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Review Article

Imaging of prostate cancer with PET/CT using ^{18}F-Fluorocholine

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Abstract: While ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Positron-Emission Tomography (PET) has limited value in prostate cancer (PCa), it may be useful for specific subgroups of PCa patients with hormone-resistant poorly differentiated cell types. ^{18}F-Fluorocholine (^{18}F-FCH) PET/CT has been increasingly used in primary and recurrent PCa and has been shown to add valuable information. Although there is a correlation between the foci of activity and the areas of malignancy in the prostate gland, the clinical value of ^{18}F-FCH is still controversial for detection of the malignant focus in the prostate. For the T-staging of PCa at diagnosis the value of ^{18}F-FCH is limited. This is probably due to limited resolution of PET system and positive findings in benign prostate diseases. Conversely, ^{18}F-FCH PET/CT is a promising imaging modality for the delineation of local and distant nodal recurrence and bone metastases and is poised to have an impact on therapy management. In this review, recent studies of ^{18}F-FCH PET/CT in PCa are summarized.

Keywords: Prostate cancer, PET/CT, ^{18}F-Fluorocholine

Introduction

Prostate cancer (PCa) is the second most common cancer (skin cancer is the first), and is one of the most common causes of cancer death in men. Due to both aging of the population and the availability of Prostate Specific Antigen (PSA) as a serum prostate biomarker, the incidence and prevalence of PCa have significantly increased [1]. Accurate diagnosis, staging, and restaging of PCa are essential for optimal therapeutic management. In this regard, diagnostic imaging has various important and challenging roles.

Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have been used for diagnosis and staging of PCa with modest accuracy [2]. MRI is especially helpful for evaluating capsular invasion and seminal vesicle involvement. Conventional nuclear medicine examinations such as bone scans with ^{99m}Tc-MDP have specific indications and limitations. There has been a growing tendency towards multi-parametric MRI and molecular imaging with Positron-Emission Tomography (PET) radiotracers in PCa. Hybrid PET/CT and PET/MR scanners with more robust attenuation correction allow images of tumor-specific function acquired with the PET component to be matched to anatomic locations on CT or MR to differentiate between physiologic activity and pathologic uptake.

^{18}F-Fluorodeoxyglucose (^{18}F-FDG), a glucose analog, is the most common radiotracer used in oncology. Although ^{18}F-FDG PET/CT has proven useful in a variety of tumors, the results in PCa have not been promising because of the relatively low metabolic activity of prostate cancer cells and the close proximity of the bladder and the high urinary excretion of ^{18}F [3, 4]. ^{18}F-FDG will most likely be useful in selected PCa patients with hormone-resistant poorly differentiated cell types [5-7].

The limited usefulness of ^{18}F-FDG led to the development of other radiotracers for PCa. Choline derivatives are one class of PET tracers that have been extensively evaluated during the last decade. Choline is a component of prostate

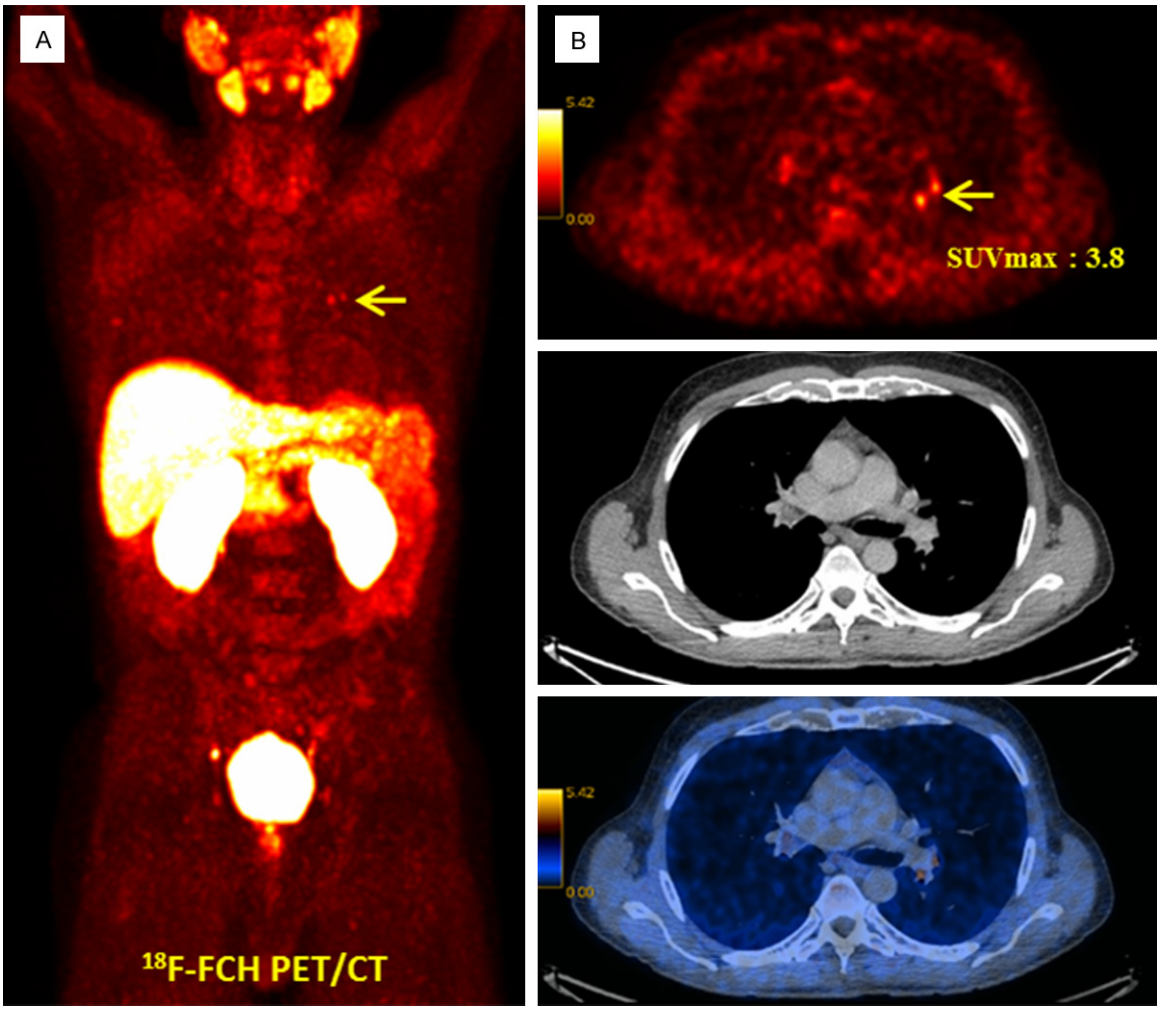

Figure 1. ^{18}F-FCH PET/CT in a 58-year-old prostate cancer patient, Gleason score 7, PSA 22.3 ng/mL, increasing PSA under anti-androgen treatment after prostatectomy and radiotherapy (biochemical recurrence). A: ^{18}F-FCH PET MIP. B: Transaxial PET (upper row), CT (middle row) and PET/CT fusion (lower row). Mildly increased tracer uptake is visible in the left hilum arrow, SUVmax: 3.8)-suggestive of reactive lymph nodes verified as benign lesion in the follow-up clinical and imaging evaluation.

cell membrane phospholipid. Many radiotracers have been synthesized to image choline, including ^{11}C-choline, and ^{18}F-fluorocholine (^{18}F-FCH). Although ^{11}C compounds have the advantage of less urinary excretion, the shorter half-life of ^{11}C (20 minutes) has limited its use in clinical practice. In this article, we review clinical studies of ^{18}F-FCH in PCa, evaluating its performance in delineation of PCa in the prostate gland and detection of nodal involvement and distant metastases.

Mechanism of uptake and normal biodistribution of ^{18}F-FCH

Choline is the precursor for the biosynthesis of phospholipids in the cell membrane and enters the cell through choline transporters. Choline is used for synthesising phosphatidylcholine via the Kennedy pathway [8]. The first step of this pathway is the rate-limiting step, in which choline kinase catalyzes the phosphorylation of choline into phosphocholine [9]. Choline kinase is overexpressed in PCa, resulting in the elevated levels of phosphocholine needed to support malignant transformation. The endogenous synthesis of choline also seems to be up-regulated in cancer cells. In 1998, Hara *et al.* described the usefulness of ^{11}C-choline in PCa imaging [10]. In 2001, DeGrado *et al.* reported their experience in synthesizing ^{18}F-FCH and other radiolabeled choline derivatives and showed that *in vitro* phosphorylation of ^{18}F-FCH by choline kinase was similar to that of choline [11].

The optimal imaging protocol has not been established. Typically, the acquisition starts 1 min after intravenous injection of ^{18}F-FCH (4.07 MBq/kg of body weight) with dynamic PET images of the pelvis acquired during the first 8-10 min (1 min/frame) to avoid the effect of urinary bladder activity, followed by a static semi-whole-body acquisition [12-14]. Delayed acquisition has also been described in the literature [15-18]. Unenhanced CT is performed for localization and attenuation correction. The effective dose of ^{18}F-FCH has been estimated as 0.03 mSv/MBq by DeGrado *et al.* [19]. The critical organs are the kidneys (0.16 mSv/MBq). The bladder wall receives 0.06 mSv/MBq [19].

After injection of ^{18}F-FCH, the radiotracer is rapidly cleared from the blood in 4-5 minutes. The liver and lung uptake plateau is reached by 10 minutes. Normal biodistribution of ^{18}F-FCH is in the salivary glands, liver, spleen, pancreas; with variable activity in the bowel, in addition to the uptake in the kidneys and bladder from excretion. There is faint uptake in the cerebral cortex. Moderate uptake is seen in the choroid plexus, cavernous sinus, and extraocular and masticatory muscles. Variable uptake occurs in the lacrimal glands and nasal mucosa [20-24]. Diffuse or focal activity in the lungs may indicate pathology, although curvilinear-shaped mild physiologic activity in the dependent areas of the lungs can be seen, likely due to the supine position during the injection and uptake period. In the majority of cases, the adrenal glands do not show any uptake; there can be occasional uptake, however, in one or both glands [25]. The normal prostate may show faint activity; diffuse or focal increased uptake can be seen in prostatitis, benign prostate hyperplasia, or malignancy.

There may also be increased uptake of ^{18}F-FCH in sites of inflammation such as the paranasal sinuses, thyroid, middle ear/mastoid and bone fractures [25, 26]. This may lead to false-positive results [23]. Mild activity may be seen in mediastinal, hilar, axillary, and inguinal lymph nodes in the setting of a nearby inflammatory process (**Figure 1**).

Local disease evaluation (imaging the prostate gland and T staging)

The diagnosis of a malignant focus in the prostate gland is usually based on ultrasound-guided biopsy when there is an elevated PSA level. However, it is not unusual to have a false-negative biopsy, which may lead to repeat biopsies. A noninvasive imaging modality to detect a malignant focus in the prostate gland would be helpful to guide biopsy and also to evaluate the size, extent, and multiplicity of the lesions inside the prostate gland [27]. Although ^{18}F-FCH PET or PET/CT is more sensitive than US or CT, and is probably comparable with MRI for evaluating focal malignancy in PCa, the reported sensitivity and specificity of ^{18}F-FCH for detection of malignancy in the prostate gland is variable, ranging from 64 to 100% for sensitivity and 47 to 90% for specificity [17, 18, 28, 29]. The limited sensitivity is probably due to the limited spatial resolution of PET systems. The limited specificity is probably due to ^{18}F-FCH uptake by benign prostatic hyperplasia and prostatitis.

Some investigators have reported poor correlation between foci of increased ^{18}F-FCH activity in the prostate and malignancy. In a study by Igerc *et al.* in 20 patients with elevated PSA and negative biopsy, uptake in the prostate was categorized into focal, multifocal, or inhomogeneous patterns. A repeat biopsy was performed after the PET study, and in cases of focal uptake, the biopsy was guided by the PET images. Focal uptake was noted in 13 out of 20 patients. Malignancy was confirmed in five patients on repeat biopsy. None of the patients with multifocal or inhomogeneous ^{18}F-FCH uptake had a malignancy found on repeat biopsy. They concluded that semi-quantitative values such as SUVmax were not helpful to differentiate benign prostate disease from malignancy [18]. Similarly, Schmid *et al.* studied the use of ^{18}F-FCH in 19 patients with PCa. In nine patients who were evaluated at initial diagnosis, histologic findings of the resected prostate were compared to ^{18}F-FCH uptake. Only in one patient did ^{18}F-FCH correctly detect the focus of malignancy [30].

Other investigators have reported a closer correlation between foci of increased ^{18}F-FCH uptake and malignancy in the prostate gland. Kwee *et al.* studied the value of ^{18}F-FCH PET for sextant localization of malignant prostate tumors in 15 patients prior to radical prostatectomy. Histopathologic analysis of step-sectioned whole-mounted prostate specimens was used as a gold standard and compared with the SUVmax values in corresponding

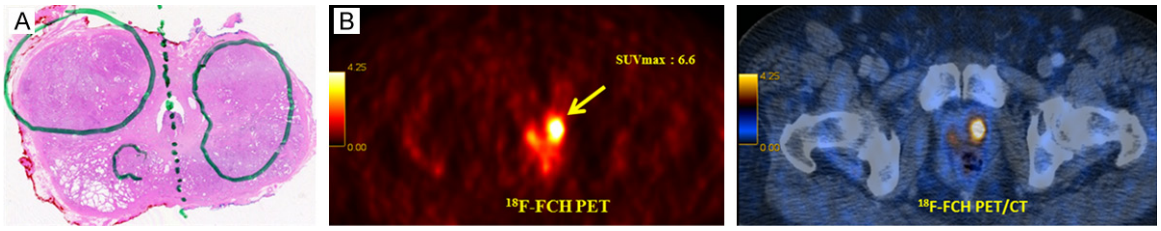

Figure 2. ^{18}F-FCH PET/CT staging in a 67-year-old prostate cancer patient, Gleason score 7, PSA 22.7 ng/mL [15]. A: Histopathology results: prostate adenocarcinoma in both lobes (marked). B: ^{18}F-FCH PET/CT: left: transaxial PET image, right: transaxial PET/CT fusion image. ^{18}F-FCH PET shows focal tracer uptake (SUVmax: 6.5) in both prostate lobes that correlate with histopathology findings (yellow arrow).

Table 1. ^{18}F-FCH PET/CT for local disease (detection of malignancy in prostate gland)

Article	Authors	Year	No. of patients	Findings
1 [28]	Kwee et al.	2005	17	Prostate sextants positive for malignancy showed higher SUV-max than biopsy negative sextants
2 [30]	Schmid et al.	2005	19	Only 1 out of 9 patients with ^{18}F-FCH uptake proved to be malignant
3 [17]	Husarik et al.	2008	43	Pathologic uptake was noted in 42 out of 43 patients with histologic proven PCa
4 [18]	Igerc et al.	2008	20	Five out of 13 positive focal ^{18}F-FCH uptake were malignant on pathology
5 [29]	Kwee et al.	2008	15	Sixty one out of 90 prostate sextants with ^{18}F-FCH uptake were malignant on pathology
6 [15]	Beheshti et al.	2010	130	Good correlation between sections with the highest ^{18}F-FCH uptake and malignancy

Abbreviations: PCa, prostate cancer; ^{18}F-FCH. [^{18}F]fluoromethyl-dimethyl-2-hydroxyethyl-ammonium; SUV, standardized uptake value.

image sections. Histopathology demonstrated malignant involvement in 61 of 90 prostate sextants. Mean SUVmax was 6.0 ± 2.0 in malignant sextants and 3.8 ± 1.4 in benign sextants ($P < 0.0001$). They reported an area under the receiver operating characteristics (ROC) curve (AUC) of 0.82 for ^{18}F-FCH uptake by means of SUVmax in predicting the presence of malignancy on a sextant basis in the prostate. However, tumor diameter directly correlated with sextant SUVmax in malignant sextants ($r = 0.54$, $P < 0.05$), and ^{18}F-FCH PET failed to detect smaller foci of malignancy [29].

In a larger series ($n = 130$) of intermediate-to-high-risk patients prior to prostatectomy, the authors found a significant correlation ($r = 0.68$; $P = 0.0001$) between sections with the highest ^{18}F-FCH uptake and sextants with the largest tumor burden on radical prostatectomy (**Figure 2**). However, we did not find good correlation between SUVmax and serum PSA levels ($P = 0.10$) or Gleason scores ($P = 0.28$) [15]. The key findings of studies on ^{18}F-FCH uptake in malignant foci of prostate cancer are summarized in **Table 1**.

In summary, ^{18}F-FCH has limited value for imaging and diagnosis of primary prostate gland malignancies. It may be helpful in cases with elevated PSA levels and negative biopsy to suggest the site for repeat biopsy. Based on currently available data, endorectal coil dynamic contrast-enhanced MRI/magnetic resonance spectroscopy (MRS) has better sensitivity than ^{18}F-FCH [31, 32]. However, this method is not widely available and the accuracy may be affected if it is done too soon after biopsy [33]. Integrated PET/MRI may eliminate the limitations of each modality alone and may have more indications in PCa [34, 35].

Lymph node metastases

In a meta-analysis by Hovels *et al.* the pooled sensitivity and specificity of CT and MRI for detecting pelvic lymph node metastases from prostate cancer were approximately 39 and 80%, respectively [36]. The reported accuracy of ^{18}F-FCH PET/CT for detecting regional lymph node metastases ranges from 10 to 100% for sensitivity, with a specificity of more than 90% (**Table 2**) [12, 15, 17, 37, 38]. This variable sensitivity is mostly due to the selected patient population (low-risk versus intermediate/high risk patients), size of the involved nodes, and the number of subjects in each study. In general, ^{18}F-FCH PET/CT has a low to modest sensitivity and a high specificity for detecting involved nodes in the pelvic region.

Table 2. ^{18}F-FCH PET/CT for detecting lymph node metastases in PCa at initial diagnosis

Article [Reference]	Authors	Year	Patient's Number	Sensitivity	Specificity
1 [12]	Hacker et al.	2006	20	10%	80%
2 [17]	Husarik et al.	2008	43	20%	
3 [15]	Beheshti et al.	2010	130	66%**	96%
4 [38]	Poulsen et al.	2010	25*	100%	95%
5 [37]	Beauregard et al.	2010	15	63%***	
				100%****	

Abbreviations: PCa, prostate cancer; ^{18}F-FCH. [^{18}F]fluoromethyl-dimethyl-2-hydroxyethyl-ammonium; LNs, lymph nodes. *Patient population was intermediate to high risk patients with PCa. **For detecting lymph nodes greater than or equal to 5 millimeters. ***For regional LNs. ****For extra-pelvic LNs.

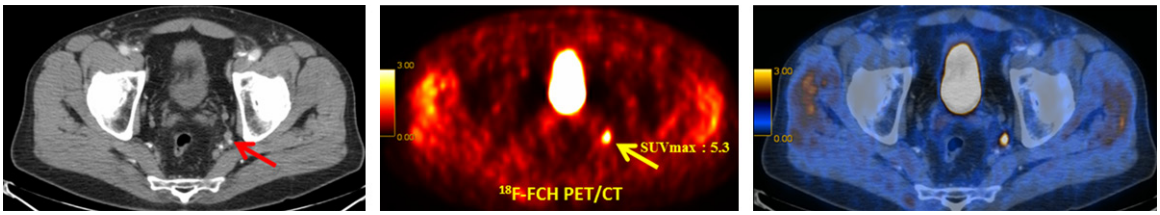

Figure 3. ^{18}F-FCH PET/CT staging in a 67-year-old prostate cancer patient, Gleason score 7, PSA 21.1 ng/mL. left: transaxial CT, middle: transaxial PET image, right: transaxial PET/CT fusion image. ^{18}F-FCH PET/CT shows markedly increased tracer uptake (SUVmax: 5.3) in a small lymph node in the left internal iliac chain (arrows), verified as lymph node metastasis by histopathology [15].

In a study by Hacker *et al.* on 20 men with intermediate-risk PCa, ^{18}F-FCH PET/CT showed a low sensitivity (10%) and good specificity (80%) for the detection of lymph node metastases. Laparoscopic radioisotope-guided sentinel lymph node biopsy was more sensitive than ^{18}F-FCH PET/CT [12]. A low sensitivity (20%) was also reported by Husarik *et al.* in 43 PCa patients undergoing preoperative PET/CT [17].

Conversely, Beauregard *et al.* reported a sensitivity of 63% for regional pelvic lymph node metastases and a sensitivity of 100% for extra-pelvic lymph node metastases with ^{18}F-FCH PET/CT among 16 patients with intermediate-to-high-risk PCa [37]. Poulsen reported a sensitivity of 100% and specificity of 95% in 25 intermediate-to-high risk PCa patients undergoing ^{18}F-FCH PET/CT [38].

The authors also described the performance of ^{18}F-FCH PET/CT in detecting lymph node metastases in 130 high-risk PCa patients. In our study the sensitivity, specificity, positive, and negative predictive values of ^{18}F-FCH PET/CT for lymph node metastases ≥ 5 mm were 66, 96, 82, and 92%, respectively [15].

In summary, ^{18}F-FCH PET/CT has a fair sensitivity and high specificity for detecting lymph node metastases ≥ 5 mm in intermediate-to-high-risk PCa patients (**Figures 3** and **4**). Radioisotope-guided sentinel lymph node biopsy/dissection is more sensitive for smaller lymph nodes [12].

Bone metastases

Bone metastases are detected in approximately 65-75% of patients with PCa and often alter the prognosis [39, 40]. Early detection of bone metastases is necessary for appropriate treatment management and to avoid complications such as fractures and spinal cord compression [41]. Whole body bone scan with ^{99m}Tc-MDP and single photon-emission tomography (SPECT) technique is still the most common examination for evaluating bone metastases with a good sensitivity but a low specificity. However, studies have revealed higher sensitivity with ^{18}F-fluoride PET, likely due to better resolution of the PET system compared with gamma cameras and higher target-to-background ratios for ^{18}F-fluoride than ^{99m}Tc-phosphonates because of its biological kinetics [42, 43]. Both ^{99m}Tc-MDP bone scans and ^{18}F-fluoride PET are nonspecific in their action; they show foci of bone with elevated bone turnover but do not specifically bind to malignancies. Choline derivatives have the advantage of binding to the actual

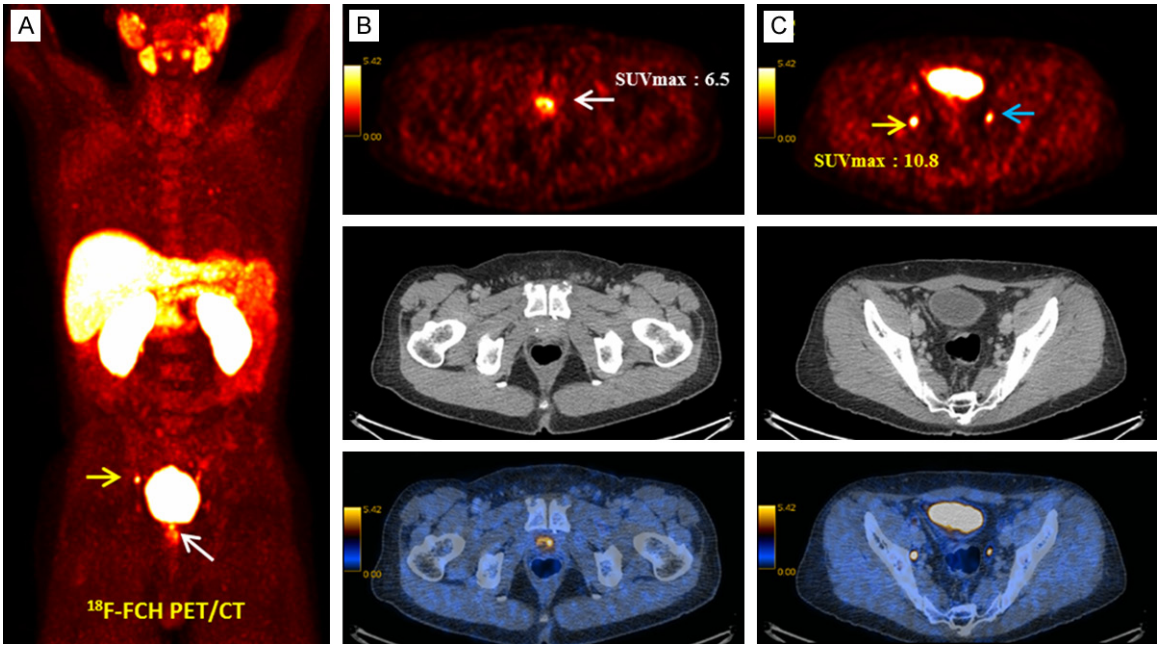

Figure 4. ^{18}F-FCH PET/CT in a 58-year-old prostate cancer patient, Gleason score 7, PSA 22.3 ng/mL, with increasing PSA under anti androgen treatment after prostatectomy and radiotherapy (Biochemical recurrence) [15]. A: ^{18}F-FCH PET MIP. B: Transaxial PET (upper row), CT (middle row) and PET/CT fusion (lower row). Focally-increased tracer uptake in the prostate bed (arrow, SUVmax: 6.5) is suggestive of local recurrence verified in the clinical and imaging follow-up. C: Transaxial PET (upper row), CT (middle row) and PET/CT fusion (lower row). Focally-increased tracer uptake in a small right external iliac chain (yellow arrow, SUVmax: 10.8), proved as lymph node metastasis in the clinical and imaging follow-up. Incidental focal tracer accumulation is noticed in the left ureter (blue arrow) [47].

Table 3. ^{18}F-FCH PET/CT for evaluating bone metastases in PCa

Article	Authors	Year	No. of patients	Sensitivity	Specificity	Comment
1 [47]	Beheshti et al.	2008	70 (210 lesions)	79%	97%	(1)
2 [37]	Beauregard et al.	2010	16	100%		67% for bone scan
3 [15]	Beheshti et al.	2010	130 (43 lesions)			Change the therapy in 15%
4 [44]	McCarthy et al.	2011	26 (183 lesions)	96%	96%	
5 [46]	Langsteger et al.	2011	17			(2)
6 [45]	Kjolhede et al.	2012	90*			(3)

Abbreviations: PCa, prostate cancer; ^{18}F-FCH. [^{18}F]fluoromethyl-dimethyl-2-hydroxyethyl-ammonium. (1): 24% of bone metastases didn't show any abnormality on CT scan. There was an inverse relationship between the intensity of ^{18}F-FCH uptake and the degree of lesion sclerosis by means of Hounsfield Units. (2): A comparative study with ^{18}F-Fluoride showed similar sensitivity. However, the specificity was slightly higher for ^{18}F-FCH. (3) In 50 out of the 90 included patients (56%) one or both PET/CT scans indicated metastases. ^{18}F-FCH PET/CT indicated lymph node metastases and/or bone metastases in 35 patients (39%). *The study was performed with both ^{18}F-Fluoride and ^{18}F-FCH on patients with normal or equivocal bone scans.

malignant foci in the skeleton as well as to lymph node metastases.

Different studies have shown the use of ^{18}F-FCH for detecting bone metastases in PCa (**Table 3**). Beauregard *et al.* reported a higher sensitivity for ^{18}F-FCH PET/CT than conventional imaging modalities (100 vs 67%) for detection of bone metastases in 16 patients with PCa [37]. In another study, McCarthy *et al.* evaluated the usefulness of ^{18}F-FCH PET compared with standard bone scans and CT in 26 patients with castration-resistant prostate carcinoma. The lesions in each modality were recorded and classified as concordant or discordant for the presence or absence of prostate cancer metastases. Discordant bone or soft tissue lesions were followed up for 2 years or until a definitive diagnosis of the discordant lesion could be made. Overall, 183 lesions were detected with 149 being concordant and 34 (19%) being discordant. Based on follow-up, ^{18}F-FCH PET cor-

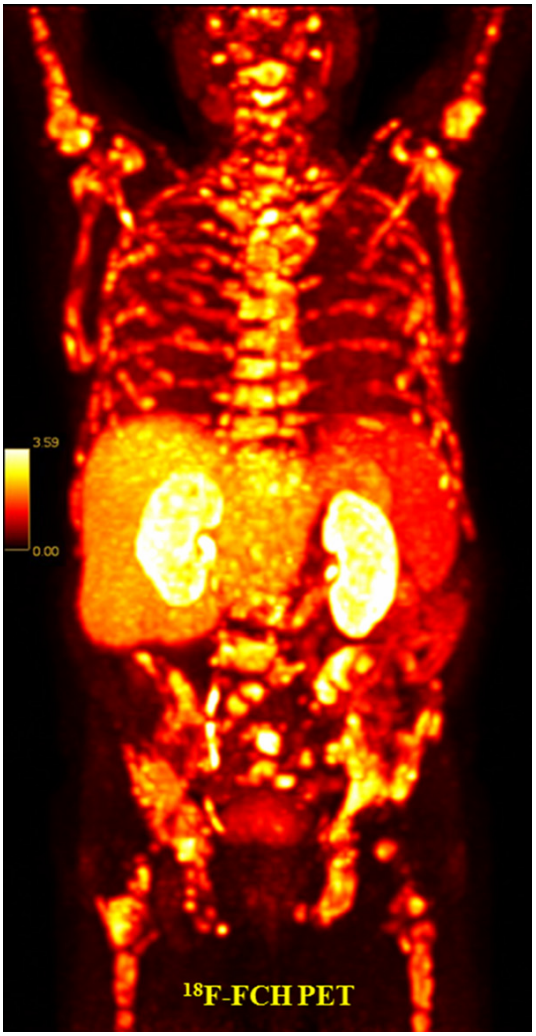

Figure 5. ^{18}F-FCH PET/CT: generalized bone metastases in the skeleton in a 74-year-old prostate cancer patient, Gleason score 9, PSA 53.22 ng/mL, status post radiotherapy to the prostate, regional lymph nodes, and lumbar spine with continued anti-androgen blockade. Planning for radionuclide treatment with ^{223}radium.

rectly identified the presence or absence of disease in 27 of 34 lesions. In 14 cases, FCH-positive lesions not identified on initial imaging were confirmed as disease on follow-up. The sensitivity, specificity, positive predictive and negative predictive values for lesion detection by ^{18}F-FCH PET were 96, 96, 99 and 81%, respectively [44].

Kjolhede *et al.* evaluated the added value of ^{18}F-FCH PET/CT and ^{8}F-fluoride PET/CT in 90 patients with high-risk prostate cancers (PSA levels between 20 and 99 ng/mL and/or Gleason score 8-10) and normal or equivocal results on bone scan with ^{99m}Tc-MDP and CT [45]. None of the patients had received hormonal therapy before the staging procedures were completed. In 50 out of the 90 patients (56%] one or both PET/CT scans indicated bone or nodal metastases. ^{18}F-FCH PET/CT indicated lymph node metastases and/or bone metastases in 35 patients (39%). ^{18}F-fluoride PET/CT was suggestive for bone metastases in 37 patients (41%). In 18 patients (20%) the PET/CT scans changed the management. They concluded that PET/CT scans with ^{18}F-FCH PET/CT and ^{18}F-fluoride commonly detect metastases in patients with high-risk prostate cancer, and a negative or inconclusive bone scan and may change the therapy management.

The authors also evaluated the performance of ^{18}F-FCH PET/CT for evaluating bone metastases in 130 PCa patients [15]. Forty-three bone metastases were detected in 13 patients. In two patients, early bone marrow infiltration was detected only with ^{18}F-FCH PET/CT. ^{18}F-FCH PET/CT led to a change in therapy in 15% of all patients and 20% of high-risk patients. We also compared the performances of ^{18}F-FCH PET/CT and ^{18}F-fluoride PET/CT in 17 patients with newly-diagnosed prostate cancer and 23 patients with suspected recurrence with a history of bone pain. Both radiotracers showed good diagnostic performance on patient-based and lesion-based analyses. However, the lesion-based analysis showed a significantly better specificity for ^{18}F-FCH PET/CT [46].

In another study, the authors noted a sensitivity, specificity, and accuracy of 79, 97, and 84%, respectively, of ^{18}F-FCH PET/CT to identify bone metastases in 70 patients undergoing either initial staging or restaging (**Figure 5**). In that study, 262 lesions showed increased ^{18}F-FCH uptake, of which 210 were interpreted as malignant on the basis of the pattern of ^{18}F-FCH uptake and CT findings. Of those 210 lesions, 207 were true positives and three were false positives. Interestingly, 49 out of 207 (24%) proven malignant lesions that were positive on ^{18}F-FCH PET/CT had no corresponding morphological changes on CT. We also found an inverse relationship between the intensity of ^{18}F-FCH uptake and the degree of lesion sclerosis measured in Hounsfield Units (HU). The lesions with more sclerosis on CT (> 825 HU) correlated

Table 4. Some examples of ^{18}F-FCH PET/CT studies in recurrent PCa

Article	Authors	Year	No. of patients	PSA level	Sensitivity or detection rate	Comment
1 [16]	Cimitan et al.	2006	100	> 0.1 ng/ml	53%	(1)
2 [32]	Vees et al.	2007	22	< 1 ng/ml	55%	
3 [51]	Pelosi et al.	2008	56	< 1, 1-5, > 5 ng/ml	42%	(2)
4 [17]	Husarik et al.	2008	68	Mean: 10.8 microg/L	86%	
5 [57]	Chondrogiannis et al.	2013	46	1.1-49.4 ng/ml	80.4%	(3)
6 [55]	Beheshti et al.	2013	250	(4)	74%	(4)

Abbreviations: PCa, prostate cancer; ^{18}F-FCH, [^{18}F]. fluoromethyl-dimethyl-2-hydroxyethyl-ammonium. (1): ^{18}F-FCH PET/CT is not likely to have a significant management impact on PCa patients with biochemical recurrence until PSA increases to above 4 ng/ml. However, in selected patients, ^{18}F-FCH PET/CT helps to exclude distant metastases when salvage local treatment is intended. (2) Sensitivity was related to PSA levels, with 20%, 44% and 81.8% sensitivity values in the PSA < or = 1, 1 < PSA < or = 5 and PSA > 5 ng/ml subgroups, respectively. (3) ^{18}F-CH PET/CT showed a high overall detection rate (80%), proportional to the trigger PSA (both for local and distant relapse) not influenced by androgen deprivation therapy. (4) ^{18}F-FCH PET sensitivity was higher with increased trigger PSA levels (33, 77.5, 80.7, 85.2, and 92.8% for the trigger PSA levels of less than 0.3, more than 0.5, 1.0, 2.0, and 4.0 ng/mL, respectively).

with normal ^{18}F-FCH activity. These lesions were mainly observed in patients who were on androgen deprivation therapy [47].

In summary, the studies suggest better detection of bone metastases with ^{18}F-FCH PET/CT and ^{18}F-fluoride PET/CT compared with conventional bone scan. ^{18}F-FCH PET/CT and ^{18}F-fluoride PET/CT are taken up by bone metastases with different mechanisms and ^{18}F-FCH PET/CT was slightly less sensitive. However, the specificity of ^{18}F-FCH PET/CT was higher than that of bone scan or ^{18}F-fluoride PET/CT.

Evaluation for recurrent disease

Approximately half of patients with PCa experience recurrence over the 10 years post initial therapy [48]. PSA is a sensitive indicator of recurrent disease. However, PSA is a biochemical marker of recurrence and does not show the site of recurrence or metastases, which is necessary for therapy planning. Conventional imaging modalities including CT, ultrasound, MRI, and bone scan have different limitations and a low-to-moderate sensitivity [49]. Transrectal ultrasound (TRUS) and MR with an endorectal coil are accurate modalities in evaluation for local recurrence [32].

^{18}F-FCH PET/CT has been used to assess for local recurrence or metastases in PCa in the setting of biochemical recurrence (**Table 4**). Sensitivities from 42 to 96% have been reported in different studies [13, 16, 17, 50-52]. The detection rate was higher in cases with higher PSA levels at the time of recurrence, and shorter PSA doubling time [50, 53-56].

Pelosi *et al.* reported a relatively low sensitivity (42%) for ^{18}F-FCH PET/CT to detect lesions in post-prostatectomy patients with rising PSA. However, their detection rates increased with increasing PSA: 20% at PSA < 1 ng/mL; 44% at PSA = 1-5 ng/mL; 82% at PSA > 5 ng/mL) [51]. Vees *et al.* reported a 55% detection rate for ^{18}F-FCH and ^{11}C-acetate PET/CT in a small population (n = 22) of PCa patients with PSA levels < 1 ng/mL who were referred for adjuvant or salvage radiotherapy [32]. Prostate MRI was locally positive in 15 of 18 patients (83%). They concluded that since PET/CT studies correctly detected local residual or recurrent disease in only half of post-prostatectomy patients with PSA levels of < 1 ng/mL (**Figure 4**), the sensitivity and specificity were too low to use it as a standard diagnostic modality for early relapse or suspicion of subclinical minimally persistent disease, and that prostate MRI is probably more helpful, especially in patients with a low likelihood of distant metastases.

Studies reporting a higher positive detection rate (PDR) for ^{18}F-FCH PET/CT for restaging include the report by Chondrogiannis *et al.*, who found an 80.4% PDR in a study on 46 patients with radiotherapy-treated PCa with suspicion of relapse [57]. Similar to Pelosi *et al.'s* findings, they found that the PDR increased with increasing trigger PSA values. They also showed that the detection rate was not significantly influenced by androgen deprivation therapy (ADT).

In a study by the authors on 250 PCa patients with PSA relapse, ^{18}F-FCH PET/CT correctly detected malignant lesions in 74% (185/250)

of patients. The sensitivity of ^{18}F-FCH PET was significantly higher (P = 0.001) in subgroups of patients with ongoing ADT (85%) compared with the patients who didn't receive ADT (59.5%). Similar to the findings of Pelosi *et al.* and Chondrogiannis *et al.*, ^{18}F-FCH PET sensitivity was higher with increasing trigger PSA levels (77.5, 80.7, 85.2, and 92.8% for trigger PSA levels of > 0.5, 1.0, 2.0, and 4.0 ng/mL, respectively). The sensitivity was 33% in patients with a trigger PSA level < 0.3 ng/mL and 77% in patients with a trigger PSA level > 0.3 ng/mL. Using a binary logistic regression analysis model, we showed trigger PSA and ADT to be the only significant predictors of positive PET findings [55]. Other studies have suggest that ADT may decrease the detection rate of ^{18}F-FCH PET/CT and should be withheld before the examination to reduce the risk of a false-negative study [17, 58-60].

A recent meta-analysis by Evangelista *et al.* (19 studies were selected with a total of 1555 patients) for the role of ^{18}F-FCH PET/CT for restaging in PCa recurrence was promising [61]. They calculated a pooled sensitivity of 85.6% and specificity of 92.6% for all sites of disease (prostatic fossa, lymph nodes, and bone), a pooled sensitivity of 75.4% and specificity of 82% for prostatic fossa recurrence, and a pooled sensitivity of 100% and specificity of 81.8% for lymph node metastases.

Despite a wide range of ^{18}F-FCH PET/CT detection rates, a patient's management may change based on the scan findings. Soyka *et al.* investigated the clinical value of ^{18}F-FCH PET/CT in treatment decisions on PCa patients. They prepared questionnaires for 156 patients and sent them to their referring physicians 14-64 months after the studies. Questions included information regarding initial extent of disease, curative first-line therapy, treatment plan before and after ^{18}F-FCH PET/CT, and also PSA values at diagnosis, after initial treatment, before ^{18}F-FCH PET/CT, and at the end of follow-up. In 75 out of the 156 patients (48%) the management was changed based on the results of ^{18}F-FCH PET/CT. They concluded that ^{18}F-FCH PET/CT has an important impact on the therapeutic strategy in patients with PCa [62].

In summary, ^{18}F-FCH PET/CT is a useful modality to detect recurrence or metastases in patients with PCa and rising PSA; the detection rate is higher with higher PSA levels; and patient management may change based on the ^{18}F-FCH PET/CT findings.

Radiotherapy planning

Due to the limited lesion-based sensitivity in primary nodal staging with ^{18}F-FCH PET/CT, radiation planning based on the choline PET/CT results is controversial. However, because of the high positive predictive value of choline PET/CT for diagnosing lymph node metastases in high-risk PCa, it is potentially useful to include the involved lymph nodes in the conventional irradiation field. Additionally, detection of unsuspected distant metastatic disease may change the management from radiation therapy to a systemic treatment [63].

^{18}F-FCH PET/CT has been also investigated in PCa patients to select and delineate target volumes in the prostate gland or prostate fossa [64-66]. In particular, with intensity modulated radiotherapy (IMRT) and imaged guided radiotherapy (IGRT), it may be possible to select a specific site for radiotherapy and to minimize unnecessary irradiation of surrounding tissues. Wurschmidt *et al.* evaluated the usefulness of ^{18}F-FCH PET/CT data in planning dose escalation to nodal sites of PCa in 26 patients [65]. The median dose to primary tumors was 75.6 Gy and to choline-positive recurrent nodal sites was 66.6 Gy. At 28 months the overall survival rate was 94%, and biochemical relapse-free survival was 83% for primary cancer and 49% for recurrent tumors. Distant disease-free survival was 100% and 75% for primary and recurrent tumors, respectively. Early and late side effects were mild in 85 and 84%, respectively. Similar findings were reported by Casamassima *et al.* in a study on 71 PCa patients with biochemical recurrence [67]. ^{18}F-FCH or ^{11}C choline PET/CT detected recurrences in 39 of 71 patients. Twenty-five patients with limited nodal recurrences received eradicative radiotherapy. At the 3-year follow-up, overall survival, disease-free survival and local control rates were 92, 17 and 90%, respectively.

Pinkawa *et al.* reported on the use of ^{18}F-FCH PET/CT to delineate dominant intra-prostatic lesions (DILs) in radiation treatment planning for 66 patients [68]. They suggested using a relative SUVmax threshold of twice the background activity to identify the DILs. These DILs

are potentially the best targets for focal dose escalation. However, since the sensitivity of ^{18}F-FCH PET/CT is modest in PCa patients with biochemical recurrence, mathematical dose modeling by Niyazi *et al.* suggested that it would be of limited value [69].

Summary

^{18}F-FCH PET/CT in prostate cancer has been widely investigated in the last decade. There is not enough data to support the usefulness of ^{18}F-FCH PET/CT for diagnosis of primary prostate cancer. However, it may be useful in patients with increased PSA levels and negative repeated biopsies to guide repeat biopsy. The role of ^{18}F-FCH PET/CT for evaluating a local tumor extent (T-staging) is also limited. Dynamic contrast-enhanced MRI/magnetic resonance spectroscopy (MRS) with an endorectal coil has better sensitivity for T-staging. The positive predictive value of ^{18}F-FCH PET/CT for the detection of lymph node involvement and the sensitivity and specificity of ^{18}F-FCH PET/CT for evaluating bone metastases is relatively high. ^{18}F-FCH PET/CT is useful for distinction between locoregional recurrence and distant metastases in cases of biochemical recurrence, particularly in intermediate-to-high risk patients with certain criteria (e.g. elevated trigger PSA values and/or a short PSA doubling time and/or Gleason score > 7). ^{18}F-FCH PET/CT may also play a role in radiotherapy dose escalation or salvage therapy.

Disclosure of conflict of interest

None declared.

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