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# $^{18}\text{F}$ -DCFPyL PET/CT in primary staging of prostate cancer



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## Abstract

**Background:** Correct primary staging is mandatory for therapy selection and to determine prognosis in prostate cancer patients. Commonly used diagnostic procedures including Computed Tomography (CT), Magnetic Resonance Imaging, Choline Positron Emission Tomography/Computed Tomography (PET/CT) and extended lymph node dissection (ePLND) have suboptimal diagnostic accuracy for primary staging. PSMA targeting radiopharmaceuticals have shown better diagnostic accuracy than commonly used imaging procedures. This study presents data of a retrospective cohort of patients that received PET/CT with  $^{18}\text{F}$ -DCFPyL for staging of primary prostate cancer.

**Methods:** From November 2016 until April 2018 all consecutive patients that received  $^{18}\text{F}$ -DCFPyL PET/CT for primary staging of prostate cancer were included in the study.  $^{18}\text{F}$ -DCFPyL PET findings in the primary tumour were scored. Detection rates of metastases were calculated for different clinical parameters, including PSA, Gleason score, clinical T-stage and risk on having lymph node metastases according to established prediction models. Subsequently, for lymph nodes,  $^{18}\text{F}$ -DCFPyL PET findings were compared to morphological features on the co-registered contrast enhanced CT and, for patients with risk on lymph node metastases > 5% according to prediction models, it was scored whether  $^{18}\text{F}$ -DCFPyL positive lymph nodes were present at locations that would be resected during ePLND, as well as presence of positive nodes or other metastases outside this area.

**Results:** One hundred thirty-three patients were analysed. Increased  $^{18}\text{F}$ -DCFPyL uptake in the primary tumour was found in 98% of the patients. In 69 patients increased  $^{18}\text{F}$ -DCFPyL uptake was found in lymph nodes, of which 48 and 45% had unsuspected morphological characteristics on CT (size cut-off  $\leq 6$  mm short axis), for locoregional and distant nodes, respectively. In 43% of patients  $^{18}\text{F}$ -DCFPyL PET/CT detected lesions suspicious for metastases outside the ePLND area.  $^{18}\text{F}$ -DCFPyL PET/CT detection rates are in line with established prediction models of risk on lymph node metastases.

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**Conclusion:**  $^{18}\text{F}$ -DCFPyL PET/CT shows more lymph nodes with pathological characteristics as compared to the co-registered contrast enhanced CT alone.  $^{18}\text{F}$ -DCFPyL PET/CT detects lesions suspicious for metastases outside the ePLND area in 43% of patients, with risk on lymph node metastases exceeding 5%, which therefore may be excluded for ePLND.  $^{18}\text{F}$ -DCFPyL PET/CT detection rates are in line with established prediction models of risk on lymph node metastases. Large prospective trials that compare  $^{18}\text{F}$ -DCFPyL findings with histopathological findings after ePLND are needed in order elucidate sensitivity of  $^{18}\text{F}$ -DCFPyL PET/CT and to position  $^{18}\text{F}$ -DCFPyL PET/CT in the staging algorithm for primary prostate cancer.

**Keywords:** PSMA,  $^{18}\text{F}$ -DCFPyL, PET/CT, Prostate cancer, Primary staging

## Background

Primary staging of prostate cancer remains challenging, while correct staging is mandatory for optimal therapy selection and to determine prognosis. Generally prostate cancer spreads to lymph nodes and/or bone before other tissues are affected and therefore screening for metastases at primary staging is primarily focussed at detection of bone and lymph node metastases. According to recent European Association of Urology (EAU) prostate cancer guidelines metastatic screening is recommended for intermediate and high risk prostate cancer, including at least cross-sectional abdominopelvic imaging and  $^{99\text{m}}\text{Tc}$ -phosphonate bone scan (Mottet et al. 2017).

Different cross-sectional imaging options are available for screening for lymph node metastases, of which abdominopelvic Computed Tomography (CT) and T1-T2-weighted Magnetic Resonance Imaging (MRI) are most commonly used. Assessment of nodal invasion is done by using of the short axis lymph node diameter and morphology. However there is a significant overlap in size of metastatic and non-metastatic lymph nodes and the best cut-off value remains a matter of debate. As a result the sensitivity of CT and MRI is around 40% with specificities around 80% (Hovels et al. 2008; Harisinghani et al. 2003).  $^{11}\text{C}$ -choline or  $^{18}\text{F}$ -fluorocholine Positron Emission Tomography/Computed Tomography (Choline PET/CT) provides functional characterisation in addition to morphological characterisation and could therefore overcome the limitations of CT and MRI. Reported sensitivities and specificities for  $^{11}\text{C}$ -choline or  $^{18}\text{F}$ -fluorocholine PET/CT are around 50 and 95%, respectively (Evangelista et al. 2013; Mapelli and Picchio 2015).

Due to limited diagnostic accuracy of abovementioned imaging modalities extended Pelvic Lymph Node Dissection (ePLND) is still considered the most accurate procedure for staging of lymph node metastases (Fossati et al. 2017). According to the EAU guidelines ePLND is recommended when risk on lymph node metastasis, as calculated by established prediction models, exceeds 5% (Mottet et al. 2017). Although considered most accurate, also ePLND has suboptimal diagnostic characteristics. Several studies have reported a considerable percentage of positive nodes outside the dissected area, even when no metastases are found in ePLND specimens (Jeschke et al. 2005; Brenot-Rossi et al. 2005; Heidenreich et al. 2002). Furthermore, this invasive procedure is accompanied by significant morbidity while presence of any therapeutic effect is still doubtful (Fossati et al. 2017).

PET/CT with radiopharmaceuticals that target the Prostate Specific Membrane Antigen (PSMA) is increasingly used for imaging of prostate cancer. PSMA is a

transmembrane protein that has 100 to 1000 fold higher expression at membranes of prostate cancer cells as compared to normal prostate cells and expression is higher in dedifferentiated tumours (Sokoloff et al. 2000). Initially PSMA PET/CT replaced Choline PET/CT for detection and localisation of lesions responsible for a biochemical recurrence after previous therapies with curative intent. Given the reported higher accuracy, including both better sensitivity and specificity of PSMA targeted radiopharmaceuticals in comparison to Choline PET/CT (Afshar-Oromieh et al. 2014; Bluemel et al. 2016), PET/CT with PSMA targeted radiopharmaceuticals may also play a role in primary staging of prostate cancer.

At present  $^{68}\text{Ga}$ -HEDB-CC ( $^{68}\text{Ga}$ -PSMA) is the most extensively studied PSMA targeting radiopharmaceutical in literature and also most widely used in clinical practice. However, the role of  $^{18}\text{F}$ -labelled PSMA targeted radiopharmaceuticals is evolving as a result of theoretically favourable imaging characteristics and the possibility to produce relatively large amounts of those tracers in cyclotron facilities (Sanchez-Crespo 2013). Clinical data on PSMA targeted PET/CT for primary staging is relatively scarce, especially for  $^{18}\text{F}$ -labelled PSMA targeting radiopharmaceuticals. Therefore, in this study data is presented of a retrospective cohort of patients that received PET/CT with  $^{18}\text{F}$ -DCFPyL, a promising  $^{18}\text{F}$ -labelled PSMA targeting radiopharmaceutical (Szabo et al. 2015), for staging of primary prostate cancer.

In order to position  $^{18}\text{F}$ -DCFPyL PET/CT between commonly used diagnostic procedures and prediction models we studied different aspects of  $^{18}\text{F}$ -DCFPyL PET/CT. First we report the detection rates of  $^{18}\text{F}$ -DCFPyL at different anatomical localisations and for different categories of serum PSA-values, Gleason-score, T-stage and risk on having lymph node metastases according to established prediction models. Second, functional characterisation of lymph nodes according to increased  $^{18}\text{F}$ -DCFPyL uptake is compared to morphological features of those lymph nodes on the co-registered contrast enhanced CT in order to indicate additional value of  $^{18}\text{F}$ -DCFPyL PET/CT. Third, it is reported for patients with risk on lymph node metastases > 5% according to prediction models, whether  $^{18}\text{F}$ -DCFPyL positive lymph nodes were present at locations that would be resected during ePLND, as well as presence of positive nodes or other metastases outside this area. Finally, the possible clinical impact, which may be derived from the presented data, of  $^{18}\text{F}$ -DCFPyL PET/CT as a diagnostic procedure in primary staging of prostate cancer is discussed.

## Methods

### Patients

From 16 November 2016 till 13 April 2018 all consecutive patients that received  $^{18}\text{F}$ -DCFPyL PET/CT for primary staging of prostate cancer at our department were included in the study. Exclusion criteria included: history of known other malignancy except basal cell skin cancer, deviation of the standard  $^{18}\text{F}$ -DCFPyL acquisition protocol and use of androgen deprivation therapy. The study passed the local scientific board and approval of the local ethical committee for the present study was waived since the study does not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (section 1.b WMO, 26th February 1998). Furthermore, as a standard procedure on our department, all included

patients gave written consent for usage of their anonymous data for scientific purposes. Besides the standard  $^{18}\text{F}$ -DCFPyL PET/CT no additional measurements or actions affecting the patient were performed.

### Image acquisition

$^{18}\text{F}$ -DCFPyL was produced and synthesized by an on-site cyclotron facility. One hundred and twenty minutes post injection of  $^{18}\text{F}$ -DCFPyL, PET images were acquired on a Siemens Biograph-16 TruePoint PET/CT (Siemens Healthcare, Knoxville, U.S.). Images were acquired from the inguinal region to the base of the skull (5 min per bed position). Data was reconstructed using an iterative OSEM-3D algorithm; 4 iterations, 16 subsets and 5 mm Gaussian filter. Image matrix size was  $256 \times 256$ , pixel spacing  $2.67 \times 2.67$  mm and slice thickness 4 mm. For attenuation correction a radiocontrast enhanced CT (110 mAs at 110–130 kV) was typically acquired. Collimation was  $16 \times 1.2$  mm, pitch 0.95, slice thickness 4 mm and matrix size  $512 \times 512$ . This resulted in voxel sizes of  $1.37 \times 1.37$  mm for CT images for attenuation correction and  $0.98 \times 0.98$  mm for diagnostic CT images.

### Data acquisition

Baseline data of all patients including age, initial PSA, Gleason-score, and cTNM-stage prior to  $^{18}\text{F}$ -DCFPyL PET/CT, other imaging prior to  $^{18}\text{F}$ -DCFPyL PET/CT (within 6 weeks), dosage of  $^{18}\text{F}$ -DCFPyL and use of androgen deprivation therapy was prospectively entered in a database. The risk on having lymph node metastases was calculated using the Memorial Sloan Kettering Cancer Center (MSKCC) nomograms ([https://www.mskcc.org/nomograms/prostate/pre\\_op](https://www.mskcc.org/nomograms/prostate/pre_op)) and the ROACH formula (Roach et al. 1994). Lesions suspected for prostate cancer were scored at different anatomical locations, including: prostate, seminal vesicles, locoregional lymph nodes (N1 according to the Prostate Cancer Staging of the American Joint Committee on Cancer, 7th edition), distant lymph nodes (M1a), bone lesions (M1b), other distant metastases (M1c). For  $^{18}\text{F}$ -DCFPyL positive lymph nodes the short axis diameter of the smallest and largest lymph node per anatomical location was measured on the co-registered diagnostic contrast enhanced CT. Thereby for CT the criterion of a short axis diameter of  $> 6$  mm was used for malignancy. Additionally, it was scored by an experienced Nuclear Medicine Physician in association with an Urologist experienced in radical prostatectomy (M.W. and T.R.), whether  $^{18}\text{F}$ -DCFPyL positive lymph nodes were present at locations that would be resected during ePLND, as well as presence of positive nodes outside this area. Nodes in the ePLND area included nodes adjacent to external iliac artery and vein, nodes within the obturator fossa located cranially and caudally to the obturator nerve, nodes medial and lateral to the internal iliac artery and common iliac lymph nodes at least up to the ureteric crossing.

### Results

A total of 134 patients were included in the study. One patient was excluded because the  $^{18}\text{F}$ -DCFPyL PET/CT was acquired at a deviant time point. The patients' characteristics of the evaluated 133 patients are presented in Table 1.

**Table 1** Patients' Characteristics

No. of patients	133	
Mean Age (y)	71 (range, 44–88)	
Median PSA at scanning (ng/mL)	25.0 (range, 0.3–3400)	
PSA category (No. of patients)		
< 10	31	
10–19.9	20	
20–49.9	48	
50–99.9	12	
> 100	19	
Gleason score (No. of patients)		
6	9	
7	28	
8	38	
9	47	
10	6	
Unknown	5	
cT stage (No. of patients)		
x	6	
1	9	
2	43	
3	64	
4	11	
cN stage (No. of patients)		
x	117	
0	10	
1	6	
cM stage (No. of patients)		
x	118	
0	11	
1a	1	
1b	3	
Risk on lymph node metastases categories (No. of patients)	MSKCC nomogram	ROACH formula
0–19.9	20	6
20–39.9	21	47
40–59.9	31	43
60–79.9	22	11
80–100	33	20
Relevant imaging before <sup>18</sup> F-DCFPyL PET/CT		
None	92	
<sup>99m</sup> Tc-HDP BS + SPECT/CT	22 <sup>a</sup>	
<sup>18</sup> F-NaF PET/CT	7	
MRI	9	
CT	2	
<sup>18</sup> F-FDG PET/CT	1	

<sup>a</sup>without SPECT/CT images in 4 cases

### Detection rates of $^{18}\text{F}$ -DCFPyL PET/CT

$^{18}\text{F}$ -DCFPyL PET/CT showed increased uptake in the prostate in 131 patients (97.8%). One patient without increased  $^{18}\text{F}$ -DCFPyL uptake in the prostate was diagnosed with Gleason 6 prostate cancer by transurethral resection of prostate tissue, the PET/CT showed increased  $^{18}\text{F}$ -DCFPyL uptake in a seminal vesicle suspicious for prostate cancer localisation. The other patient with a  $^{18}\text{F}$ -DCFPyL negative prostate had a Gleason 7 adenocarcinoma of the prostate at needle biopsy and a needle biopsy proven left iliac lymph node metastasis of 37 mm short axis diameter, which was also negative on  $^{18}\text{F}$ -DCFPyL PET/CT (Broos et al. 2018). Increased uptake in seminal vesicles was seen in 51 patients (38.1%).

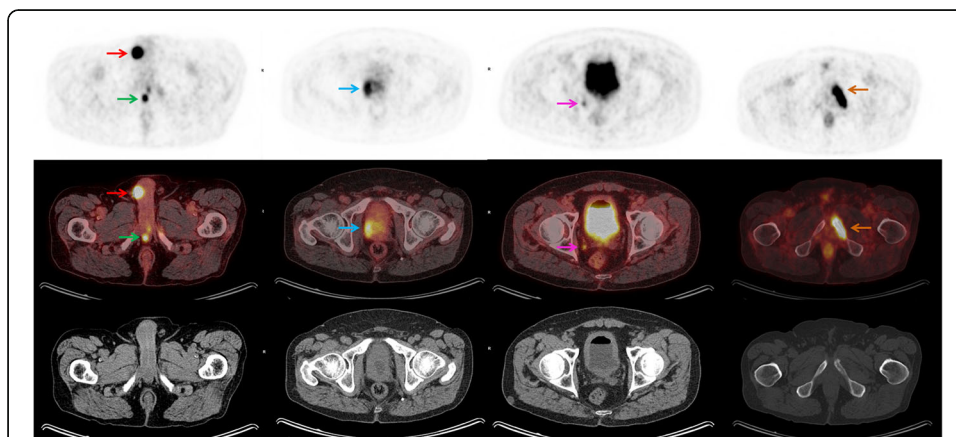
Increased  $^{18}\text{F}$ -DCFPyL uptake was found in locoregional and distant lymph nodes in 69 (51.5%) and 29 patients (21.6%), respectively. Nine patients (6.7%) had suspected lymph node metastases in the mediastinum and 7 (5.2%) had positive Virchow nodes.

Thirty-six/133 patients (26.9%) showed evidence of bone metastases, of which 11 (8.3%) had diffuse skeletal disease. Suspicion on metastases in other organs was raised in 7 patients, of which 6 had suspicion of lung metastases and 1 patient had positive lesions in the penile bulb and corpora cavernosa suggestive for metastases (Fig. 1).

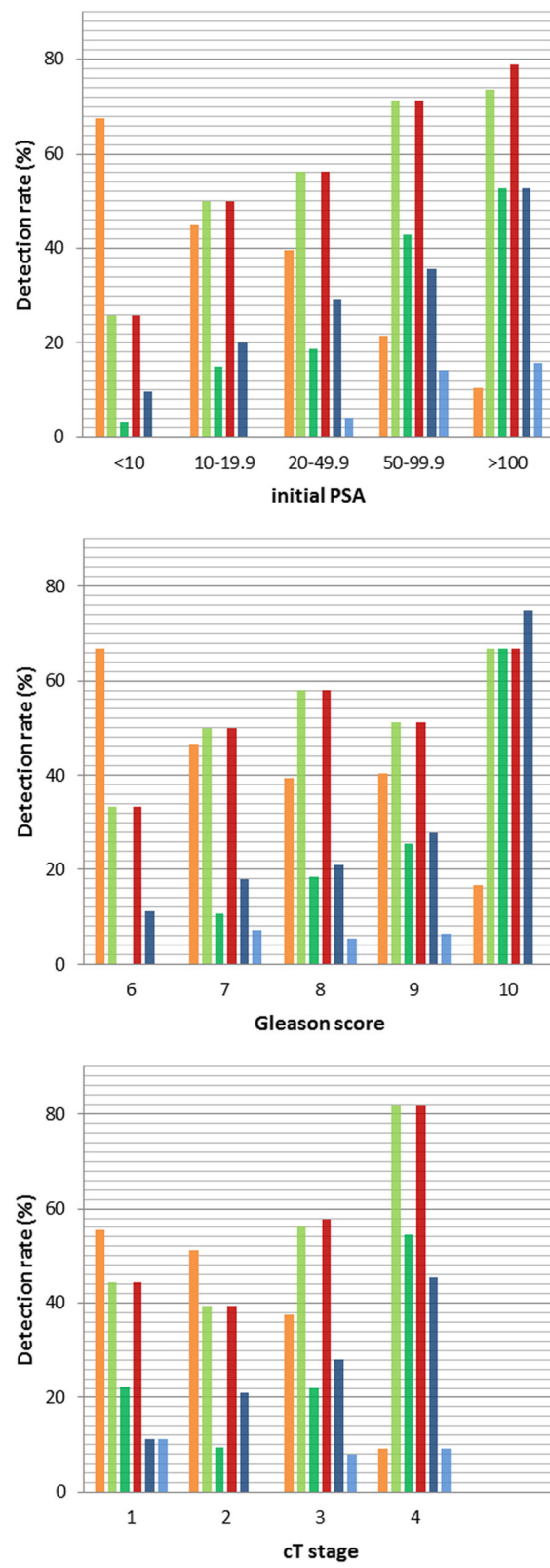
Detection rates of  $^{18}\text{F}$ -DCFPyL PET/CT in relation to PSA, Gleason score, clinical T-stage and risk on lymph node metastases according to MSKCC nomograms and ROACH formula are presented in Figs. 2 and 3.

### $^{18}\text{F}$ -DCFPyL positive lesions compared to morphological characteristics on CT

In comparison with morphological characteristics on contrast enhanced CT, in 61/69 patients (98.4%) with evidence of locoregional lymph node metastases increased  $^{18}\text{F}$ -DCFPyL uptake was found in at least one locoregional node with a short axis diameter of  $\leq 6$  mm, while in 33/69 of those patients (47.8%) all locoregional node with increased  $^{18}\text{F}$ -DCFPyL had a short axis diameter of  $\leq 6$  mm. Twenty-six/29 patients (89.7%) had  $^{18}\text{F}$ -DCFPyL positive distant nodes with a short axis of  $\leq 6$  mm, while for



**Fig. 1** Increased  $^{18}\text{F}$ -DCFPyL uptake in the penile bulb (green arrow) and the right corpus cavernosa (red arrow) in a patient with adenocarcinoma of the prostate (T3a G17 (4 + 3) iPSA 41.0). The  $^{18}\text{F}$ -DCFPyL PET/CT showed also increased uptake in the prostate (blue arrow) and evidence of lymph node (pink arrow) and bone metastases (light brown arrow). No histopathological biopsies were taken from the penile lesions, since this would not affect clinical management. No imaging follow-up of those lesions was present



**Fig. 2** (See legend on next page.)



(See figure on previous page.)

**Fig. 2** Detection rate of <sup>18</sup>F-DCFPyL PET/CT in relation to initial PSA, Gleason score and clinical T-stage at different anatomical localisations. No metastases (orange), locoregional lymph nodes (light green), distant lymph nodes (dark green), both locoregional and distant lymph nodes (red), bone (dark blue) and other sites (light blue)

13 of those patients (44.8%) the largest suspicious node did not exceed 6 mm (Table 2). In only one patient an enlarged lymph node on contrast enhanced CT was found without increased <sup>18</sup>F-DCFPyL uptake. This case is already discussed in a former paragraph (Broos et al. 2018).

**<sup>18</sup>F-DCFPyL findings in- and outside the ePLND area**

All but one patient in the cohort had a chance exceeding 5% on having lymph node metastases according to MSKCC nomograms and ROACH formula. Therefore for 132 patients it was scored whether <sup>18</sup>F-DCFPyL positive lymph nodes were present at locations that would be resected during ePLND; as well as presence of positive nodes or metastases outside this area.

Forty-one/132 patients (31.1%) had evidence of lymph node metastases only (N1 or M1a according to TNM 7th edition). Of those 41 patients 36 (87.9%) had positive nodes in the ePLND area, of which 15 (36.6%) had also positive nodes outside the ePLND area. Suspected lymph nodes outside the ePLND area included nodes in the pelvis (prevesical lymph nodes in 4 patients, mesorectal lymph nodes in 7 patients and nodes dorsally from the psoas muscle in 2 patients) and distant lymph nodes in 9 patients. Five/41 patients (12.2%) had only positive nodes outside the ePLND area, all mesorectally localised. Thirty-seven patients/132 (28.0%) showed evidence of distant metastases other than lymph nodes metastases (M1b or M1c). Fifty-four/132 patients (40.1%) had no evidence of any metastasis on <sup>18</sup>F-DCFPyL PET/CT (N0 M0).

**Table 2** Frequency table showing short-axis diameter of smallest and largest <sup>18</sup>F-DCFPyL positive lymph nodes in the pelvis and outside the pelvis on a per patient basis

Short-axis diameter (mm)	Locoregional lymph nodes				Distant lymph nodes			
	Smallest		Largest		Smallest		Largest	
	Frequency	Cumulative (%)	Frequency	Cumulative (%)	Frequency	Cumulative (%)	Frequency	Cumulative (%)
1	3	4.3	1	1.4	2	6.9		
2	16	27.5	5	8.7	7	31.0	1	3.4
3	19	55.1	8	20.3	5	48.3	2	10.3
4	14	75.4	9	33.3	10	82.8	6	31.0
5	6	84.1	3	37.7	2	89.7	2	37.9
6	3	88.4	7	47.8	0	89.7	2	44.8
7-8	6	97.1	8	59.4	1	93.1	5	62.2
9-10			5	66.7	1	96.6	2	69.0
11-15	1	98.6	13	85.5	1	100	5	86.2
> 15	1	100	10	100			4	100

According to EAU prostate cancer guideline lymph nodes with a short axis > 8 mm in the pelvis and > 10 mm outside the pelvis are usually considered malignant



### Other imaging performed

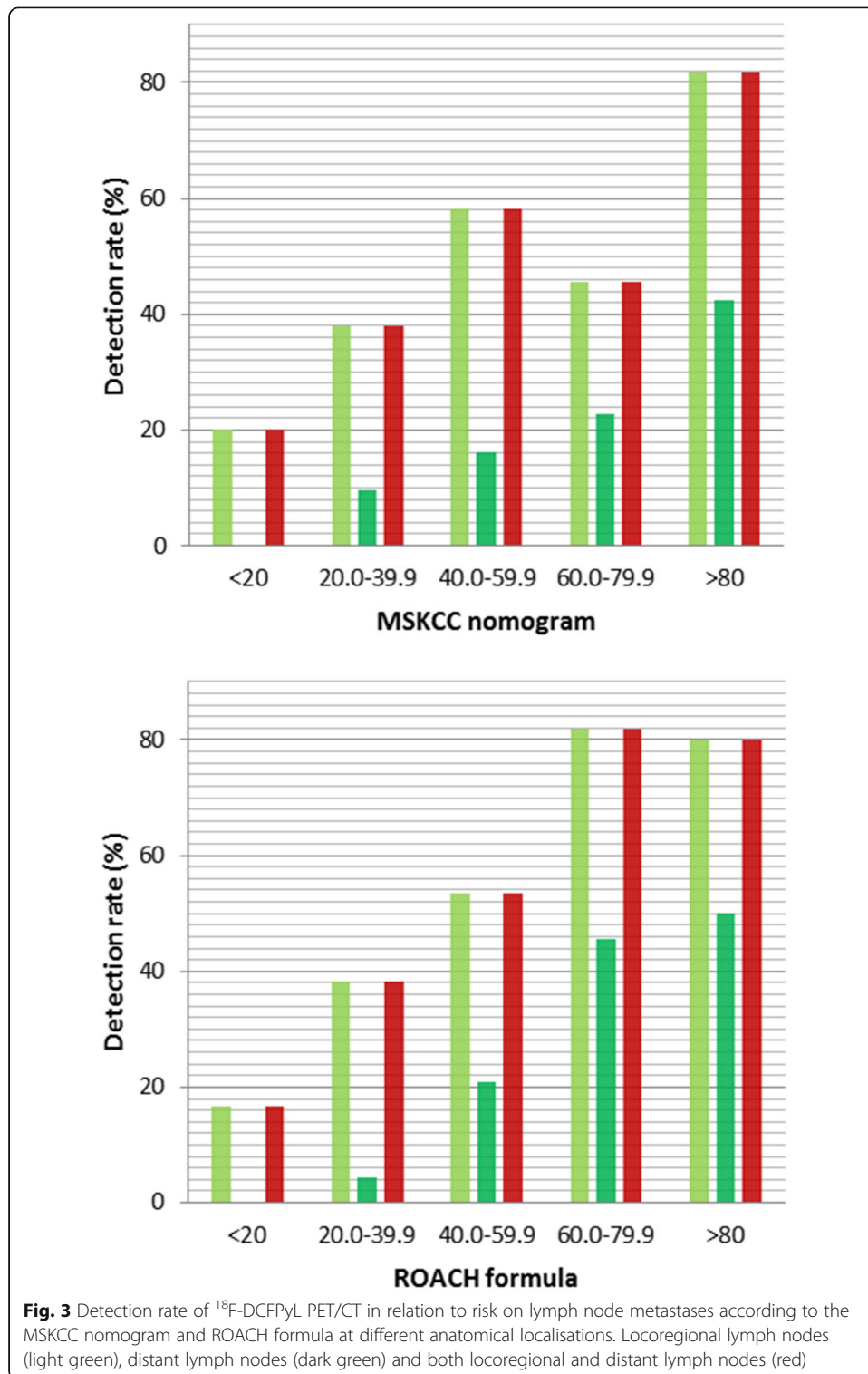
For 95 patients (71.4%)  $^{18}\text{F}$ -DCFPyL PET/CT was the first imaging procedure used for staging purposes. In the other 38 patients, other imaging modalities for staging were used prior to  $^{18}\text{F}$ -DCFPyL PET/CT, including 22  $^{99\text{m}}\text{Tc}$ -HDP bone scans (18 SPECT/CT), 7  $^{18}\text{F}$ -NaF PET/CTs and 9 T1-T2 weighted MRIs of pelvis and spine. Of the bone scans and  $^{18}\text{F}$ -NaF PET/CTs respectively, 17 and 3 were negative and 5 and 4 showed equivocal findings, none were positive. In 2 and 1 patients enlarged lymph nodes were encountered on SPECT/CT and  $^{18}\text{F}$ -NaF PET/CT, respectively. MRI showed signs of bone metastases in 1 patient and in 3 patients equivocal findings were encountered. In 1 patient, enlarged lymph nodes were found with MRI.

In 17 patients with negative bone scans,  $^{18}\text{F}$ -DCFPyL detected 3 bone metastases in 1 patient and in 5 patients with equivocal findings bone metastases were detected in 2 patients, respectively 1 and 38 metastases. In 1 patient with equivocal findings on  $^{18}\text{F}$ -NaF PET/CT, 6 bone metastases were detected with  $^{18}\text{F}$ -DCFPyL PET/CT, while no bone metastases were detected with  $^{18}\text{F}$ -DCFPyL PET/CT in the other 6 patients previously scanned with  $^{18}\text{F}$ -NaF.  $^{18}\text{F}$ -DCFPyL PET/CT showed no bone metastases in 1 patient with suspicion on diffuse bone disease on MRI. All 3 equivocal MRI findings were negative on  $^{18}\text{F}$ -DCFPyL PET/CT. In 1/4 patients with negative bone findings on MRI,  $^{18}\text{F}$ -DCFPyL PET/CT showed 2 bone metastases. In all 4 patients with enlarged lymph nodes on MRI or the CT accompanying bone scan or  $^{18}\text{F}$ -NaF PET, lymph node metastases were found with  $^{18}\text{F}$ -DCFPyL PET/CT. Out of 30 patients without enlarged nodes on imaging before  $^{18}\text{F}$ -DCFPyL PET/CT, 16 patients had positive nodes on  $^{18}\text{F}$ -DCFPyL PET/CT.

Additionally 3 patients received imaging for other purposes within 6 weeks prior to  $^{18}\text{F}$ -DCFPyL. In 2 patients that received CT,  $^{18}\text{F}$ -DCFPyL PET/CT showed bone metastases, which were only seen on CT in 1 patient. No lymph node metastases were found in those patients. In 1 patient lymph node metastases on  $^{18}\text{F}$ -FDG PET/CT were confirmed by  $^{18}\text{F}$ -DCFPyL PET/CT, which additionally showed a bone metastasis.

### Discussion

There is very limited data on the value of  $^{18}\text{F}$ -DCFPyL PET/CT in primary staging of prostate cancer in present literature.  $^{18}\text{F}$ -DCFPyL PET/CT has been intra-individually compared with  $^{18}\text{F}$ -PSMA-1007 for primary staging in a pilot study in 12 prostate cancer patients (Giesel et al. 2017). Imaging with both tracers resulted in identical clinical findings. No histopathological confirmation of metastases is reported in this study. To our knowledge no other data is present in literature on  $^{18}\text{F}$ -DCFPyL PET in primary staging, therefore this study is the first to present data of a large cohort (> 100 patients) in the setting of primary staging. Also for other  $^{18}\text{F}$ -labelled PSMA targeting radiopharmaceuticals there is no data present on its role in newly diagnosed prostate cancer. For  $^{68}\text{Ga}$  labelled PSMA targeting radiopharmaceuticals, a recent systematic review focusing on primary staging of prostate cancer shows a substantial variation in methodology and outcomes amongst studies. However it is concluded that the ability of  $^{68}\text{Ga}$ -PSMA PET to detect malignant lesions is evident across studies, with most studies demonstrating increased detection rates with respect to conventional imaging modalities (Corfield et al. 2018).



All but two studies included a limited number of up to 30 patients. A study by Maurer et al. included 130 patients with intermediate to high risk prostate cancer staged with <sup>68</sup>Ga-PSMA PET/CT or PET/MRI and compared PET findings for lymph nodes with morphological findings on CT or MRI with histopathological evaluation as

the standard of reference (Maurer et al. 2016). In 119 (91.6%) patients increased uptake in the primary tumour was found. Increased tracer uptake was found in lymph nodes in 28 patients (21.5%). Compared to histopathology  $^{68}\text{Ga}$ -PSMA-PET detected 27 of 41 patients with histologically proven lymph node metastases while 1 of 89 patients without metastatic disease in lymph node was positive on  $^{68}\text{Ga}$ -PSMA PET. As a result sensitivity and specificity of  $^{68}\text{Ga}$ -PSMA PET for lymph node metastases was 66 and 99%, respectively. The other large cohort study by Uprimny et al. included 90 patients, which received  $^{68}\text{Ga}$ -PSMA PET/CT for primary staging (Uprimny et al. 2017). Eighty-two patients (91.1%) demonstrated pathologic tracer accumulation in the primary tumour, 24 patients (26.7%) lymph nodes with pathologic tracer accumulation consistent with metastases were detected and 11 patients (12.2%) revealed lesions suspicious for bone metastases. The relatively high detection rate of the primary tumour in studies with  $^{68}\text{Ga}$ -PSMA is in line with the results of the present study. However, in the present study metastases in lymph nodes and bone marrow were detected more frequently compared to the studies using  $^{68}\text{Ga}$ -PSMA. This can possibly be explained by the relatively higher PSA at time of PET/CT in the present cohort (median PSA 25.0 ng/ml) in contrast to the studies using  $^{68}\text{Ga}$ -PSMA (median PSA respectively 9.7 and 11.5 ng/ml). The  $^{68}\text{Ga}$ -PSMA studies did not present detection rates for different PSA categories and therefore a fair comparison cannot be made.

According to morphological imaging (contrast enhanced CT), the presented data show that  $^{18}\text{F}$ -DCFPyL PET/CT is superior to morphological criteria found on the co-registered contrast enhanced CT alone, which is in agreement with findings with  $^{68}\text{Ga}$ -PSMA PET/CT (Corfield et al. 2018). Locoregional lymph node and distant lymph node metastases were detected with  $^{18}\text{F}$ -DCFPyL PET/CT in 33 and 13 patients, respectively, without lymph nodes > 6 mm in these areas on CT. According to ePLND, 57/133 of the patients (43.2%) with risk on lymph node metastases exceeding 5%, had evidence of metastasised disease outside the ePLND area. Twenty of those patients had lymph node metastases only. Patients with metastases outside the ePLND area will not benefit from ePLND and can be excluded for this procedure by  $^{18}\text{F}$ -DCFPyL PET/CT. Twenty-one patients (15.9%) had evidence of lymph node metastases in the ePLND area only. It could be speculated that those patients might benefit from ePLND. Another 54 patients (40.9%) showed no evidence of metastases at all, given the generally moderate sensitivity found in studies with  $^{68}\text{Ga}$ -PSMA (Maurer et al. 2016; Budaus et al. 2016; van Leeuwen et al. 2017; Rahbar et al. 2016), this category of patients may also benefit from ePLND. Although, the sensitivity of  $^{18}\text{F}$ -DCFPyL in this patient category remains unknown, which emphasizes the need of histopathological confirmed studies with  $^{18}\text{F}$ -DCFPyL PET/CT.

In comparison to established prediction models of risk on lymph node metastases, detection of lymph node metastases with  $^{18}\text{F}$ -DCFPyL PET/CT shows great similarities. In comparison to MSKCC nomograms,  $^{18}\text{F}$ -DCFPyL only finds a lower number of patients with lymph node metastases (45.5%) in the category with a risk between 60.0 and 79.9%. While in comparison with the ROACH formula,  $^{18}\text{F}$ -DCFPyL PET/CT detected at least as much patients with lymph node metastases as predicted in all categories. Those prediction models are based on lymph node dissection templates (Roach 3rd et al. 1994). Therefore the similarities found between those prediction models and  $^{18}\text{F}$ -DCFPyL PET/CT detection rates suggest a good sensitivity of  $^{18}\text{F}$ -DCFPyL PET/

CT, which may suggest that  $^{18}\text{F}$ -DCFPyL PET/CT can be used to deselect patients for ePLND if no lymph node metastases are found with  $^{18}\text{F}$ -DCFPyL PET/CT, which would be in contrast to the relatively low sensitivity found for  $^{68}\text{Ga}$ -PSMA PET/CT. Therefore this finding warrants large prospective trials that compare  $^{18}\text{F}$ -DCFPyL findings with histopathological findings after ePLND in order to position  $^{18}\text{F}$ -DCFPyL PET/CT in the staging algorithm for primary prostate cancer.

Since there is a significant overlap in size of metastatic and non-metastatic lymph nodes the best cut-off value remains a matter of debate. In literature it can be found that a short-axis diameter larger than 6 mm on CT images of patients with prostate cancer, results in specificity for the detection of a malignant nodes of 97% (Oyen et al. 1994). If the threshold is changed to a short-axis diameter larger than 5 mm for metastases (in pelvic malignancies), the specificity drops to 78% (McMahon et al. 2010). Therefore in this study a cut-off value of larger than 6 mm was used for determination of malignant nodes on CT.

Although this cohort shows heterogeneity regarding some aspects, it is representative for the clinical practice in hospitals that treat large numbers of patients with prostate cancer. As an example of heterogeneity this cohort includes 38 patients that received other imaging studies for prostate cancer staging prior to  $^{18}\text{F}$ -DCFPyL PET/CT, which may introduce bias in the cohort. Most of those prior studies had equivocal or negative results for metastases, especially for bone metastases. The pre-test likelihood of presence of metastases in these patients is probably lower than in patients without any prior imaging study, which is supported by the fact that bone metastases were found in 18.5% of patients that had prior imaging procedures and in 29.2% of patients without prior imaging. Therefore, it is likely that the detection rates of  $^{18}\text{F}$ -DCFPyL PET/CT in a non-biased cohort will be at least as high as found in the present cohort.

Another limitation of the present study is the lack of histopathological confirmation of the suspected metastases on  $^{18}\text{F}$ -DCFPyL PET/CT, which is a consequence of the retrospective nature of the study and loss to follow-up of patients, which were referred for  $^{18}\text{F}$ -DCFPyL PET/CT by other hospitals. However, other PSMA targeting radiopharmaceuticals, of which those labelled with  $^{68}\text{Ga}$  are most extensively studied, show generally high specificities and positive predictive values both exceeding 90% (Maurer et al. 2016; Budaus et al. 2016; van Leeuwen et al. 2017; Rahbar et al. 2016; Afshar-Oromieh et al. 2015). Therefore lesions with increased  $^{18}\text{F}$ -DCFPyL, which fit in the pattern of metastatic spread of prostate cancer, should be considered as highly suggestive of prostate cancer.

## Conclusion

$^{18}\text{F}$ -DCFPyL PET/CT shows more lymph nodes with pathological characteristics as compared to the co-registered contrast enhanced CT alone.  $^{18}\text{F}$ -DCFPyL PET/CT detects lesions suspicious for metastases outside the ePLND area in 43% of patients, with risk on lymph node metastases exceeding 5%, which therefore may be excluded for ePLND.  $^{18}\text{F}$ -DCFPyL PET/CT detection rates are in line with established prediction models of risk on lymph node metastases. Large prospective trials that compare  $^{18}\text{F}$ -DCFPyL findings with histopathological findings after ePLND are needed in order elucidate sensitivity of  $^{18}\text{F}$ -DCFPyL PET/CT and to position  $^{18}\text{F}$ -DCFPyL PET/CT in the staging algorithm for primary prostate cancer.

**Abbreviations**

CT: Computed Tomography; EAU: European Association of Urology; ePLND: Extended Pelvic Lymph Node Dissection; MRI: Magnetic Resonance Imaging; MSKCC: Memorial Sloan Kettering Cancer Center; PET/CT: Positron Emission Tomography/Computed Tomography; PSMA: Prostate Specific Membrane Antigen

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**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

MW Protocol/project development, Data collection or management, Data analysis Manuscript writing. FvdZ Protocol/project development, Data collection and management, Manuscript editing. TR Protocol/project development, Data collecting and analysis, Manuscript editing. SS Data collection, Manuscript editing. MK Data collection, Manuscript editing. AD Data collection, Manuscript editing. VF Data collection, Manuscript editing. RK Protocol/project development, Data collection, Manuscript editing. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study passed the local scientific board and approval of the local ethical committee for the present study was waived since the study does not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (section 1.b WMO, 26th February 1998). As a result the need for informed consent was waived for this retrospective study.

**Competing interests**

The authors declare that they have no competing interests.

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