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Angaben zur Veröffentlichung / Publication details:

Rowe, Steven P., Andreas Buck, Ralph A. Bundschuh, Constantin Lapa, Sebastian E. Serfling, Thorsten Derlin, Takahiro Higuchi, Michael A. Gorin, Martin G. Pomper, and Rudolf A. Werner. 2022. "[18F]DCFPyL PET/CT for imaging of prostate cancer." *Nuklearmedizin - NuclearMedicine* 61 (03): 240–46. https://doi.org/10.1055/a-1659-0010.

Article published online: 2022-01-14

Review

[18F]DCFPyL PET/CT for Imaging of Prostate Cancer

[18F]DCFPyL PET/CT zur Prostatakarzinom-Bildgebung

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Schlüsselwörter

Prostatakarzinom, Theranostik, ^{18}F-DCFPyL

Key words

Prostate Cancer, Theranostics, ^{18}F-DCFPyL

received 12.09.2021
accepted 17.09.2021
published online 14.01.2022

Bibliography

Nuklearmedizin 2022; 60: 240–246
DOI 10.1055/a-1659-0010
ISSN 0029-5566

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ABSTRACT

Prostate-specific membrane antigen (PSMA)-directed positron emission tomography (PET) has gained increasing interest for imaging of men affected by prostate cancer (PC). In recent years, ^{68}Ga-labeled PSMA compounds have been widely utilized, although there is a trend towards increased utilization of ^{18}F-labeled agents. Among others, [^{18}F]DCFPyL (piflufolastat F 18, PYLARIFY) has been tested in multiple major trials, such as OSPREY and CONDOR, which provided robust evidence on the clinical utility of this compound for staging, restaging, and change in management. Recent explorative prospective trials have also utilized [^{18}F]DCFPyL PET/CT for response assessment, e. g., in patients under abiraterone or enzalutamide, rendering this ^{18}F-labeled PSMA radiotracer as an attractive biomarker for image-guided strategies in men with PC. After recent approval by the U.S. Food and Drug Administration, one may expect more widespread use, not only in the U.S., but also in Europe in the long term. In the present review, we will provide an overview of the current clinical utility of [^{18}F]DCFPyL in various clinical settings for men with PC.

ZUSAMMENFASSUNG

Die Positronen-Emissions-Tomografie (PET) mit PSMA (Prostata-spezifisches Membran-Antigen) gerichteten Liganden ist zunehmend in den Fokus der Bildgebung des Prostatakarzinoms (PC) bei Männern gerückt. In den letzten Jahren wurden in großem Umfang ^{68}Ga-markierte PSMA-Tracer verwendet, obwohl ein Trend zum verstärkten Einsatz von ^{18}F-markierten

Tracern zu beobachten ist. Unter anderem wurde [^{18}F]DCFPyL (Piflufolastat F 18, PYLARIFY) in mehreren großen Studien wie OSPREY und CONDOR untersucht, die eine belastbare Evidenz für den klinischen Nutzen dieses Tracers hinsichtlich Staging, Restaging und Änderung des Managements zeigten. Neuere prospektive Untersuchungen haben [^{18}F]DCFPyL PET/CT auch zur Beurteilung des Ansprechens eingesetzt, z. B. bei Patienten unter Abirateron oder Enzalutamid, was diesen ^{18}F-markierten PSMA-Radiotracer zu einem attraktiven Biomarker für bildgestützte Strategien bei Männern mit PC macht. Nach der kürzlich erfolgten Zulassung durch die U.S. Food and Drug Administration (FDA) ist nicht nur in den USA, sondern langfristig auch in Europa mit einer breiteren Anwendung zu rechnen. Im vorliegenden Review geben wir einen Überblick über den aktuellen klinischen Nutzen von [^{18}F]DCFPyL bei Männern mit PC in verschiedenen klinischen Situationen.

Introduction

Prostate-specific membrane antigen (PSMA)-targeted molecular imaging has seen an unprecedented success in recent years for staging, restaging, and response assessment in men with prostate cancer (PC) [1]. These imaging agents have not only demonstrated high accuracy for identifying putative sites of disease, but also allow for quantification of the therapeutic target *in vivo*[2]. As, such, PSMA is also increasingly utilized in a theranostic context using beta-particle-emitting therapeutic equivalents with favorable outcomes, e. g., when compared to best supportive care in advanced disease [3].

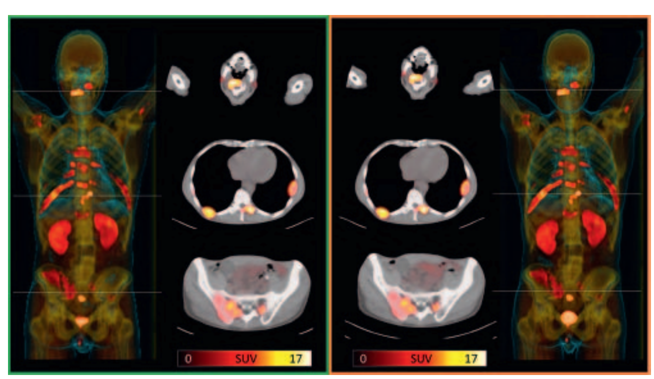
To date, ^{68}Ga-labeled PSMA positron emission tomography (PET) compounds have been widely used, but are being increasingly replaced by novel ^{18}F-labeled imaging agents [4]. Given their increased half-life of 110 min, the latter radiotracers have multiple advantages relative to their predecessors, such as potential of inter-center distribution [4]. In addition, the longer half-life of ^{18}F also allows for delayed imaging protocols, e. g., by application of furosemide to improve contrast in the pelvis for identifying potential PSMA-avid lymph node metastases [5]. Last, physical properties such as lower positron energy allow for substantial improvement of image quality and noise reduction [4].

Multiple ^{18}F-labeled PSMA PET radioligands have entered the clinical arena, e. g., [^{18}F]JK-PSMA-7, [^{18}F]PSMA-1007 or [^{18}F]DCFPyL (piflufolastat F 18, PYLARIFY) [4]. Of note, the latter imaging agent has been extensively investigated in multiple prospective clinical trials in various clinical contexts. Among others, the phase III, multicenter CONDOR (NCT03739684) trial demonstrated a high safety profile and substantial accuracy in identifying sites of disease in the setting of negative standard imaging, along with change in intended management in more than 63 % of patients [6]. In light of such benefit for the referring clinicians, [^{18}F]DCFPyL was recently approved by the U.S. Food And Drug Administration (FDA) [7]. As such, one may expect more widespread use of this agent not only in the United States, but also in Europe and other parts of the world in the long term. In this review we provide an overview of the current clinical utility of [^{18}F]DCFPyL PET/computed tomography (CT) in men with PC.

Biodistribution, safety, and quantitative considerations

Along with extensive preclinical evaluation [8, 9], [^{18}F]DCFPyL was first tested prospectively by Szabo and coworkers in nine hormone-naïve and castration-resistant patients with histologically confirmed metastatic PC. After injecting a maximum of 333 MBq, dosimetry revealed that kidneys received the highest absorbed dose, followed by the bladder wall, submandibular glands and liver, ranging from 0.0945 to 0.0380 mGy/MBq, giving a similar whole-body dose when compared to the most widely used radiotracer in oncology, 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG). Normal biodistribution included liver, spleen, kidneys, the lacrimal and salivary glands, and small bowel. No serious adverse events were recorded [10].

Furthermore, Jansen et al. conducted a test-retest study using [^{18}F]DCFPyL in 12 patients and reported high repeatability of both lesion detection rate and uptake [11]. That was further confirmed in another prospective trial with 23 subjects; relative to volumetric parameters, standardized uptake values (SUV) demonstrated better reproducibility with ^{18}F-DCFPyL, in particular for lymph node metastases (▶ **Fig. 1**). As such, if changes in semi-quantitative parameters are recorded between baseline and follow-up ^{18}F-DCFPyL PET/CT, the reader has certainty that such findings are not caused by uptake variability, suggesting this compound may be a reliable image biomarker for response assessment [12]. Li et al. also reported on variability in normal organ uptake using [^{18}F]DCFPyL and demonstrated less variability in normal liver relative to other organs [13]. Of note, the variability was even lower when compared to liver uptake using [^{18}F]FDG (coefficient of variation, [^{18}F]DCFPyL, 13.8–14.5 % vs. [^{18}F]FDG, 21–23 %) [13, 14]. In addition, a recent study also investigated whether uptake in normal organ correlates with higher tumor burden. However,



▶ **Fig. 1** Test [^{18}F]DCFPyL PET/CT (left) compared to retest [^{18}F]DCFPyL PET/CT (right). Maximum intensity projections of both scans showed almost identical tumor burden, predominantly in the skeleton. Transaxial PET/CTs are also displayed.

only a minimal tumor sink effect was noted in patients with increased [^{18}F]DCFPyL-avid tumor volume [15], but interpatient and intrapatient factors may impact the intrinsic organ variability [16]. Based on such findings, dosimetry for PSMA-targeted radioligand therapy (RLT) could be further improved [16] or PET protocols could be further refined to enhance uptake in putative sites of disease.

An initial lesion-by-lesion analysis with [^{18}F]DCFPyL compared to conventional imaging found that the detection rate for putative sites of disease was much higher with [^{18}F]DCFPyL. By re-analyzing the previously reported nine patients, a total of 138 definitive sites of abnormal uptake (1 equivocal) were recorded by using PSMA-PET, whereas conventional imaging including CT and bone scans revealed only 30 definitive sites attributable to PC (15 equivocal) [17]. Dietlein et al. also performed a head-to-head comparison of [^{18}F]DCFPyL with a ^{68}Ga-labeled agent in 14 PC patients with biochemically recurrent disease and reported not only an increased detection rate for the ^{18}F-labeled compound, but also an improved tumor-to-background ratio [18]. Of note, a head-to-head comparison of [^{18}F]DCFPyL with the clinically established ^{18}F-labeled agent PSMA-1007 has also been conducted in 12 PC patients 2 days apart. Both radiotracers identified identical lesions, with no significant differences in a semi-quantitative assessment. Normal organ uptake, however, was significantly different and the non-urinary excretion of [^{18}F]PSMA-1007 may allow for a more accurate read-out of local recurrence of pelvic lymph node metastases, whereas the lower liver background of [^{18}F]DCFPyL may provide higher interpretative certainty in cases of hepatic involvement [19]. A recent matched-pair analysis of 120 [^{18}F]PSMA-1007 PET/CTs and 120 [^{18}F]DCFPyL PET/CTs and also reported on an increased rate of less equivocal findings in the skeleton for the latter compound, thereby increasing the agreement rate for [^{18}F]DCFPyL PET/CT for bone lesions [20]. Another prospective study investigated the latter radiotracer relative to the bone-seeking PET agent Na^{18}F, with both scans occurring within 24 hours. Sensitivities were almost identical for lesions in the skeleton, but [^{18}F]DCFPyL also provided information on soft tissue. The authors concluded that there was no additional benefit to conducting a Na^{18}F PET/CT when a PSMA-targeted PET/CT has already been performed [21].

Imaging protocols and image interpretation

In brief, a fasting period is not required and patients should be well hydrated prior to the scan. Voiding before the scan is recommended, as such an approach may increase diagnostic certainty in the pelvis and also reduce the frequency of halo effects around the bladder [1]. 200 to 370 MBq are injected intravenously and current guidelines endorse an uptake time of 60 minutes [22]. Up to 4 min imaging per bed position is recommended and the field of view should include the base of the skull to midthigh [1, 22]. A recent study investigating a ^{68}Ga-labeled PSMA PET agent reported on higher accuracy if late imaging protocols and furosemide are used [5]. For [^{18}F]DCFPyL, the accurate timing of such forced diuresis protocols is important. Comparing patients who received furosemide simultaneously with [^{18}F]DCFPyL vs. a cohort 85 min after radiotracer injection, Wondergem et al. reported improved diagnostic accuracy for the late protocol, preferably with an image acquisition 120 min post-injection. [23]. For [^{18}F]DCFPyL, such delayed imaging protocols should be considered as such an approach reveals more than 38 % more sites of disease when compared to the commonly used 60 min protocol [24].

As use of PSMA-PET became more widespread, an increased rate of findings not attributable to PC were recorded. Those false-positive and -negative findings encompass a broad spectrum, including benign entities with increased PSMA expression, such as in the bone (Paget disease), lung (benign opacities), lymph nodes (reflecting a granulomatous process), gynecomastia, or adrenal adenoma [25]. In addition, an increased accumulation of PSMA-targeted radiopharmaceuticals has also been reported in patients after cerebral radionecrosis [26] or in sympathetic chain ganglia [27]. In light of those potential interpretative pitfalls, structured reporting systems for PSMA-PET have been proposed [28]. For instance, Eiber et al developed the "PROMISE" system, which refers to a molecular imaging-based TNM staging system ("miTNM"). Lesions can be rated using an expression score, which considers uptake levels relative to normal organ uptake (with blood pool, liver, and parotid glands serving as references). Local tumor is classified as "miT0" to "miT4", lymph nodes in the pelvis can be rated as "miN0" to "miN1b" (outside the pelvis, "miM1a") [29]. Organ metastases are categorized as "miM1b" in the skeleton, but "miM1c" if other distant organs are affected. Of note, a substantial inter-reader reproducibility was recorded in a recent prospective study [30].

Rowe and coworkers introduced the PSMA Reporting and Data System (RADS), which utilizes a scale related to reader confidence in a given lesion representing cancer for RADS-based imaging interpretation, e. g., for the breast (BI-RADS) [31, 32]. With an increasing PSMA-RADS score, the likelihood of malignancy also increases. That standardized framework also recommends further clinical work-up, e. g., to recommend biopsy or follow-up imaging for equivocal findings (PSMA-RADS-3A or -3B). Last, PSMA-RADS also assists in selecting patients for specific therapeutic regimens, including evaluation of PSMA expression in patients scheduled for ^{177}Lu-PSMA directed radioligand therapy (RLT) [32]. A recent study reported high interobserver agreement when PSMA-RADS was applied to [^{18}F]DCFPyL [33]. As such, a comprehensive characterization of segmented [^{18}F]DCFPyL PET/CTs in the context of PSMA-RADS has already been provided [34]. Recently, a novel standardized reporting guideline was endorsed by the European Association of Nuclear Medicine (E-PSMA), further emphasizing the need to harmonize PSMA PET/CT reports [35].

Staging

PSMA PET/CT has been more extensively evaluated in the setting of recurrent disease, although multiple studies focusing on [^{18}F]DCFPyL for staging have been published. In a retrospective study investigating 133 PC patients, [^{18}F]DCFPyL PET/CT revealed significantly more putative sites of disease when compared to the co-registered CT alone. Increased radiotracer accumulation in the prostate was revealed in the vast majority of included subjects

(97.8 %). In up to 48 % of the patients, an increased uptake was identified in lymph nodes, which were not enlarged on concomitant CT [36]. Gorin et al. investigated 25 men in a preoperative prospective setting with [^{18}F]DCFPyL before patients were scheduled for radical prostatectomy with standardized extended pelvic lymph node dissection. Such an approach allowed the use of surgical pathology as reference standard. First, sites of uptake were identified in the prostate of all imaged patients. Moreover, when compared with surgical specimen, analysis at the level of individual nodal packets resulted in 66.7 % sensitivity and 92.7 % specificity for [^{18}F]DCFPyL [37]. Of note, [^{18}F]DCFPyL PET/CT has not been compared against another imaging standard, but pathology, which may increase the rate of false-negatives, e. g., in terms of only very low PSMA expression identified by immunohistochemistry.

Further confirming the findings of Gorin et al. [37], the recent prospective, multi-center Phase II/III OSPREY trial (NCT02981368) reported on 252 patients who underwent [^{18}F]DCFPyL PET/CT for preoperative staging. For three readers, specificity and sensitivity for pelvic nodal involvement was 97.9 % and 40.3 %, respectively [38]. Of note, such rather low sensitivities have also been noted for ^{68}Ga-PSMA PET/CT and this may be partially explained by the heterogenous reader training and experience in interpreting such scans [1, 39]. As such, expertise is needed once PSMA-PET with [^{18}F]DCFPyL or other PSMA-targeting radiotracers become available outside of tertiary care medical centers [24], e.g, by introducing standardized reporting [28].

Restaging

A common indication for [^{18}F]DCFPyL PET/CT is the evaluation of patients with recurrent disease. Meijer et al. reported 262 patients with biochemical recurrence (BCR) and performed clinical verification of imaging findings, including histopathology or decrease in prostate-specific antigen (PSA) serum levels after therapy. In 226/262 (86.3 %) of the patients, at least one lesion was identified on [^{18}F]DCFPyL PET/CT and diagnostic certainty increased in the presence of characteristic abnormalities on CT, with a peak SUV of ≥ 3.5, when PSA levels was more than 2.0 ng/mL or in patients with more than two PET-positive lesions [40]. Dietlein and coworkers conducted a comparative study using [^{18}F]DCFPyL and a ^{68}Ga-labeled PSMA equivalent in patients with BCR. For both radiotracers, sensitivity increased when PSA values were > 0.5 μg/L. For PSA between 0.5–3.5 μg/L, however, PSA-stratified sensitivity was higher for [^{18}F]DCFPyL (88 %) when compared to ^{68}Ga-PSMA. Of note, in patients after radiotherapy, sensitivity was independent of PSA at time of PET/CT, supporting the notion that such scans should be conducted after radiation therapy despite PSA fluctuations. The authors concluded that with [^{18}F]DCFPyL, improved sensitivity for relapse detection after prostatectomy can be achieved, even for only moderately increased PSA levels [41].

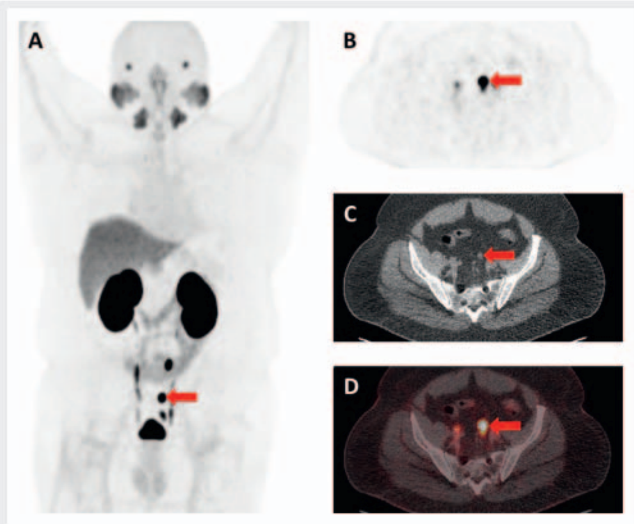
Based on those encouraging findings, multiple recent prospective trials further provided evidence on high detection efficiency in patients with BCR. Song et al. investigated [^{18}F]DCFPyL in 72 men with BCR after primary definitive treatment with prostatectomy or radiotherapy, and findings on PET/CT were compared with other conventional imaging modalities, such as bone scan, CT, magnetic resonance imaging (MRI), [^{18}F]NaF PET/CT or [^{18}F]fluciclovine PET/CT. The overall positivity rate was 85 %, with increasing PSA demonstrating higher detection rate (50 % [PSA < 0.5], 69 % [0.5 ≤ PSA < 1], 100 % [1 ≤ PSA < 2], 91 % [2 ≤ PSA < 5], and 96 % [PSA ≥ 5]). [^{18}F]DCFPyL PET/CT outperformed MR, bone scan, CT, MRI, and ^{18}F-NaF PET. Compared to [^{18}F]fluciclovine, results were congruent in 44 %, whereas another 28 % of the patients with negative [^{18}F]fluciclovine scans had positive [^{18}F]DCFPyL PET/CT findings. In 60 % of the patients, [^{18}F]DCFPyL triggered a change in management, with 24 % having lesions only detected on PET [42].

Rowe et al. also conducted a prospective study that evaluated patients with BCR after radical prostatectomy. In 31 patients with PSA levels of at least 0.2 ng/mL and negative conventional imaging results, 21/31 (67.7 %) had at least one [^{18}F]DCFPyL-avid finding, with a positive rate of 59.1 % in subjects with a PSA value < 1.0 ng/mL, rendering this agent as a valuable tool in patients with BCR following prostatectomy, even at low PSA levels. Of note, uptake was generally substantial, with median maximum SUV of 11.6, ranging from 1.5–57.6, supporting the notion that [^{18}F]DCFPyL may be used to stratify patients for RLT in a theranostic approach [43].

Lindenberg et al. prospectively recruited PC patients after prostatectomy and/or radiation therapy with rising PSA level (median, 2.27 ng/mL) and a negative result on conventional imaging [44]. Relative to MRI, [^{18}F]DCFPyL improved positive predictive value by 38 %, and histologically validated findings demonstrated high sensitivity and specificity of up to 91 %.

The OSPREY trial reported that a second cohort of 93 PC patients with suspected recurrent/metastatic PC on conventional imaging and [^{18}F]DCFPyL PET/CT achieved a median sensitivity and positive predictive value for extraprostatic lesions of 95.8 % and 81.9 %, respectively [38]. The recently published phase III, multicenter CONDOR trial (NCT03739684) enrolled patients with BCR and uninformative standard imaging (median baseline PSA, 0.8 ng/mL) and reported a change in intended management in 63.9 % of the cases, with a disease detection rate of 59 % to 66 %. The authors concluded that [^{18}F]DCFPyL demonstrated disease localization in the setting of negative standard imaging and, most importantly, provided actionable information [6]. Of note, the study design only involved patients with negative prior imaging (CT, MRI, bone scintigraphy, or PET/CT with [^{18}F]fluciclovine or [^{11}C]choline), which further emphasizes the additional benefit of [^{18}F]DCFPyL PET/CT [45].

The ORIOLE trial (NCT02680587) reported on the potential use of [^{18}F]DCFPyL for image-guided strategies in men with PC. Phillips et al. included men who either received stereotactic ablative body radiation (SABR) or observation for oligometastatic disease identified on conventional imaging. SABR improved progression-free survival; the authors also demonstrated that if all [^{18}F]DCFPyL-avid disease sites were included in the radiation plan, there were benefits in progression-free and distant-metastasis-free survival [46]. Independent of staging or restaging, a recent meta-analysis including 426 patients reported on a pooled detection rate of 89 % for PSA ≥ 0.5 ng/mL and 49 % for PSA



▶ **Fig. 2** 62-year-old man with history of Gleason 3 + 3 = 6 prostate cancer status post radical prostatectomy with biochemical recurrence and PSA rise to 5.8 ng/mL Conventional imaging with bone scan and CT did not demonstrate evidence of disease. **A** ^{18}F-DCFPyL PET maximum intensity projection image demonstrates multiple foci of abnormal uptake corresponding to lymph nodes in the pelvis and retroperitoneum (representative example denoted with red arrow). **B** Axial ^{18}F-DCFPyL PET, **C** axial attenuation-correction CT, and **D** ^{18}F-DCFPyL PET/CT images through the pelvis show one of the lymph nodes with intense uptake (red arrows).

< 0.5 ng/mL, confirming [^{18}F]DCFPyL as a valuable tool for identifying putative sites of disease in patients with at least slightly elevated PSA [47].

▶ **Fig. 2** displays a case of a 62-year old PC patient imaged with [^{18}F]DCFPyL post radical prostatectomy with biochemical recurrence and PSA rise to 5.8 ng/mL. Conventional imaging did not identify sites of disease, while [^{18}F]DCFPyL PET/CT revealed multiple lymph node metastases in the pelvis and retroperitoneum.

Response assessment

[^{18}F]DCFPyL has further been used for response assessment in various clinical scenarios. In an exploratory prospective trial, Zukotynski and coworkers included men with castration-resistant PC initiating abiraterone or enzalutamide, with each patient imaged with [^{18}F]DCFPyL prior to therapy and during follow-up (2 to 4 months). Using delta percent SUV_{max} (DPSM) and delta absolute SUV_{max} (DASM) derived from the changes in uptake between both scans, the authors found that high DPSM/DASM were negatively associated with time to therapy change and overall survival. As such, increasing radiotracer accumulation between subsequent scans is indicative of poor response, suggesting [^{18}F]DCFPyL PET/CT may provide a biomarker for oncologically meaningful endpoints in patients initiating therapy with abiraterone or enzalutamide [48].

[^{18}F]DCFPyL has been used in the setting of new PC therapies, such as bipolar androgen therapy. On short-term follow-up with [^{18}F]DCFPyL PET/CT, the appearance of any new lesion was linked to early progression [49], supporting the notion that [^{18}F]DCFPyL can be used to identify high-risk individuals even under such therapies.

In another prospective Phase II trial enrolling patients with newly diagnosed PC, patients underwent a baseline [^{18}F]DCFPyL pelvic PET/MRI followed by 3 cycles of neoadjuvant docetaxel and androgen deprivation therapy. Patients were then rescheduled for a second scan prior to prostatectomy. Preliminary analysis demonstrated that PET/CT-based baseline tumor volume, baseline total lesion PSMA and baseline PSA levels were significant predictors of time to progression. Multivariable analysis, however, showed that the latter parameter was the most significant predictor of outcome. As such, semi-quantification of [^{18}F]DCFPyL PET/CT along with PSA may predict disease progression in PC patients undergoing neoadjuvant chemohormonal therapy, and response prediction may also be refined by combining laboratory (PSA) and imaging biomarkers (PSMA) [50].

Future perspectives

Machine learning approaches have gained increasing interest in the context of PSMA-directed molecular imaging. Leung et al. recently reported on a fully automated deep-learning method using [^{18}F]DCFPyL in 207 patients and performed a comparison with conventional semi-automated thresholding-based methods. The deep-learning approach yielded more accurate segmentation, potentially assisting in response monitoring and treatment planning [51]. As PSMA is also tightly linked to neovasculature in other non-prostatic tumors [52], [^{18}F]DCFPyL has also been used in clear cell renal carcinoma, suggesting that it may be helpful for metastasis-directed therapies in such patients [53, 54]. A recent preclinical study also reported on direct retrograde installation of the non-radioactive standard of [^{18}F]DCFPyL, that is DCFPyL, into the salivary glands, potentially decreasing salivary uptake. Such blocking experiments may pave the way to mitigate xerostomia in a clinical setting, e. g., in patients scheduled for RLT [55]. Last, in patients scheduled for RLT, PET/CT-based parameters at baseline may predict early biochemical response and overall survival [56, 57]. However, such studies have been conducted using ^{68}Ga-PSMA agents and remain to be carried out with [^{18}F]DCFPyL PET/CT.

Conclusion

An increasing body of evidence suggests that [^{18}F]DCFPyL PET/CT is beneficial in a variety of clinical scenarios, including staging, restaging and response assessment of men afflicted with PC. Multiple major clinical trials have demonstrated the additional benefit for identifying putative sites of disease in such patients, e. g., relative to conventional imaging, but also reported substantial changes in management based on [^{18}F]DCFPyL PET/CT. Not surprisingly, this compound is the only U.S.-wide ^{18}F-labeled FDA-approved PET agent for molecular imaging of patients with PC. Nonetheless, future studies are needed to evaluate the clinical utility of [^{18}F]DCFPyL PET/CT in currently emerging clinical applications, such as risk stratification for PSMA-targeted RLT.

Funding

“RECTOR” Program at Okayama (RECTOR)

Conflict of Interest

Under a license agreement between Progenics (a wholly-owned subsidiary of Lantheus) and the Johns Hopkins University, MGP and the University are entitled to royalties on an invention described in this article. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. SPR is a consultant for Progenics Pharmaceuticals, Inc. MAG has been a consultant for Progenics Pharmaceuticals, Inc. This work was supported by the “RECTOR” Program at Okayama (TH). All other authors declare that there is no conflict of interest as well as consent for scientific analysis and publication.

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