PET-CT system, and relatively low sensitivity and low specificity were observed for patients who were examined using a digital PET-CT system with FCH. However, the overall diagnostic performance (measured as the AUC in the ROC curve analysis) was similar (\( p = 0.89 \)) between the two PET-CT systems. This study compared the diagnostic performance of two generations of PET-CT systems in a clinical setting, including both hardware and software. There are some differences between the systems that could explain the results. The NEMA sensitivity differs between the systems (7 and 13 cps/kBq for the Philips PET-CT system and GE PET-CT system, respectively). The higher sensitivity of the GE PET-CT system is mostly due to a larger axial field of view.

The GE system also has a better time-of-flight, and a smaller pixel size was used in this setting. The reconstruction algorithm differs, and the GE system comes with an algorithm that includes a point-spread function and regularization with a prior (BSREM). The BSREM reconstruction algorithm has been shown to increase the visualization of small lesions (Bjöersdorff et al., 2019; Howard et al., 2017; Lindstrom et al., 2018; Teoh et al., 2015). The CT also differs from the PET-CT systems. The conventional system was equipped with a 16-slice CT, and the digital one had a more modern 128-slice CT. However, the 16-slice CT was found to be good enough to visualize lymph nodes, which can be seen in Figure 2.

The combination of new detector technology and new reconstruction algorithms has been found to increase image quality, the lesion-to-blood-pool SUV ratios in smaller lesions, the maximum SUV in lesions, and the number of detected lesions compared to the previous generation of scanners (Lindstrom et al., 2018; Nguyen et al., 2015; Oddstig et al., 2019; van der Vos et al., 2017; Zhang et al., 2018). However, this does not 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 the utmost 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 (Schillaci et al., 2010). The present 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 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.

### TABLE 2
Per patient analysis and per side analysis of \(^{18}F\)-fluorocholine PET-CT in detecting lymph node metastases using histology as a reference method

|                             | Histology |     |     |
|-----------------------------|-----------|-----|-----|
|                             | +         | -   | %   |
| Per patient analysis        |           |     |     |
| Philips Gemini               | +         | 9   | 10  | 20  |
|                            | -         | 21  | 53  | 80  |
|                            | %         | 32  | 68  |     |
| GE Discovery MI             | +         | 11  | 25  | 43  |
|                            | -         | 8   | 40  | 57  |
|                            | %         | 23  | 77  |     |
| Per side analysis           |           |     |     |
| Philips Gemini               | +         | 11  | 14  | 13  |
|                            | -         | 49  | 112 | 87  |
|                            | %         | 32  | 68  |     |
| GE Discovery MI             | +         | 14  | 42  | 33  |
|                            | -         | 24  | 88  | 67  |
|                            | %         | 23  | 77  |     |

Abbreviation: PET-CT, positron emission tomography-computed tomography.

### TABLE 3
Per patient and per side analysis for Philips Gemini PET-CT system and GE Discovery MI PET-CT system of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for prediction of lymph node metastases by PET-CT (95% confidence interval) with histopathology report as reference method

|                             | Per patient analysis | Per side analysis |
|-----------------------------|----------------------|-------------------|
|                             | Philips Gemini       | GE Discovery MI   | Philips Gemini | GE Discovery MI |
| Sensitivity                 | 0.30 (0.14–0.46)     | 0.58 (0.36–0.80)  | 0.18 (0.09–0.28) | 0.37 (0.22–0.52) |
| Specificity                 | 0.84 (0.75–0.93)     | 0.62 (0.50–0.73)  | 0.89 (0.83–0.94) | 0.68 (0.57–0.76) |
| PPV                         | 0.47 (0.25–0.70)     | 0.31 (0.16–0.46)  | 0.44 (0.25–0.64) | 0.25 (0.14–0.36) |
| NPV                         | 0.72 (0.61–0.82)     | 0.83 (0.71–0.94)  | 0.70 (0.63–0.77) | 0.79 (0.71–0.86)  |

Abbreviation: PET-CT, positron emission tomography-computed tomography.
study. However, the results of the dual imaging can 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 (note that these patients were not included in the present study). The SUV in small objects, such as lymph nodes, was higher when using the Discovery MI system compared with the Philips Gemini system due to differences in reconstruction methods and technology, such as the spatial resolution of the PET-CT system (Oddstig et al., 2019). This results 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 it is suggested that more lymph nodes may be interpreted as malignant when reviewing images that were obtained using the Discovery MI (Economou Lundeberg et al., 2019).

Similar to our results on the accuracy of FCH for detecting lymph node metastases with conventional PET-CT systems, previous studies have also observed 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 (Beheshti et al., 2010). This is similar to the results obtained by Kjolhede et al. (2014), 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 (Puterman et al., 2021), which was 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. The study included 252 patients over 4 years who were 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 [18F]-fluorodeoxyglucose rather than FCH (Economou Lundeberg et al., 2019; Hsu et al., 2017). Similar to our study, the sensitivity was higher for SiPM-based PET-CT than for conventional PET-CT systems.

4.1 Limitations

There were some limitations in our study. First, the study design was retrospective. This study included only patients who were clinically selected as suitable for prostatectomy using ePLND based on clinical factors and findings on the PET-CT. 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 was performed, but not a lesion-based analysis, because such data were not
available from the histopathological reports. Third, information about the size of the lymph nodes was not available in the pathology report. Fourth, the patients were not examined on both PET-CT systems, which makes a direct comparison impossible. Although all nuclear medicine physicians were experienced, there is a possibility of inconsistent image interpretation over time. Finally, there were some significant differences between the study groups regarding patient characteristics, with higher PSA values and higher pathological tumor stage in the patients imaged on the Philips Gemini system. Although the overall risk group classification was similar between the patient groups, it cannot be ruled out that differences in baseline characteristics influenced the results.

5 | CONCLUSIONS

Conventional and digital FCH PET-CT, including reconstruction algorithms according to the vendor recommendations, had similar overall diagnostic performance 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 was probably due to differences in both hardware and software, including reconstruction algorithms, and should be considered when new technology is introduced.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

ORCID

Mimmi Bjöersdorff https://orcid.org/0000-0001-8715-507X
Jenny Oddstig https://orcid.org/0000-0002-7588-5873
Sophia Zackrisson https://orcid.org/0000-0001-5678-3882
Henrik Kjölhede https://orcid.org/0000-0001-6441-4729
Anders Bjartell https://orcid.org/0000-0002-5761-3786
Per Wollmer https://orcid.org/0000-0003-2448-9931
Elin Trägårdh https://orcid.org/0000-0002-7116-303X

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