University of Olomouc

Medical Faculty

Nuclear Medicine Department

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

HABILITAČNÍ PRÁCE

Marina Hodolič, MD, PhD

Nuclear Medicine Physician, Assist. Prof of Nuclear Medicine

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Marína

CONTENT

Abbreviations

ADT - Androgen Deprivation Therapy

BS - Bone Scintigraphy

CT - Computed tomography

DCE – Dynamic Contrast Enhancement

DWI - diffusion weighted imaging

EBRT - external beam radiotherapy

FDG - 2-Deoxy-2-[18F]fluoroglucose

FCH - [18F]-fluoromethyl-dimethyl-2-hydroxyethylammonium

FEC - 2-[18F]-fluoroethyldimethyl-2-hydroxyethylammonium

GS - Gleason score

LHRH - Luteinizing hormone-releasing hormone

MRI - Magnetic resonance imaging

MRS – Magnetic resonance spectroscopy

PET/CT – Positron emission tomography/ Computed tomography

PSA - Prostate specific antigen

PSAve - PSA velocity

PSAdt - PSA doubling time

RP - radical prostatectomy

SUV - Standardized Uptake Value

[^{99m}Tc-MDP] - Tc-99m methylene diphosphonate

[^{99m}Tc-HDP] - Tc-99m hydroxymethylene diphosphonate

[^{99m}Tc-DPD] - Tc-99m 3,3-diphosphono-1,2-propanodicarboxylicacid

US - Ultrasound

1. Introduction

Cancer Statistics estimates the number of new cancer cases and deaths that will occur in United States in year 2017: Prostate cancer, cancer of lung and bronchus and colorectal cancer account for 42% of all cases in men, with prostate cancer alone accounting for almost 1 in 5 new diagnoses (1).

App. 26 730 (8%) man will die from prostate cancer disease in the USA in year 2017 (1). App. 68% of patients with prostate cancer is from more developed countries. Initiatives for screening and availability of new treatment modalities have a major impact on disease epidemiology. It is usually growing slowly, and it is frequently asymptomatic; as a consequence, some males affected with this malignancy undergo no diagnosis or therapy, and they usually dye of other unrelated causes. In the development of prostate cancer, many factors have been implicated, but yet there is no established relationship between any environmental factor and the incidence or aggressive nature of prostate cancer.

1.1. Clinical management of patients with prostate cancer

In the majority of cases, in the early stages, prostate cancer is harmless and seems to be symptom free. For this reason, sensitive diagnostic procedures are crucial for appropriate management and a good survival rate.

Prostate specific antigen (PSA), serum marker, can be an early clue to the presence of prostate cancer. Although nonspecific biomarker, elevated PSA level should lead to other diagnostic procedures. Using PSA alone, a 70–80% specificity and a 70% sensitivity is mediocre (2, 3, 4). Free PSA/total PSA, PSA doubling time (PSAdt) measurements, followed by digital rectal examination, endorectal ultrasound and biopsy are basic procedures performed in patients with suspicion of prostate cancer. Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI – including PI-RADS score: T2 weighted images, DWI -

diffusion weighted imaging and DCE – dynamic contrast enhancement) showed their importance in the detection of primary disease but still remain weak in early detection of affected lymph nodes and distal metastases (5); identification of lymph node involvement by either CT or MRI is based primarily on size and shape criteria. Also, these modalities cannot determine the degree of aggressiveness of the tumour, a feature that is important to guide therapy (to avoid under- or overestimating therapeutic options). In accordance with European (6, 7) and American guidelines (8), in patients with prostate cancer, to assess the extent of disease, nuclear medicine has traditionally been limited to bone scintigraphy (BS) with Tc-99m methylene diphosphonate [^{99m}Tc-MDP], Tc-99m hydroxymethylene diphosphonate [^{99m}Tc-HDP] or Tc-99m 3,3-diphosphono-1,2-propanodicarboxylicacid [^{99m}Tc-DPD]. Their sensitivity and specificity remains low. Also, patients with low-risk prostate cancer are unlikely to have metastatic bone involvement. Some studies showed that at PSA levels >20 ng/mL, almost 30% of all BS performed in patients with prostate cancer will be positive for bone metastases (9). This conventional nuclear medicine modality is mainly reserved for patients with high-risk prostate cancer (Gleason score>7) or with a PSA>10 ng/ml and palpable disease (cT2/T3) prior to treatment (10). Regardless of whether it is positive or negative, BS does not exclude soft tissue involvement.

Nowadays, more than 95% of PET studies worldwide are performed using ^{18}F-FDG. The role of ^{18}F-FDG PET in patients with prostate cancer is still reserved for patients who are at high risk for having poorly differentiated prostate cancer (based on the high Gleason score of biopsied prostate tissue). Since ^{18}F-FDG uptake correlates with tumour aggressiveness, identification of metastatic prostate cancer disease with ^{18}F-FDG PET/CT indicates a poor prognosis for the patient. Nuclear medicine physicians should be alert to the incidental finding of focal ^{18}F-FDG uptake in the prostate, as it may represent prostate malignancy.

Despite widespread usage of ^{18}F-FDG, the need for more sensitive and specific tracer, to increase overall diagnostic accuracy is permanently present. For this reason, application of radiotracers other than ^{18}F-FDG in patients with prostate cancer is crucial.

1.2. Choline, ^{11}C-choline and ^{18}F-choline

Choline, a quaternary ammonium cation, is an essential nutrient for humans and is mostly derived from the diet (11, 12). Radiolabelled choline is one of the most commonly applied PET tracers for prostate cancer imaging in Europe. Choline is a substrate for the synthesis of major phospholipid in the cell membrane – phosphatidylcholine. Malignant transformation of the cell is associated with increased choline metabolism due to cell multiplication. For that reason, enhanced concentration of choline in malignant cell is based on increasing growing rate but also on up-regulation of enzyme choline-kinase.

In 1997 choline was labelled with ^{11}C, short-lived isotope (half-life: 20 minutes). In early 2000s DeGrado took an advantages of longer-lived radionuclide ^{18}F (half-life: 110 minutes) and synthesized nocarrier-added choline analogue, [18F]-fluoromethyl-dimethyl-2-hydroxyethylammonium chlorid (FCH) (13). Hara et al. synthetized 2-[18F]-fluoroethyl-dimethyl-2-hydroxyethylammonium chlorid (FEC) (14). Both compounds showed similar properties - rapid uptake in prostate cancer tissue and rapid blood clearance, with minor differences, such as FEC showing later peak uptake in the prostate.

In comparison to ^{11}C-choline, the longer half-life of ^{18}F allows ^{18}F-choline analogues to be distributed to centres lacking an on-site cyclotron. Additionally, shorter positron range of ^{18}F provides better spatial resolution and better imaging quality. In comparison to ^{11}C-choline, week point of ^{18}F-choline analogues is that they are eliminated via the kidneys so urinary activity can obscure, or can be mistaken for malignant processes in the pelvis. This effect can

be minimized with early acquisition, prior to tracer appearance in the bladder, delayed imaging after voiding as well as usage of diuretics.

1.3. Radiation dosimetry of ^{18}F-FCH. Toxicity studies

Based on the biokinetic compartmental model in prostate cancer patients, dosimetry of ^{18}F-FCH has been calculated. The distribution of radioactivity varies in various organs: kidneys and liver are critical organs; the highest radioactivity has been found in the kidneys (reference patient, 0.079 mGy/MBq; individual values, 0.033 to 0.105 mGy/MBq) and liver (reference patient, 0.062 mGy/MBq; individual values, 0.036 to 0.082 mGy/MBq) (15). Urinary bladder wall of reference patient received between 0.017 and 0.030 mGy/MBq dose, depending on frequency of voiding. Radiation dosimetry limits administrations levels of ^{18}F-FCH to 4.07 MBq/kg (0.110 mCi/kg) in human research studies. The effective whole-body dose equivalent from administration of 4.07 MBq/kg is approximately 5,6 mSv (16). Prostate cancer tissue uptake is rapid, significant already after 1.5 minutes. Optimal tumour-to-background contrast is reached within 5-7 minutes after injection of tracer. This allows early acquisition and provides scans of good diagnostic quality.

In the acute toxicity studies, neither death nor behavioural or movement abnormalities were noted for up to 48h after administration of 1 mg/kg of body weight of nonradioactive [^{19}F]FCH into mice. Based on these findings, it has been estimated that normal dose of ^{18}F-FCH in the radiotracer preparation would be a factor of 300,000 times lower than the dose given in toxicity study of DeGrado et al. (16).

1.4. Patient Preparation and ^{18}F-FCH PET/CT acquisition protocols

Before ^{18}F-FCH PET/CT scanning, patients should be well hydrated (app. one litre of liquid). To minimize physiologic distribution of the tracer in the in the bowel fasting is recommended 4 up to 10 hours prior to the acquisition. The influence of androgen deprivation therapy

(ADT) on choline uptake in patients with prostate cancer disease has not yet been clarified (this topic is discussed in "*^{18}F-FCH PET/CT in treatment monitoring in patients with prostate cancer disease*"). Most European nuclear medicine centres recommend intravenous administrations of 2.5 to 4 MBq/kg of ^{18}F-FCH. At present, there is no standardized ^{18}F-FCH PET/CT acquisition protocol, but many protocols incorporate late with early imaging (immediately after tracer injection), to avoid interference visualization of the pelvic disease with interference from physiologic filling of urinary activity in the bladder. Late acquisition is usually performed 45 to 60 minutes after tracer injection. Late acquisition allows better sensitivity for distal disease (17, 18, 19). Early and late PET imaging as well as co-registered low dose CT data are sufficient for good scan interpretation.

1.5. Physiologic distribution of ^{18}F-FCH

Physiologic ^{18}F-FCH uptake (Fig.1.) is noted in salivary glands, liver, pancreas, renal parenchyma and urinary bladder. Faint uptake is seen in spleen, bone marrow, and muscles. Bowel activity is variable and depends on duration of fasting before acquisition. There is no physiologic uptake of ^{18}F-FCH in the brain.

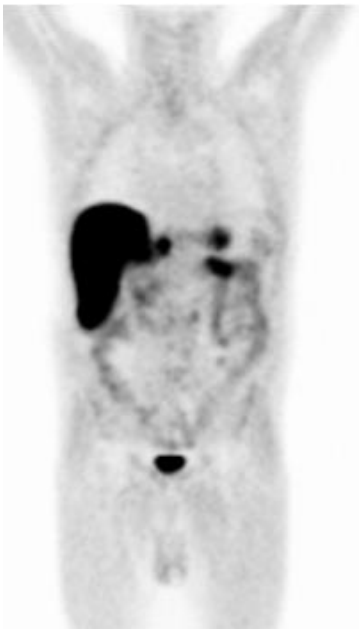

Fig.1. Physiologic distribution of ^{18}F-FCH in healthy men

1.6. Problems and Pitfalls in the interpretation of ^{18}F-FCH PET/CT scans

In patients with prostate cancer disease, results of ^{18}F-FCH PET/CT can be either false-negative (mainly in lesions under 5 mm or minimally involved lymph nodes) or false-positive (reactive lymph nodes or benign prostatic lesions). Additionally, to avoid non-specific ^{18}F-FCH uptake, correct timing for ^{18}F-FCH PET/CT in patients who have undergo surgery, radiotherapy, or chemotherapy is required: A PET scan should be performed at least 4-6 weeks after surgery, 4-6 months after radiation therapy and app. 4 weeks after chemotherapy.

2. Clinical indication for ^{18}F-FCH PET/CT in patients with prostate cancer

Patient's referral criteria for ^{18}F-FCH PET/CT still have to be defined. Yet there is no threshold of serum PSA level (ng/ml) under ^{18}F-FCH PET/CT shouldn´t be used. Also, importance of Gleason score (GS), the influence of hormonal treatment (antiandrogen therapy), PSA velocity (PSAve) and PSAdt should be clarified.

Despite lack of precise guidelines when to use ^{18}F-FCH PET/CT in patients with prostate cancer disease, we can robustly divide most important clinical indications into:

1. Restaging of prostate cancer disease (in case of biochemical recurrence)
2. Initial staging of prostate cancer disease (in case of high-risk prostate cancer patients)
3. Biopsy target definition (in case of repeated negative biopsy and elevated PSA level)
4. Radiotherapy planning in patients with prostate cancer disease
5. Treatment monitoring in patients with prostate cancer disease

2.1. ^{18}F-FCH PET/CT in restaging of prostate cancer disease (in case of biochemical recurrence)

Despite highly successful radical prostatectomy (RP) and external beam radiotherapy (EBRT) treatments, prostate cancer relapses in 20% up to 40% of patients within 10 years of potentially curative local therapy (20, 21).

After RP and EBRT, positive PSA value is considered to represent recurrence of the disease. The PSA level measurement as well as PSA kinetics after RP or EBRT is routinely performed tool for detecting prostate cancer recurrence (so called biochemical recurrence), although it cannot distinguish between local, regional, or distant recurrence (22, 23). Recent article on 187 patients (24) showed that endorectal-coil MRI should be considered as the first imaging evaluation for biochemical recurrence for identifying patients suitable for localized salvage therapy; endorectal-coil MRI showed a high level of sensitivity in identifying local recurrence

of prostate cancer following RP, even at low PSA level: For patients with a PSA < 0.4 ng/mL the sensitivity of endorectal-coil MRI was 86% (24).

Currently, there are no guidelines regarding nuclear medicine imaging procedures in patients with biochemical relapse of prostate cancer. However, in Europe many hospitals successfully applied ^{18}F-FCH PET/CT as first line imaging modality in patients with biochemical relapse, of prostate cancer (Fig.2A. and Fig.2B.). Unfortunately, ^{18}F-FCH PET/CT has low sensitivity at low PSA level (25-28). In patients with PSA <2 ng/mL, the detection rate is only 30% to 40% (27). Some authors proved that ^{18}F-FCH PET/CT is sensitive modality to detect recurrent prostate cancer disease if PSA is higher than 2 ng/mL (29, 30). Study on 1000 patients (31) showed that ^{18}F-FCH PET/CT detection rate is not linked just to PSA serum level but also to Gleason score (GS). For suspected recurrence of prostate cancer, a high GS at diagnosis can be associated with positive ^{18}F-FCH PET/CT scan results, regardless of the serum PSA level at the time of imaging. Therefore, the GS is an independent predictive factor for a positive ^{18}F-FCH PET/CT scan, even at low PSA levels (<1 ng/ml; detection rate: 47%) (31). Positivity of ^{18}F-FCH PET/CT is also influenced by PSAve (the time it takes for PSA to rise to a certain level) and PSAdt (the time it takes for PSA levels to double). Schillaci et al. recommended ^{18}F-FCH PET/CT in patients with PSA >2 ng/ml, PSAdt ≤6 months and PSAve >2 ng/ml per year (32). The detection rate is higher in cases of high PSAve (>5 ng/ml/year) and short PSAdt (<2 or 3 months). PSAdt is an independent predictor of positivity of ^{18}F-FCH PET/CT scan also in patients with normal PSA level (33).

In conclusion, in patients with recurrent prostate cancer disease, the overall sensitivity of ^{18}F-FCH PET/CT seems to be higher among patients with higher PSA, higher initial GS, and shorter PSAdt.

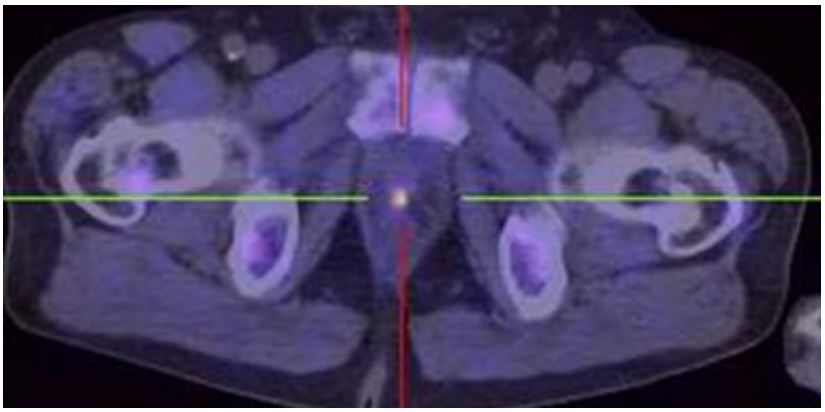

Fig.2A. ^{18}F-FCH PET/CT scan showing focal tracer uptake in the prostatic bed (Patient after RP; PSA=0.8 ng/mL);

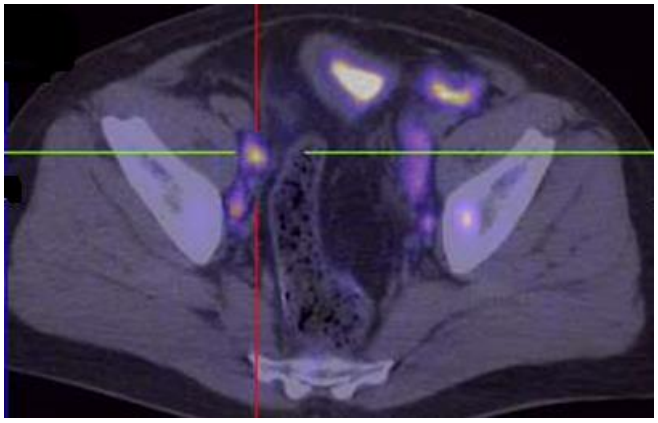

Fig.2B. ^{18}F-FCH PET/CT scan showing increased tracer uptake in the right iliac lymph nodes (Patient after RP; PSA= 1.5 ng/mL)

2.2. ^{18}F-FCH PET/CT in the initial staging of prostate cancer disease (in case of high-risk prostate cancer patients)

App. 1.5% of patients who are diagnosed with prostate cancer has clinically evident metastatic disease (34). Pelvic and retroperitoneal lymph nodes, prostatic bed and skeleton are the most frequently affected site of metastatic spread, relating to 66%, 34%, and 29% of patients, respectively (35). The demonstration that the disease is localized to the prostate

gland or it has also extra glandular spread is of key importance when defining the therapeutic approach. PSA is able to determine presence of the disease but not the disease extension. Therefore, imaging modalities plays main role in the initial staging of patients with prostate cancer. Their optimal use is still under debate, as their diagnostic value, i.e. sensitivity and specificity is not agreed upon (36, 37). The spread within the pelvis is most often evaluated by CT or MRI. However, meta-analysis from Hovels et al. showed that the pooled sensitivity of CT scans in predicting lymph-node metastases is only 42% (38). On the other hand, MRI an detect extracapsular prostatic extension, seminal vesicle invasion, the presence of enlarged locoregional lymph nodes and quantify the spectrum of cancer metabolites using spectroscopic techniques. Endorectal MRI allows imaging of spread of the disease to the prostatic capsule and seminal vesicles.

Despite different opinions in numerous studies, ^{18}F-FCH PET/CT appears to have a role in the initial staging in patients with biopsy-proven intermediate to high-risk prostate cancer. It is unique whole-body imaging modality that represents extent of prostate cancer disease in the entire body, both soft tissue and the skeleton. Retrospective study from Evangelista et al. showed higher sensitivity in detection of bone metastases and lymph nodes disease involvement with ^{18}F-FCH PET/CT in intermediate to high risk prostate cancer patients. In comparison to dedicated CT scan, ^{18}F-FCH PET/CT showed a higher sensitivity and a similar specificity: 46.2% vs. 69.2% and 92.3% vs. 92.3%, respectively in detecting lymph node involvement. Moreover, the sensitivity and specificity of ^{18}F-FCH PET/CT were higher than those of bone scan: 100% vs. 90% and 86.4% vs 77.2%, respectively. The overall accuracy of ^{18}F-FCH PET/CT for lymph-node involvement was 83.3%. In contrast to CT and bone scintigraphy, ^{18}F-FCH PET/CT changed the staging of the prostate cancer disease in 33.3% patients (39). In case of occult lymph node metastases, the study of Hacker et al. showed that ^{18}F-FCH PET/CT is not an useful tool in searching for occult lymph node metastases in clinically confirmed prostate cancer (a sensitivity of only 10% and a specificity of 80% was

observed). In this study sentinel node guided pelvic lymph node dissection allowed the detection of even small lymph node metastasises (40). In a large study involving 912 lymph node samples in 130 patients with intermediate or high-risk prostate cancer, better sensitivity to detect lymph node involvement using ^{18}F-FCH PET/CT was found in the lymph nodes ≥ 0.5 cm in diameter: sensitivity, specificity, positive and negative predictive value was: 66%, 96%, 82%, and 92%, respectively. ^{18}F-FCH PET/CT led to a change in therapy in 15% of all patients and 20% of high-risk patients (18). The same group of authors comprising assessment of bone metastases with ^{18}F-FCH PET/CT and diagnostic CT alone showed that 24% of bone lesions detectable on ^{18}F-FCH PET/CT had no detectable morphological changes on CT, probably due to bone marrow metastases. In this study the sensitivity, specificity, and accuracy of ^{18}F-FCH PET/CT in detecting bone metastases from prostate cancer was 79%, 97%, and 84%, respectively (41). Finally, based on the published data, the change in management, by the inclusion of ^{18}F-FCH PET/CT for the initial staging prostate cancer patients, ranged between 5% (42) and 36% (43).

Due to the facts mentioned, ^{18}F-FCH PET/CT at initial staging can help to determine appropriate way of treatment (RP, EBRT, antiandrogen treatment, salvage surgery, chemotherapy, or combination of these) and despite different opinions in various studies, it appears to have a role in the initial staging, especially in patients with biopsy-proven high-risk prostate cancer (Fig. 3.).

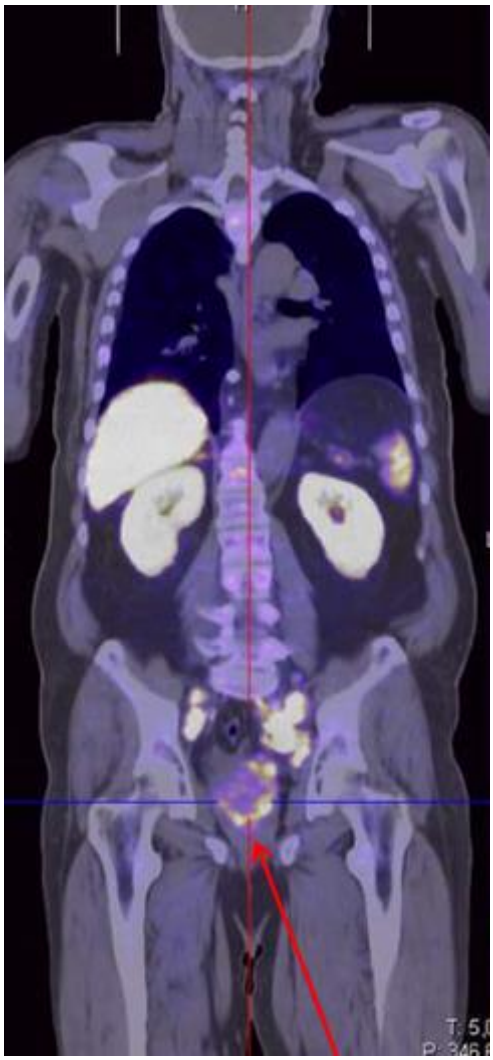

Fig.3. ^{18}F-FCH PET/CT scan showing increased tracer uptake in multiple enlarged iliac lymph nodes bilaterally (Patient at initial staging; PSA= 22 ng/mL; GS=9)

2.3. ^{18}F-FCH PET/CT in biopsy target definition (in case of repeated negative biopsy and elevated PSA level)

Twenty percent of patients with prostate cancer who undergo fine needle biopsy will have false-negative biopsy result (44). Several studies have shown that a significant number of patients with an initial negative prostate needle biopsy and persistently elevated serum PSA levels will have prostatic malignancy found on subsequent biopsy (45, 46). Operator´s ability in guiding the biopsy needle is of great importance. Because of possible source of error,

different morphological imaging modalities have been implemented in localization of prostate cancer, e.g. ultrasound (Transrectal, Colour flow Doppler, Power Doppler) and Multiparametric Magnetic Resonance Imaging (including PI-RADS score: T2 weighted images, DWI - diffusion weighted imaging and DCE – dynamic contrast enhancement).

None of them totally solved the problem of precise localization of malignant process in the prostate. PET/CT modality with choline analogues can be potentially helpful for localisation of malignant process in the prostate, especially when morphological diagnostic methods are inconclusive. A study on 20 patients, with elevated PSA level and negative biopsy, showed that ^{18}F-FCH PET/CT was able to identify malignant zone in the prostate just in 25% of patients (47). In Igerc´s study neither Semiquantitative analysis (SUVmax) nor dual-phase protocol (early acquisition: 3-5 min and late acquisition: 30 min after tracer injection) was helpful. Image analysis was performed visually: described as focal, multifocal or inhomogeneous tracer uptake (47). In the group of patients who had a focal tracer uptake, ^{18}F-FCH PET/CT had a sensitivity of 100%, a specificity of 46.7% and a positive predictive value of 38.5% for the detection of prostate cancer, however validated by biopsy and not histology (47). Another study dealing with this topic (48) found that 1 hour delayed imaging leads to an improvement of malignant to benign contrast ratio of uptake in the prostate: they reported decreasing SUVmax over one hour in benign zones and either stable or increasing SUVmax in malignant zones. Dual time point imaging in this setting requires further investigation and evaluation.

In 80% of cases prostate cancer is located in the peripheral zone of the prostate, in the additional 20% of cases prostate cancer is developed anterior to the urethra (49).

^{18}F-FCH uptake seems to be present in benign changes (prostatitis and prostatic hypertrophy) as well as in prostate cancer, therefore because the tracer is not specific, ^{18}F-FCH PET/CT cannot be generally recommended as the primary procedure for the localization of prostate cancer.

In conclusion, at the present time, the routine use of ^{18}F-FCH PET/CT cannot be recommended as a first-line screening procedure for primary prostate cancer. A potential application of ^{18}F-FCH PET/CT may be to increase the detection rate of clinically suspected prostate cancer with multiple negative prostate biopsies (Fig.4.). New procedures such as ^{18}F-FCH MRI/PET are being evaluated in imaging of primary prostate cancer (50).

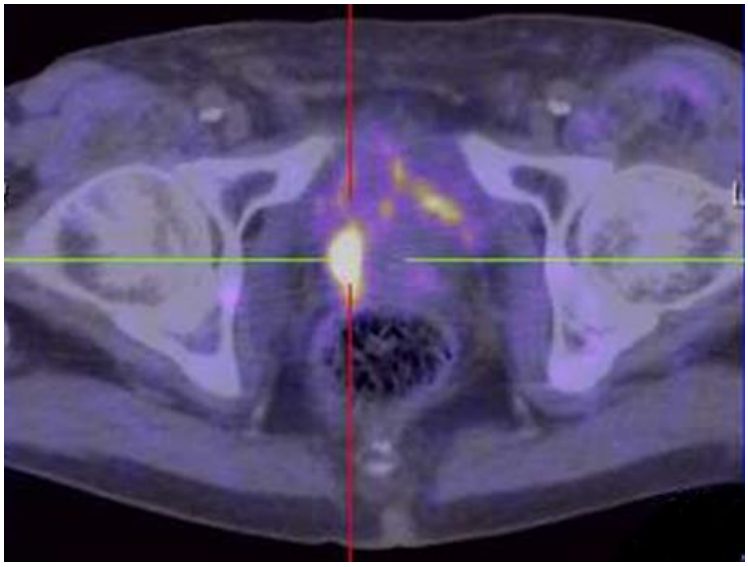

Fig.4. ^{18}F-FCH PET/CT scan showing increased tracer uptake in the right lobe of prostate (Patient with PSA= 10.2 ng/mL, after negative biopsy and negative MRI scan)

2.4. ^{18}F-FCH PET/CT in radiotherapy planning in patients with prostate cancer disease

For many years MRI as well as magnetic resonance spectroscopy (MRS) have been proposed as first line modalities in precise definition of intraprostatic lesions (51, 52). Precise detection of the site of prostate cancer process is crucial for a good radiotherapy treatment outcome. Additionally, organs at risk such as the rectum and bladder need to be protected. In their review article Schwarzenböck et al. (53) presented most common indication for radiotherapy usage in patients with prostate cancer: 1) Irradiation of the former prostate bed with

enlargement of irradiation field to the pelvic lymphatics in order to include all pelvic lymph nodes with or without a boost to PET-positive lymph nodes; 2) Irradiation of the former prostate bed and PET-positive lymph nodes and the corresponding lymphatic drainage vessels; 3) Irradiation of the former prostate bed and irradiation of PET-positive lymph nodes only (without irradiation of any lymphatic drainage vessels) (53). According to available scientific sources, neither ^{11}C-choline nor ^{18}F-FCH PET/CT is strongly recommended for target volume definition both for primary or recurrent prostate cancer. However, several articles are showing promising results for choline PET/CT as an image guide tool for the irradiation of prostate cancer relapse (54-60).

The weak point of ^{18}F-FCH PET/CT in target volume delineation is that visual ^{18}F-FCH uptake does not totally correlate with malignant process, inflammation can be still present. The study of Bundschuh et al. showed that choline uptake pattern corresponded to the histological localization of prostate cancer in fewer than 50% of lesions and that SUVmax thresholding with standard algorithms did not lead to satisfying results with respect to defining tumour tissue in the prostate (61).

However, prospective, comparative studies with histopathological specimens are required to validate various approaches in usage of ^{18}F-FCH PET/CT in target volume delineation of primary and recurrent prostate cancer as well as in the identification of prostate cancer lymph node involvement. In this field, the potential role of ^{18}F-FCH PET/MRI is becoming interesting.

2.5. ^{18}F-FCH PET/CT in treatment monitoring in patients with prostate cancer disease

Over the past decades, different therapeutic options have been included in management of patients with rising PSA after primary therapy or in cases of systemic spread of prostate

cancer disease. For this purpose androgen deprivation therapy is used: Luteinizing hormone-releasing hormone (LHRH) agonists and antagonists as well as androgen receptor blockers. Androgens stimulate growth, function and proliferation in normal and malignant prostate cells; on the other hand deprivation of androgens induce prostate cell apoptosis (62). Despite treatment with ADT, most men will progress to castrate-resistant prostate cancer. This group of patients undergo chemotherapy with Docetaxel or Cabazitaxel (Fig.5.). In the area of therapy, nuclear medicine proposes treatments of skeletal metastases with α-emitting radiopharmaceutical ^{223}Ra (Xofigo®) as well as some β-emitting agents: ^{89}Sr, ^{153}Sa and ^{188}Re.

PSA is the most commonly used marker for evaluation treatment response in patients with progressive prostate cancer disease. PSA alone is not sufficiently reliable for monitoring disease activity in castrate resistant prostate cancer patients, since visceral metastases may develop in men even without an increase in PSA level (63). Where is a role of nuclear medicine in evaluation of therapeutic response of ADT or chemotherapy in patients with rising PSA after primary therapy or with disseminated prostate cancer disease? In Guidelines from European Association of Urology 2014 there is no precise indication for choline PET/CT in castrate resistant prostate cancer patients (7). In 2015 the Prostate Cancer Clinical Trials Working Group 2 recommended a combination of BS, CT scan, PSA measurements and clinical findings in patients with metastatic castrate-resistant prostate cancer (64). In mentioned group of patients Guidelines presented MRI and PET as “useful” techniques St. Gallen’s Consensus Conference recommended BS and CT scan as baseline investigations, PSA should be considered for monitoring treatment response in conjunction with alkaline phosphatase and lactate dehydrogenase (65).

Up to 45 % of the patients going for choline PET/CT are under ADT at the time of the examination. In this regard, there is a question whether ADT influences the choline uptake and therefore, whether ADT should be withdrawn before PET. Some studies support the

theory that there is no influence of ADT on detection rate of ^{18}F-FCH PET/CT, therefore it is not necessary to withdraw ADT before performing ^{18}FCH PET/CT scan (62, 66, 67, 68).

On the other hand, some authors postulate an inhibitory effect of ADT on choline uptake and thus recommend that the choline PET scan should be performed either before starting ADT or the treatment should be interrupted for a certain time before the scan (69, 70). It remains unclear if differences in choline uptake can be contributed to an effect caused by the therapeutic effect of ADT, e.g. the reduced tumour volume or changes in metabolism (71).

Patients who do not respond to ADT and who present with PSA elevation despite the ongoing ADT are the main candidates to perform choline PET (62). In their study McCarthy et al. showed better sensitivity of ^{18}F-FCH PET/CT in comparison to conventional imaging modalities (CT and bone scintigraphy) in follow up of patients with castration-resistant prostate carcinoma: ^{18}F-FCH PET/CT showed good initial concordance (81%) with BS and CT in the detection of active metastatic prostate carcinoma. Follow-up of the cases where ^{18}F-FCH was initially discordant with subsequent BS or CT shows that ^{18}F-FCH is accurate in determining the presence or absence of prostate metastasis in 79% of lesions (72). Another group of authors showed that combination of decrease in PSA level and ^{18}F-FCH PET/CT can be an early predictor of outcome in castrate resistant prostate cancer patients treated with enzalutamide (73).

It seems that ^{18}F-FCH PET/CT is still searching for its role in therapy monitoring of patients with rising PSA after primary therapy or in cases of systemic spread of prostate cancer disease. Nevertheless, it seems that ^{18}F-FCH PET/CT has a role in selected group of patients.

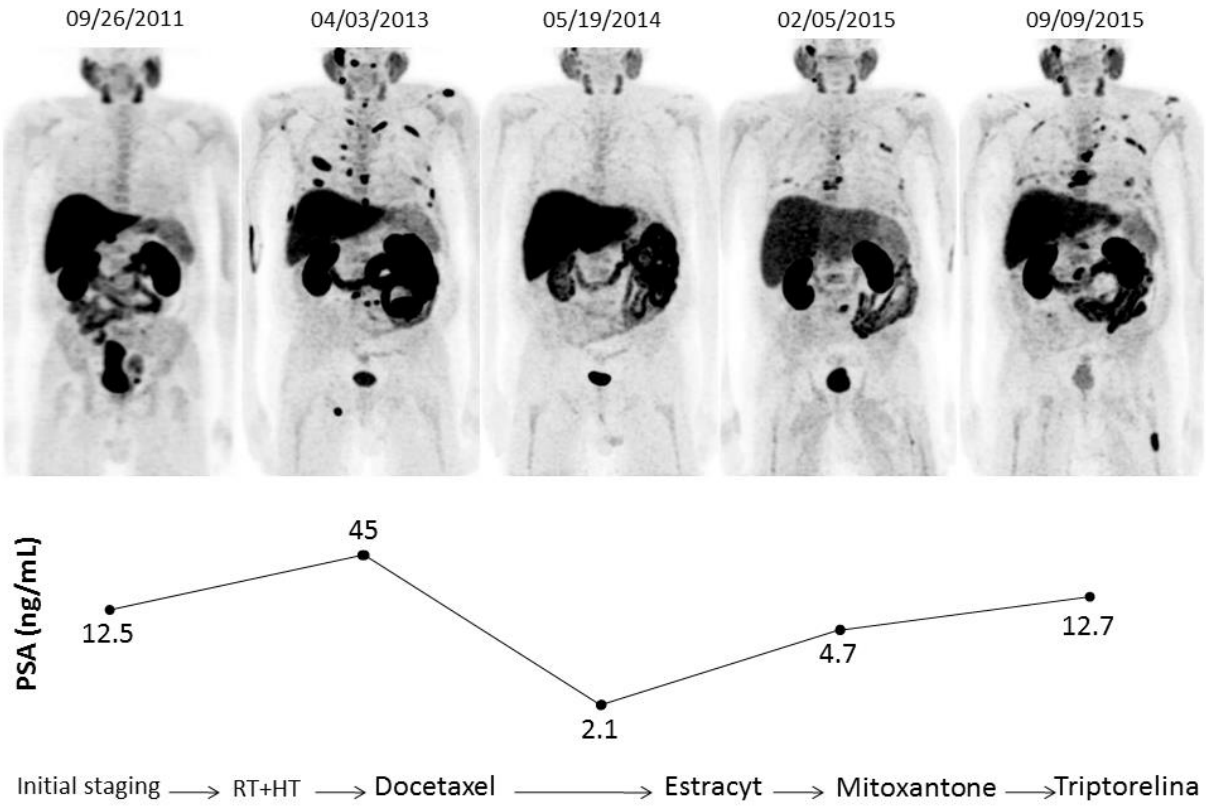

Fig.5. ^{18}F-FCH PET/CT scan showing treatment monitoring in patient with prostate cancer disease

3. Aims

We have set the following objectives for our research:

3.1. To estimate the diagnostic contribution of ^{18}F-choline in patients with histological (or cytological) confirmed prostate cancer. (see study 4.1. performed at the time of implementation of this radiopharmaceutical in practice - 2010)

3.2. To analyse the causes of incidental uptake of ^{18}F-choline in the head or the neck in patients with prostate cancer. (see study 4.2. - 2013)

3.3. To compare the evolution of diagnostic imaging in patients with prostate cancer using a new radiopharmaceutical ^{18}F-FCH, observed in France and in Slovenia, and to quantify the consequence of the results of new imaging modality on the detection rate of abnormal metastases and recurrences of prostate cancer. (see study 4.3. - 2014)

Topics of co-operative research:

3.4. To explore the ability of ^{18}F-choline PET/CT to identify local recurrence of prostate cancer. (see study 4.4. - 2015)

3.5. To explore the ability of the initial Gleason score to predict the rate of detection of recurrent prostate cancer with ^{18}F-choline PET/CT in a large cohort of patients (1000 patients). (see study 4.5. - 2015)

4. Studies - published data

4.1. ***Role of (18)F-choline PET/CT in evaluation of patients with prostate carcinoma.***

Hodolič M.

Radiol Oncol. 2011 Mar;45(1):17-21.; IF:1.97

The Aim of the study:

To estimate the diagnostic contribution of ^{18}F-choline in patients with histological (or cytological) confirmed prostate cancer (study performed at the time of implementation of this radiopharmaceutical in practice - 2010).

Conclusion of the study:

^{18}F-choline PET/CT seems to be useful imaging modality in patients with prostate carcinoma.

Indications for ^{18}F-choline PET/CT imaging modality in evaluation of patients with prostate cancer cover a wide spectrum of clinical settings: localisation of intraprostatic neoplastic lesions, initial staging, detection of occult recurrences and characterisation of images on conventional imaging modalities, which are questionable or difficult to interpret. PSA level can influence sensitivity of ^{18}F-FCH PET/CT, but most probably doubling time of serum PSA increase is more important as PSA level itself. Accurate knowledge of the normal biodistribution of ^{18}F-choline is essential for the correct interpretation of PET/CT images. Delayed or dual-phase imaging after injection of ^{18}F-choline may improve the performance of ^{18}F-choline PET for localising malignant areas of the prostate.

research article

Role of ^{18}F-choline PET/CT in evaluation of patients with prostate carcinoma

Marina Hodolic

Department for Nuclear Medicine, University Medical Centre Ljubljana, Slovenia

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Correspondence to: Marina Hodolič, MD, PhD, Department for Nuclear Medicine, University Medical Centre Ljubljana, Zaloška 7, Slovenia; Phone:+386 1 522 3548; Fax:+386 1 522 22 37; E-mail: marina.hodolic@kclj.si

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Background. Choline presents a high affinity for malignant prostate tissue. It can be labelled with positron emitting ^{18}F, and used for the evaluation of patients with prostate carcinoma by PET/CT imaging. The aim of this paper is to summarise our experience with fluoromethylcholine (^{18}F-choline) PET/CT in patients with prostate cancer.

Methods. In 4 months we investigated the patients with histopathological (or cytological) confirmed prostate cancer. Two observers evaluated the early and late ^{18}F-choline PET images in correlation with corresponding localising CT images and using the semiquantitative standard uptake value (SUV) calculation.

Results. The ^{18}F-choline PET/CT was made in 50 patients with prostate cancer. There were 18 patients after radical prostatectomy and 32 without surgery. In all patients without surgery the pathological uptake was seen in the prostate. In 14 (44 %) patients of this group there was evidence of metastatic spread in local or distant lymph nodes and/or bones. In out of 18 patients after radical prostatectomy the local recurrence was detected in 6 patients (33%) and distant metastases were present in 2 patients (10%).

Conclusions. ^{18}F-choline PET/CT seems to be useful imaging modality in patients with prostate carcinoma; it can demonstrate spread of the disease preoperatively and detect the local recurrence after radical prostatectomy.

Key words: prostate carcinoma; ^{18}F-choline PET/CT; diagnosis; staging; follow-up

Introduction

Prostate carcinoma is the most common life-threatening cancer affecting men in the Western world. The mortality is around 10%. The major goals of pretherapeutic imaging are to determine the local extent of prostate carcinoma in terms of intraprostate localisation, extracapsular extension, seminal vesicle invasion, tumour infiltration into neurovascular bundles, surrounding tissues and organs in the small pelvis, detection of loco-regional metastases via the lymph nodes and detection of distant metastases. The exact pretherapeutic diagnosis and staging are essential, because the tumour treatment must be selected in strict dependence on the clinical tumour stage and risk profile.[1,2]

Both anatomic and functional molecular imaging of prostate carcinoma is important especially when there are problems with diagnosis, for example when prostate punch biopsies are negative while the suspicion of prostate carcinoma persists (for example rising PSA). They may also be helpful in localising the carcinoma, revealing how the carcinoma relates to the surrounding intra- and extraprostatic structures and organs.

^{18}F-Fluorodeoxyglucose (FDG) PET/CT is a nuclear medicine procedure currently most widely used to diagnose primary and metastatic cancers.[3] Unfortunately, not all tumours show a significant increase of metabolic activity on ^{18}F-FDG PET/CT imaging. This is particularly true for neuroendocrine tumours, hepatic tumours and prostate cancer.[4]

Choline presents a high affinity for malignant prostate tissue, even if low grade. Choline can be labelled with either ^{11}C or ^{18}F, the former being the preference due to the lower urinary excretion and patients' exposure. The latter is more useful for a possible distribution to centres lacking in on-site cyclotron. The sensitivity of ^{18}F-choline PET/CT to detect prostate cancer preoperatively is 73%, greater than with ^{18}F-FDG PET/CT (31%). Also the accu-

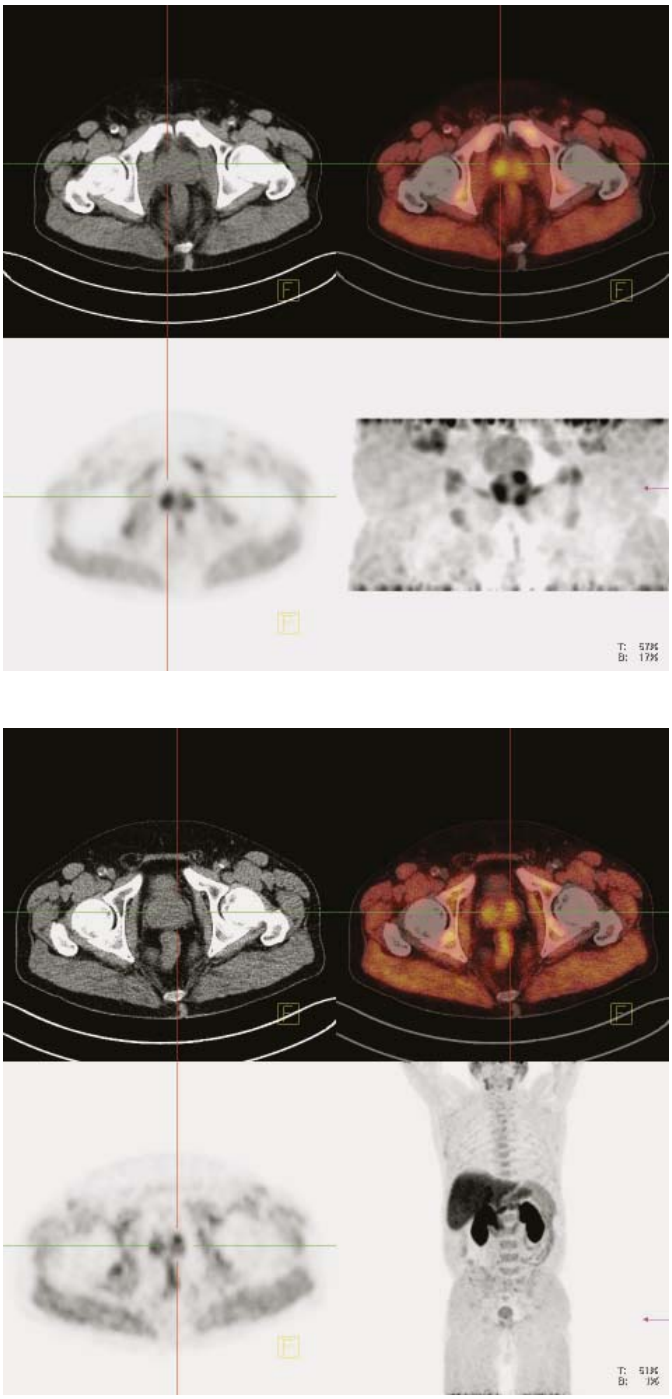


FIGURE 1. Prostate carcinoma: A prostatic bed (early images), B whole body (late images). Upper left panel: CT image. Upper right panel: fused PET/CT image. Lower left panel: PET image. Lower right panel: maximum intensity projection (MIP).

racy is greater with ^{18}F-choline PET/CT (67%) than using ^{18}F-FDG PET/CT (53%).[5] The use of ^{18}F-FDG in prostate cancer is limited to the most aggressive cancers.[6]

The aim of this paper is to summarise our experience with fluoromethylcholine (^{18}F-choline) and PET/CT in patients with prostate cancer.

Patients and methods

From 12.05.2010 to 15.09.2010 months we investigated the patients with cytological or histological confirmed prostate cancer.

The patients were fasting 6-10 hours prior the scan. ^{18}F-choline (IASOcholine® from IASON Austria) was injected *i.v.* (200 – 300 MBq, according to the weight of the patient) using the automatic radionuclide injector (Medrad). List mode acquisition over prostatic bed started immediately after the injection of the tracer and lasts for 5 minutes. After this early phase patients rested for approximately one hour. The whole body acquisition was performed thereafter, 2 min per bed position from base of the skull to midthigh (9 bed positions on average). Siemens Biograph mCT PET/CT scanner has been used.

Early images were reconstructed from the list mode acquisition study before the activity appeared in the bladder (Figure 1A). Early (0-5 min *p.i.*) images and late (60 min *p.i.*) whole body images were presented in the usual transaxial, coronal and sagital planes. Two observers evaluated the images in correlation with corresponding localising CT images and using semiquantitative standard uptake value (SUV) calculation.

Results

The ^{18}F-choline PET-CT was performed in 50 patients with prostate cancer. The mean age was 67.7 years. There were 32 patients before radical prostatectomy and 18 after surgery (Table 1.).

The early phase has been used to evaluate prostate or prostate bed. The findings corresponded to late phase images in all patients (Figures 1 A, B). In patients with bony metastases in the pelvis the pathological uptake was seen in metastases already during the first 5 min after the tracer injection (Figures 2 A, B).

In all patients without surgery the pathological uptake was seen in the prostate. In 14 (44 %) patients of this group there was evidence of metastatic spread in local or distant lymph nodes (Figure 3) and/or bones (Figure 2 B). In patients after radical prostatectomy the local recurrence was detected in 6 patients (Figure 4) (33%) and distant metastases

TABLE 1. Results of ^{18}F-choline PET/CT scans in 50 patients with prostate carcinoma

	Number of patients	Prostatic bed (positive)	Metastases (positive)
After radical prostatectomy	18	6 (33 %)	2 (10%)
No surgery	32	32 (100%)	14 (44%)
Total	50	38 (96%)	16 (33%)

were present in 2 patients one had also the local recurrence; the other one has no evidence of local recurrent disease (Table 1).

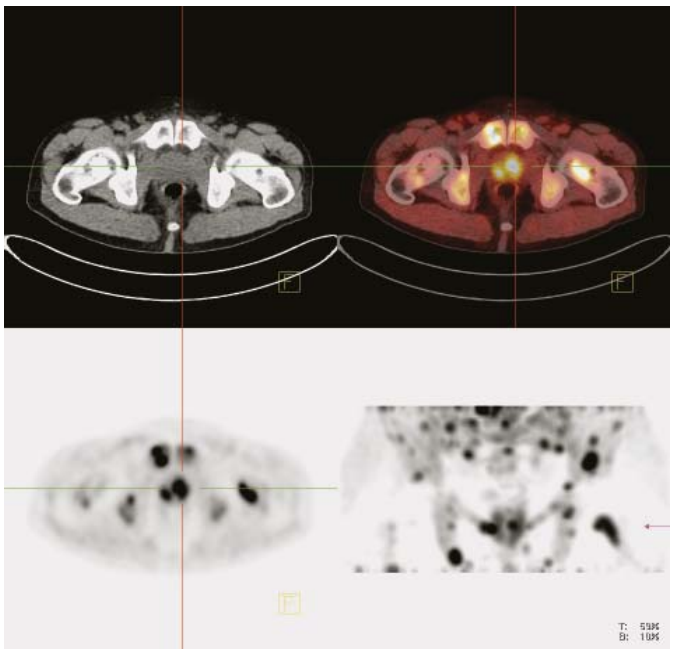
Discussion

Indications for ^{18}F-choline PET/CT imaging modality in evaluation of patients with prostate cancer cover a wide spectrum of clinical settings: localisation of intraprostatic neoplastic lesions, initial staging, detection of occult recurrences and characterisation of images on conventional imaging modalities, which are questionable or difficult to interpret. ^{18}F-choline is taken up by prostatic carcinoma as well as distant metastases very fast, already during 5 min after the injection (Figure 2).

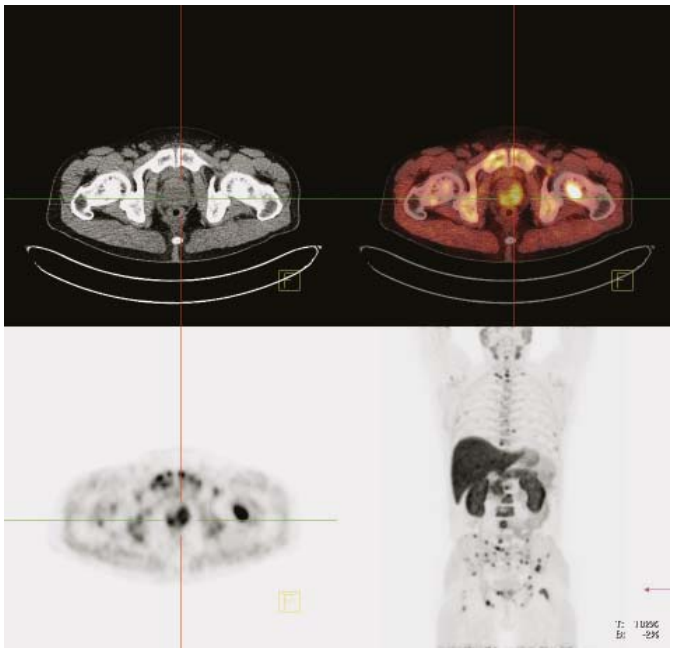
The accurate knowledge of the normal biodistribution of ^{18}F-choline is essential for the correct interpretation of PET/CT images. CT enables the differentiation of physiological bowel activity and ^{18}F-choline excretion in the ureters. ^{18}F-choline uptake in benign pathological conditions mainly includes sites of inflammation; nevertheless, the accumulation in tumour deposits not due to prostate cancer cannot be excluded.[7]

Similarly to FDG, choline is also taken up by infection.[8] The differentiation between inflamed and metastatic lymph nodes can be achieved either by two phases PET or by appropriate antimicrobial treatment preceding ^{18}F-choline PET/CT. On dual-phase PET of the prostate, areas of malignancy consistently demonstrated the stable or increasing ^{18}F-choline uptake, whereas most areas containing benign tissue demonstrated the decreasing uptake.

Delayed or dual-phase imaging after the injection of ^{18}F-choline may improve the performance of ^{18}F-choline PET for localising malignant areas of the prostate.[9] ^{18}F-choline PET/CT showed a fast progressively increasing max. SUV in biopsy confirmed cancer lesions up to 14 min post injection while decreasing in inguinal lymph nodes interpreted as benign. Furthermore, it was very useful in differentiating local recurrences from confounding blood pool and urinary activity.[10] Although more data need to be obtained, it appears that ^{18}F-choline



A



B

FIGURE 2. Bone metastases due to prostate cancer: A prostatic bed (early images), B whole body (late images). Upper left panel: CT image. Upper right panel: fused PET/CT image. Lower left panel: PET image. Lower right panel: maximum intensity projection (MIP).

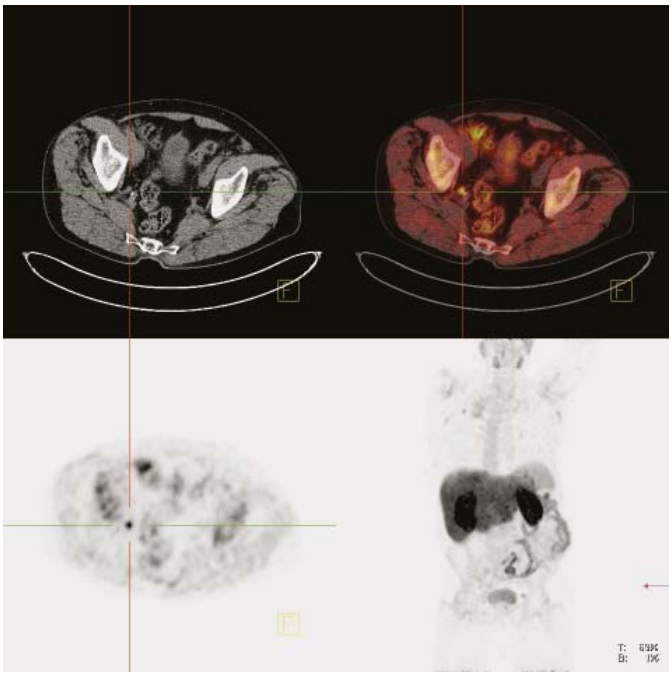


FIGURE 3. Lymph node metastases due to prostate cancer: whole body scan (late images). Upper left panel: CT image. Upper right panel: fused PET/CT image. Lower left panel: PET image. Lower right panel: maximum intensity projection (MIP).

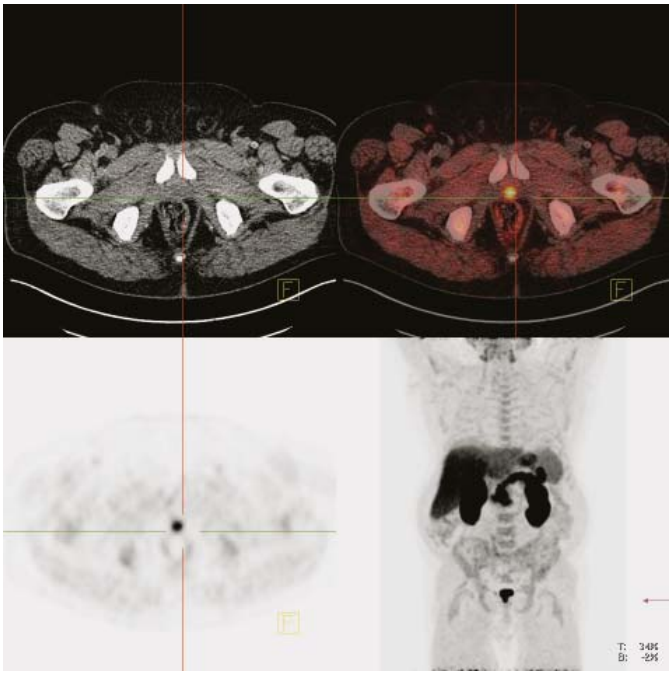


FIGURE 4. Relapse of prostate cancer: whole body (late images). Upper left panel: CT image. Upper right panel: fused PET/CT image. Lower left panel: PET image. Lower right panel: maximum intensity projection (MIP).

PET/CT is highly efficient in preoperative management regarding N and M staging of prostate cancer once metastatic disease is strongly suspected or documented.[11] ^{18}F-choline PET/CT could be useful in the evaluation of patients with prostate cancer who are at high risk for extracapsular disease, and it could be used to preoperatively exclude distant metastases.[12]

Patients with persistent elevated PSA and repeated negative prostate biopsy, (*i.e.* prostate being biopsied at multiple times), were investigated with ^{18}F-choline PET/CT to delineate prostate cancer and guide renewed prostate biopsy. In 25% of patients, ^{18}F-choline PET/CT allowed the identification of neoplastic prostatic zones.[13]

The sensitivity, specificity and accuracy of ^{18}F-choline PET/CT in the detection of bone metastases in prostate cancer are 74%, 99% and 85%, respectively. ^{18}F-choline PET-CT may be superior to bone scintigraphy for the early detection of metastatic bone disease due to the detection of bone marrow metastases.[13]

Out of all patients with carcinoma of the prostate undergoing therapeutic regimes with curative intent, 15-23% will ultimately relapse and 16-35% will need some sort of salvage therapy within 5 years. Of relapsing patients, 50% will have local recurrence and 50% systemic disease with or without local recurrence. Therefore, the localisation of recurrent prostate cancer is critical for selecting a local or systemic therapeutic strategy.[15] Modern fusion imaging with ^{18}F-choline PET/CT has augmented the diagnostic imaging spectrum for the assessment of relapsing prostate cancer. In 60-70% of patients with biochemical relapse, recurrent tumour can be detected and anatomically precisely localised. Imaging with ^{18}F-choline PET/CT and MRI possesses a high potential for the early localisation of recurrent prostate carcinoma.[16]

In patients with biochemical relapse after the radical treatment for prostate cancer, ^{18}F-choline PET/CT represents a single step, whole-body, non-invasive study that allows disease detection and localisation. Detection sensitivity is probably negatively correlated with serum PSA concentration. Pelosi *et al.* reported that ^{18}F-choline PET scan detected the disease relapse in 42.9% of cases (24/56). PET sensitivity was 20% in the PSA ≤ 1 ng/ml subgroup, 44% in PSA > 1 and ≤ 5, and 81.8% in PSA > 5 ng/ml subgroup, respectively.[17] According to other investigators ^{18}F-choline PET/CT is not likely to have a significant impact on the care of prostate cancer patients with biochemical recurrence until PSA increases to above 4 ng/ml. However,

in selected patients, ^{18}F-choline PET/CT helps to exclude distant metastases when the salvage local treatment is intended.[18] Most probably doubling time of serum PSA increase is more important as PSA level itself.

^{18}F-choline PET/CT seems to be useful also for the evaluation of other cancers with poor FDG uptake, such as hepatocellular carcinoma.[19]

Conclusions

In future studies some of dilemmas that appear in presented study need to be solved: to correlate PET/CT results with standard prognostic factors and to determine their prognostic significance (correlation of our PET/CT results with starting PSA, clinical T stage, Gleason score in surgically treated/biopsied patients and PSA doubling time in patients with biochemical recurrence).

^{18}F-choline PET/CT seems to be useful imaging modality in patients with prostate carcinoma for demonstrating the spread of the disease preoperatively and to detect local recurrent disease after radical prostatectomy.

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4.2. ***Incidental uptake of (18)F-fluorocholine (FCH) in the head or in the neck of patients with prostate cancer.***

Hodolič M, Huchet V, Balogova S, Michaud L, Kerrou K, Nataf V, Cimitan M, Fettich J, Talbot JN.

Radiol Oncol. 2014 Jul 10;48(3):228-34.; IF: 1.912

The Aim of the study:

We searched for incidental ^{18}F -FCH uptake in the head (including brain) or in the neck in patients with prostate cancer: solitary or multiple lesion(s), excluding only images evocative of bone metastatic spread or non-focal uptake such as diffuse intense uptake by the thyroid gland or the physiologic ^{18}F-FCH uptake by the salivary or the lachrymal glands. When such foci were visible in the head or in the neck, we requested further data in order to try to characterise the lesions.

Conclusion of the study:

We described incidental ^{18}F-FCH uptake in the head or in the neck, in 1.9% of the PET/CTs performed for staging or restaging prostate cancer. Some of those incidental ^{18}F-FCH foci corresponded to malignancies, but more frequently (80%) to various benign tumours. In particular, for the first time, we observed ^{18}F-FCH uptake in pituitary adenomas and in hyperfunctioning parathyroid glands. Such foci should be mentioned in the report, as meningioma or hyperparathyroidism may directly impact on management of a patient with prostate cancer. Since ^{18}F-FCH is taken-up by slow-growing malignancies it could be expected that ^{18}F-FCH PET/CT can detect benign tumours even more frequently than ^{18}F-FDG PET/CT. Furthermore, there might be a future indication for ^{18}F-FCH PET/CT when one such tumour is already known or suspected: for post-operative control of a resected pituitary adenoma, to guide surgery or radiotherapy of a meningioma or to localise hyperfunctioning parathyroid glands. In those indications, comparative studies with reference PET tracers could be undertaken, on basis of published case reports and the present preliminary series.

case reports

Incidental uptake of ^{18}F-fluorocholine (FCH) in the head or in the neck of patients with prostate cancer

Marina Hodolic[1], Virginie Huchet[2], Sona Balogova[2,3], Laure Michaud[2,4], Khaldoun Kerrou[2], Valérie Nataf[2,5], Marino Cimitan[6], Jure Fettich[1], Jean-Noël Talbot[2,4]

[1] Department for nuclear medicine, University Medical Centre, Ljubljana, Slovenia
[2] Médecine nucléaire, Hôpital Tenon, AP-HP, Paris, France
[3] Comenius University, Bratislava, Slovakia
[4] Université Pierre et Marie Curie, Paris, France
[5] Radiopharmacie, Hôpital Tenon, AP-HP, Paris, France
[6] Nuclear Medicine Unit, National Cancer Institute CRO IRCCS, Aviano, Italy

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Correspondence to: DR. Marina Hodolič, Department for Nuclear Medicine, University Medical Centre, Zaloška 2, SI-1000 Ljubljana, Slovenia. Phone: +386 1 522 35 48; Fax: +386 1 522 22 37; E-mail: marina.hodolic@gmail.com

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Background. Positron emission tomography-computed tomography (PET/CT) with ^{18}F-fluorocholine (FCH) is routinely performed in patients with prostate cancer. In this clinical context, foci of FCH uptake in the head or in the neck were considered as incidentalomas, except for those suggestive of multiple bone metastases.

Case reports. In 8 patients the incidental focus corresponded to a benign tumour. The standard of truth was histology in two cases, correlative imaging with MRI in four cases, ^{99m}Tc-SestaMIBI scintigraphy, ultrasonography and biochemistry in one case and biochemistry including PTH assay in one case. The final diagnosis of benign tumours consisted in 3 pituitary adenomas, 2 meningiomas, 2 hyperfunctioning parathyroid glands and 1 thyroid adenoma. Malignancy was proven histologically in 2 other patients: 1 papillary carcinoma of the thyroid and 1 cerebellar metastasis.

Conclusions. To the best of our knowledge, FCH uptake by pituitary adenomas or hyperfunctioning parathyroid glands has never been described previously. We thus discuss whether there might be a future indication for FCH PET/CT when one such tumour is already known or suspected: to detect a residual or recurrent pituitary adenoma after surgery, to guide surgery or radiotherapy of a meningioma or to localise a hyperfunctioning parathyroid gland. In these potential indications, comparative studies with reference PET tracers or with ^{99m}Tc-sestaMIBI in case of hyperparathyroidism could be undertaken.

Key words: FCH, PET/CT; incidentaloma; meningioma; pituitary adenoma; hyperparathyroidism; thyroid adenoma

Introduction

Positron emission tomography-computed tomography (PET/CT) with radiolabeled choline is becoming the first line nuclear medicine examination in patients with prostate cancer[1], especially where there is evidence of biochemical recurrence.[2] ^{11}C-choline has low urinary excretion, which is favourable for detecting pelvic foci, but its routine use is not possible in centres lacking an on-site cyclotron. ^{18}F-fluorocholine (FCH), which can be delivered as easily as ^{18}F-fluorodeoxyglucose (FDG), has proven clinical utility for PET imaging of cancers with slow growth and low aggressiveness, frequently missed with FDG.[3]

FCH is currently registered in several EU countries for the detection of bone metastasis in prostate cancer, which is currently its most frequent indica-

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TABLE 1. Patients with incidentaloma in the head or in the neck on FCH PET/CT performed for prostate cancer staging or restaging benign tumours

No.	Age	Prostate cancer setting for FCH PET/CT	Incidental FCH uptake in head and neck region	Diagnostic modality(ies) for characterisation
1.	78	Biochemical recurrence under HT	Pituitary	MRI: Macroadenoma of pituitary gland
2.	64	Biochemical recurrence after HT	Pituitary	MRI: Residual pituitary adenoma in the right side of sella turcica
3.	81	Biochemical recurrence after prostatectomy, under HT	Pituitary	Post-surgical histology: non-functioning pituitary adenoma
4.	72	Initial staging	Frontal lobe	MRI: Meningioma in the anterior cranial fossa
5.	70	Biochemical recurrence, under HT	Between cerebellum and medulla	MRI: Meningioma at the level of foramen magnum on the right side
6.	56	Initial staging	Behind the left thyroid lobe	Serum PTH: 160 ng/L, ultrasonography and 99mTc-SestaMIBI/123I scintigraphy: recurrent parathyroid adenoma at the same location
7.	75	Biochemical recurrence after high intensity focused ultrasound, no HT	Behind the left thyroid lobe	Serum PTH: 134 ng/L, calcemia: 2.6 mmol/L, normal serum calcidiol
8.	52	Biochemical recurrence after prostatectomy, under HT	Left thyroid lobe	Ultrasonography: multinodular thyroid gland. Cytology of the target nodule: thyroid adenoma

HT: hormonal treatment; PTH: parathyroid hormone; MRI: magnetic resonance imaging

tion for use. FCH foci can reveal secondary lesions of prostate cancer not only in the skeleton but also in soft tissue, and may be found in unexpected locations such as penis.[4] But FCH foci may also correspond to other primary cancers[3] or inflammatory lesions.[5]

Foci in the head or in the neck are unexpected in patients referred for prostate cancer.[6] We reviewed the reports of FCH PET/CTs performed in our centres in patients with prostate cancer, to select those in which such foci have been reported. We then searched whether the origin and the nature of each focus has been characterised during follow-up. As FCH PET/CT is developing rapidly, we consider it is useful to share experience about the frequency of incidental FCH foci in the head or in the neck, about their possible benign non-inflammatory aetiology and to speculate on a potential indication of FCH PET/CT in the management of those tumours, in comparison with other PET tracers according to a review of literature.

Patients and methods

The patients, referred for prostate cancer staging or restaging, were fasting for 6-10 hours prior to FCH PET/CT. PET/CT was performed after intravenous injection of 200-300 MBq of FCH (IASOcholine®, Graz, Austria, or Advanced Accelerator Applications, Saint Genis-Pouilly, France), according to the body weight of the patient. Whole body acquisition was performed during two minutes for each of 9-10 bed positions, from midthigh to skull, using Siemens Biograph mCT or Philips TF16 PET/CT scanners. Whole body images were presented in the usual transaxial, coronal and saggital slices, for PET, CT and PET/CT fusion.

In University Medical Centre Ljubljana, the reports of FCH PET/CTs performed in prostate cancer patients were reviewed from 29th February 2012 until 11th November 2012. FCH PET/CTs were performed in compliance with Slovenian marketing authorisation granted to Iasocholine in April 2011.

In Hospital Tenon, in Paris, the reports of FCH PET/CTs performed in prostate cancer patients were reviewed from 12th November 2004 until 11th November 2012. FCH PET/CTs were performed as part of two successive clinical studies (CH02 Eudra CT number: 2004-003019-21 and then Ichorpro EudraCT number 2007-004419-69) until November 2009 and then in compliance with the French marketing authorisation granted to Iasocholine in April 2010.

We searched for solitary or multiple lesion(s) in the head (including brain) or in the neck, excluding only images evocative of bone metastatic spread or non-focal uptake such as diffuse intense uptake by the thyroid gland or the physiologic FCH uptake by the salivary or the lachrymal glands. When such foci were visible in the head or in the neck, we requested further data in order to try to characterise the lesions.

Results

In 8 patients referred to FCH PET/CT for prostate cancer, an incidental focus was found in the head

and neck region, which was finally diagnosed as corresponding to a benign tumour (Table 1). The standard of truth was histology in 2 cases, correlative imaging with MRI in 4 cases, 99mTc-sestaMIBI scintigraphy, ultrasonography and biology in one case, biology including PTH assay in one case. There were 3 pituitary adenomas (Figure 1), 2 meningiomas (Figure 2), 2 hyperfunctioning parathyroid glands (Figure 3) and 1 thyroid adenoma (Figure 4).

In 2 patients, the incidental focus corresponded histologically to a malignant lesion: 1 papillary carcinoma of the thyroid 45 mm in size and 1 cerebellar metastasis of a second primary cancer in the lung.

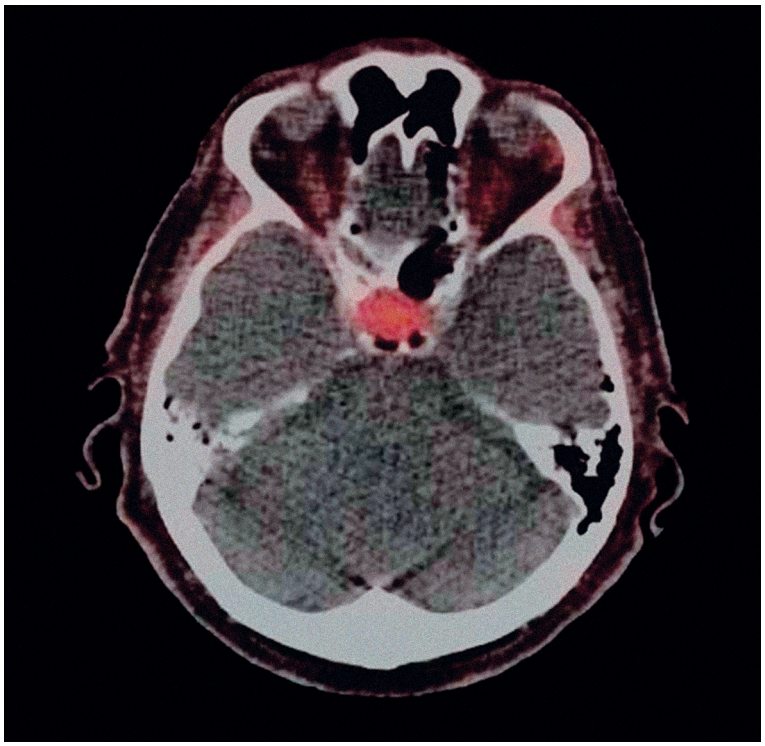

FIGURE 1. Positron emission tomography-computed tomography axial slice: Macroadenoma of pituitary gland that incidentally took-up ^{18}F-fluorocholine (SUVmax 3.7).

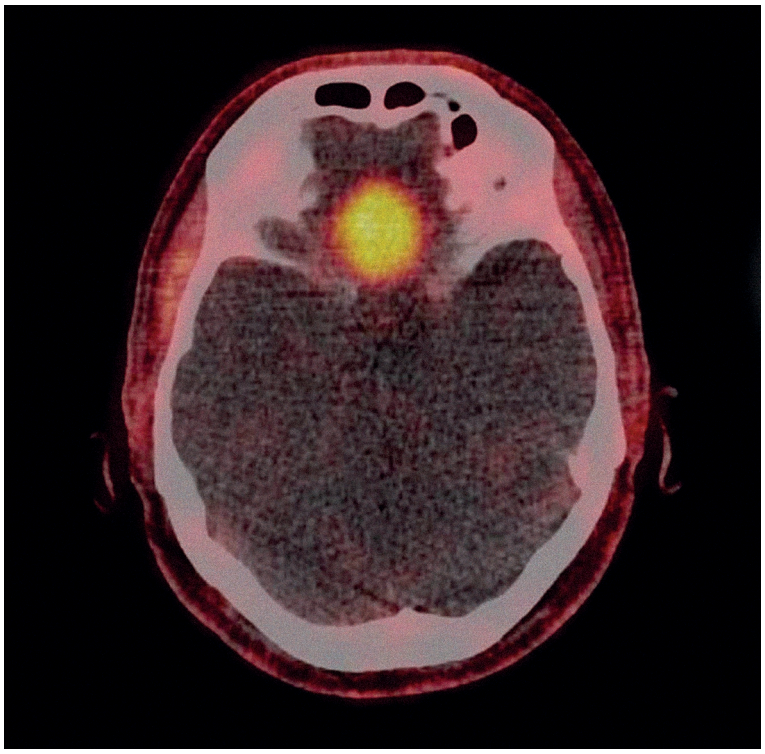

FIGURE 2. Positron emission tomography-computed tomography axial slice: Meningioma in the anterior cranial fossa that incidentally took-up ^{18}F-fluorocholine (SUVmax 3.7).

Discussion

To the best of our knowledge, the frequency of incidentalomas discovered on FCH PET/CT in head or in the neck has never been published. It was estimated to be 1.9% in our series, a thyroid nodule being the most frequent cause of incidentaloma (41%). Actually, our survey showed that the mention in the report of an incidental FCH uptake in the head or the neck led to further investigations in only 52% of cases. The variable impact of this discovery on patient management is probably due to the fact that, in patients with known prostate cancer, the characterisation of a brain lesion was considered more important than that of thyroid nodule or a focus in the thyroid bed. Overall the final diagnosis of those incidental foci which were further explored corresponded to a non-malignant lesion in 80% of cases (8/10).

The main limitation of this study is the fact that not all incidentalomas have been explored and that the final diagnosis of benign tumour is based on histology in only two cases (Table 1): one pituitary adenoma (patient #3) and one thyroid adenoma (patient #8). In the other cases, it has been set by a multidisciplinary medical team on follow-up data which were independent from FCH PET/CT.

Providing that those preliminary findings would be confirmed in larger series, we will briefly discuss if deliberately performing FCH PET/CT in patients presenting with or suspected of a benign tumour in the head or in the neck could be justified.

Pituitary adenomas

The pituitary gland has a moderately intense physiologic uptake of FCH, as shown on PET/MRI[7], although it has been neglected in some previous

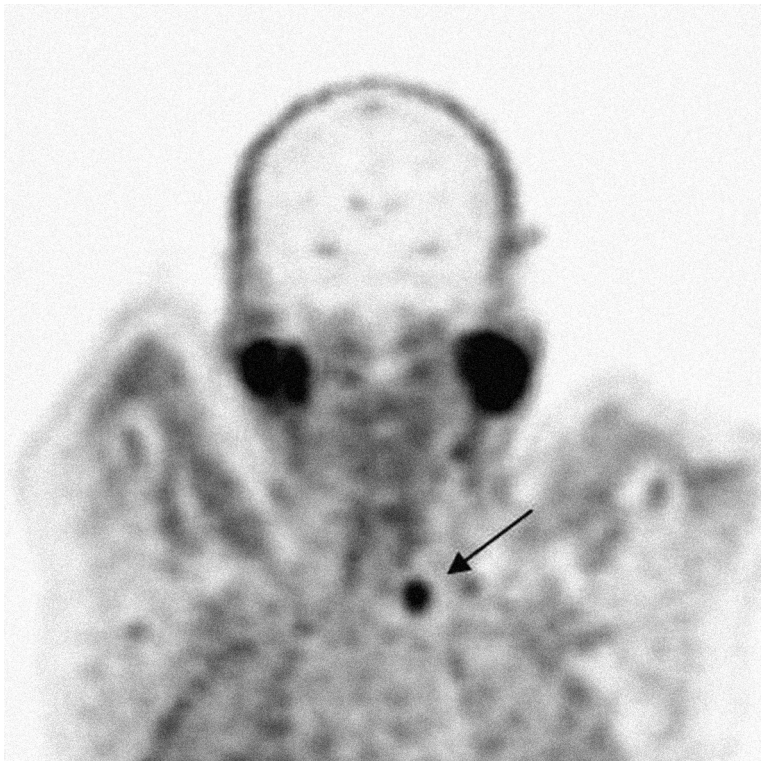

FIGURE 3. Positron emission tomography-computed tomography coronal slice: Adenoma of the parathyroid that incidentally took-up ^{18}F-fluorocholine (SUVmax 3.4).

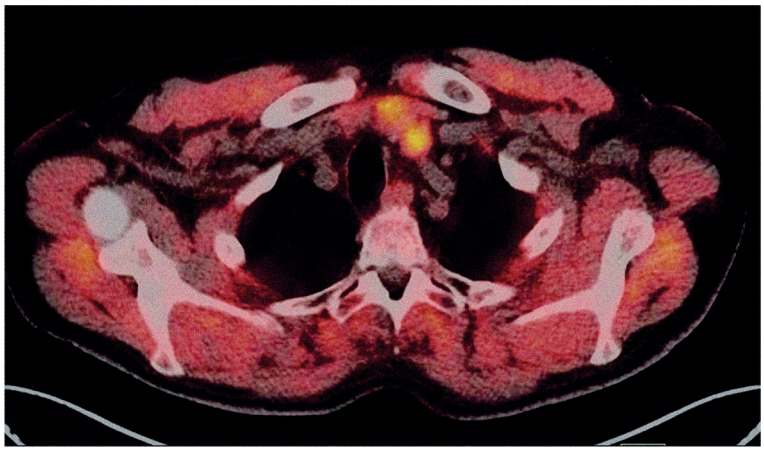

FIGURE 4. Positron emission tomography-computed tomography axial slice: Thyroid adenoma that incidentally took-up ^{18}F-fluorocholine (SUVmax 3.3).

articles using PET/CT.[5] In the 3 cases of pituitary adenoma of our series, an intense tumour uptake was observed.

To the best of our knowledge, this is the first mention of this incidental finding on FCH PET/CT. In one case, unexpected recurrence of a resected adenoma, suspected on FCH PET/CT, was confirmed by MRI. An inflammatory reaction after the surgical resection cannot be ruled out but seems improbable after three years. In another case, a non-functioning pituitary adenoma was confirmed at surgery; the patient also had another incidental FCH focus in the left vocal cord which was demonstrated to correspond to a calcified granuloma, confirming that inflammatory head and neck lesions can also show FCH uptake.[5]

The FDG uptake by functioning and non-functioning pituitary adenomas had been documented by several case reports and one series of such cases.[8] FDG pituitary focus corresponded in most cases to macroadenoma and only rarely to microadenoma or malignancy.[9] However, in case of adrenocorticotrophic hormone (ACTH) or growth hormone (GH) producing microadenomas, FDG PET, as a complement to MRI, resulted in 12 positive readings of 20 surgically verified pituitary microadenomas.[10] The potential superiority of aminoacid PET tracers ^{11}C-tyrosine and ^{11}C-methionine over FDG in the visualisation and therapy follow-up of pituitary adenomas, in particular ACTH-secreting adenomas has been demonstrated.[11-13] PET imaging of prolactinomas and GH-secreting adenomas with ^{11}C-raclopride, a D2 radioligand, was proposed in the differential diagnosis with meningiomas and skull base neuromas and in treatment monitoring.[14] Somatostatin receptors (SSR) can also be over-expressed in functioning pituitary adenomas, in particular those which are ACTH-secreting. On the other hand, no incidental uptake by a pituitary adenoma on SSR PET/CT has been reported until now, probably due to the physiologic pituitary uptake of the somatostatin analogue labelled with ^{68}Ga. In contrast SSR-PET/CT performed in a deliberate search for the source of inappropriate ACTH serum levels may lead in rare cases to detecting a pituitary adenoma in an unexpected location.[15-16]

We conclude from our observations that a definite FCH uptake in the pituitary should lead to characterisation of a probable lesion, at least with MRI. If recurrence or persistence of a known pituitary adenoma is suspected, it is doubtful whether FCH PET/CT will have any indication, or whether FDG should be preferred if PET/CT is indicated and ^{11}C-labeled tracers not available. Similarly to ^{11}C-methionine and in contrast with FDG, FCH has the advantage of a low background activity in the brain cortex.

Meningiomas

FCH uptake is faint in the normal brain parenchyma, which permits PET/CT detection of gliomas,

even in some low grade tumours, and also of meningiomas[5], as illustrated in the present study. It has been suggested that dynamic FCH PET acquisition can differentiate between those tumours.[17] PET/MRI may also be useful to distinguish between glioblastoma and meningioma that both showed moderately intense FCH uptake while it was faint in brain tumours of a lower grade.[7]

Detection of meningiomas with ^{11}C-choline PET/CT was also reported.[18] Relative to the contralateral side, ^{11}C-choline uptake was increased in all 7 meningiomas, whereas FDG uptake was decreased in 6 patients and increased in 1 of the 2 patients with grade II meningiomas. ^{11}C-acetate, another lipid PET tracer, showed high uptake in all 20 meningiomas, in contrast to the low uptake in surrounding normal brain tissue[19], whereas with FDG 17 foci appeared photopenic and 3 hyperintense. ^{13}N-ammonia also had relatively greater uptake in 10 meningiomas when compared with FDG.[20] Aminoacid PET tracers are also capable of demonstrating meningiomas: for delineation of gross tumour volume in stereotactic radiotherapy using ^{11}C-methionine[21], or in recurrent cases using ^{18}F-fluoroethyltyrosine[22], or in one patient referred to FDOPA PET for Parkinson's disease.[23] Furthermore, imaging meningioma with SSR scintigraphy has been reported for more than two decades and, more recently, a potential role for SSR PET/CT has been assessed, the detection rate being better than that of MRI.[24]

In conclusion, an intense incidental FCH uptake may lead to discovery of a meningioma; in prostate cancer patients, this can have a major impact on their management since anti-androgen therapy would favour tumour development and put them at risk for neurological symptoms. It is clear that the field of view of the "whole-body" FCH PET/CT acquisition should include the brain[6] in case of prostate cancer. In case of a known meningioma, determination of metabolic volume prior to radiotherapy or for surgery guidance is a valid indication for PET imaging. However many tracers can be used; for the moment, FCH may be seen as a newcomer.

Hyperfunctioning parathyroid glands

To the best of our knowledge, FCH uptake by hyperfunctioning parathyroid glands has never been described before. In one recent case report, a parathyroid adenoma was discovered on ^{11}C-choline PET/CT.[25] The discovery of an incidental hyperfunctioning parathyroid gland on FDG PET has been reported.[26-27] FDG has been proposed to stage parathyroid carcinoma, being more aggressive than adenoma or hyperplasia.[28] Discrepant results have been reported with FDG in the detection of adenoma or hyperplasia, a very low sensitivity in two short series[29,30] or, in comparison with ^{99m}Tc-SestaMIBI, a better sensitivity (86% *vs*. 43%) but a lower specificity (78% *vs*. 90%)[31]; no recent series have been published. ^{11}C-methionine is currently the PET competitor for the detection of parathyroid adenomas, with a patient-based sensitivity of 81% and specificity of 70% according to a recent meta-analysis.[32]

In conclusion, in the case of patient #6, unexpected parathyroid tumours can be localised on FCH PET/CT, on basis of the anatomical location on CT of a cervical FCH focus. Such an incidental image should prompt biochemical work-up, including serum PTH assay (patient #7), as prolonged hyperparathyroidism will be detrimental in those elderly patients and requires medical or surgical treatment.

Whether localising hyperfunctioning parathyroid glands could become an indication for FCH PET/CT requires comparative studies *vs*. the reference functional imaging ^{99m}Tc-SestaMIBI/^{123}I scintigraphy and/or vs. ^{11}C-methionine, the PET competitor. FCH PET imaging will benefit from a better resolution than SPECT, and delivery will be easier than for ^{11}C-methionine. But differential diagnosis with thyroid nodules taking-up FCH, as illustrated in our series, will be difficult, in particular in case of multinodular goitre, since dual isotope acquisition is not possible and subtraction technique will be very difficult.

Thyroid adenomas

Concerning FCH uptake by a benign thyroid nodule, two cases similar to that of patient #8 have been reported recently.[33,34] Numerous articles addressed the diagnostic value of incidental FDG uptake by a thyroid nodule. It actually corresponds to a non-malignant origin in a majority of cases, 70%, 59% or 65% as derived from two recent large series and a meta-analysis.[35-37]

The FCH foci in the thyroid gland previously reported in literature corresponded to benign adenomas.[33,34] However, in the present series 1 of the 2 incidental thyroid foci of FCH uptake which could be characterised corresponded to a papillary carcinoma. ^{11}C-choline has even been proposed in the detection of thyroid carcinoma and its metastases, performing better than FDG in a preliminary

series of 4 patients.[38] Therefore, it seems prudent that FCH uptake by a thyroid nodule prompts an adequate work-up to rule-out thyroid cancer.

In contrast it is unlikely that FCH may helpful in characterising a thyroid nodule as malignant or benign. Even FDG lacks specificity for the detection of cancer in a thyroid nodule and, since FCH usually detects less-aggressive tumours, it may be expected non-malignant nodules would take-up FCH even more frequently.

Cost and cost-effectiveness

In the present study, the detection of those incidental lesions per se implied no extra-cost since FCH PET/CT was indicated because of prostate cancer. In the above discussion, we then speculated that the present finding of FCH uptake in some of those incidentalomas could lead to a deliberate indication of FCH PET/CT in patients with a diagnosed or suspected benign tumour. In this case, the cost-effectiveness of FCH PET/CT should be re-evaluated for each type of benign tumour, bearing in mind the cost of FCH PET/CT and of the alternative nuclear medicine examinations.[39] Briefly, PET/CT with FCH is more expensive than with FDG, and PET/CT is usually more expensive than SPECT/CT due to the higher price of the machine, but this is not always true *e.g.* 111In-pentretrotide, somatostatin receptor ligand for SPECT, one of the alternatives for meningioma detection, is more expensive than FDG or FCH.

Conclusion

We described incidental FCH uptake in the head or in the neck, in 1.9% of the PET/CTs performed for staging or restaging prostate cancer. Some of those incidental FCH foci corresponded to malignancies, but more frequently (80%) to various benign tumours. In particular, for the first time, we observed FCH uptake in pituitary adenomas and in hyperfunctioning parathyroid glands. Such foci should be mentioned in the report, as meningioma or hyperparathyroidism may directly impact on management of a patient with prostate cancer. Since FCH is taken-up by slow-growing malignancies it could be expected that FCH PET/CT can detect benign tumours even more frequently than FDG PET/CT.

Furthermore, there might be a future indication for FCH PET/CT when one such tumour is already known or suspected: for post-operative control of a resected pituitary adenoma, to guide surgery or radiotherapy of a meningioma or to localise hyperfunctioning parathyroid glands. In those indications, comparative studies with reference PET tracers could be undertaken, on basis of published case reports and the present preliminary series.

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4.3. Consequence of the introduction of routine FCH PET/CT imaging for patients with prostate cancer: a dual centre survey.

Hodolič M, Michaud L, Huchet V, Balogova S, Nataf V, Kerrou K, Vereb M, Fettich J, Talbot JN.

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The Aim of the study:

The aim of the study was to compare the evolution of diagnostic imaging in patients with prostate cancer using a new radiopharmaceutical ^{18}F-FCH, observed in France and in Slovenia, and to quantify the consequence of the results of new imaging modality on the detection rate of abnormal metastases and recurrences of prostate cancer.

Conclusion of the study:

A rapid development of ^{18}F-FCH PET/CT was observed in both centres and led to a higher detection rate of prostate cancer lesions.

research article

Consequence of the introduction of routine FCH PET/CT imaging for patients with prostate cancer: a dual centre survey

Marina Hodolic[1], Laure Michaud[2,3], Virginie Huchet[2], Sona Balogova[2,4], Valerie Nataf[5], Khaldoun Kerrou[2], Marika Vereb[6], Jure Fettich[1], Jean-Noël Talbot[2,3]

[1] Department for nuclear medicine, University Medical Centre, Ljubljana, Slovenia
[2] Médecine nucléaire, Hôpital Tenon, AP-HP, Paris, France
[3] Université Pierre et Marie Curie, Paris, France
[4] Comenius University, Bratislava, Slovakia
[5] Radiopharmacie, Hôpital Tenon, AP-HP, Paris, France
[6] Nuklearmedizin, Kassel Klinikum, Kassel, Germany

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Correspondence to: Assist. Prof Marina Hodolič, MD, PhD, Department for Nuclear Medicine, University Medical Centre, Ljubljana, Zaloška 7, 1525 Ljubljana, Slovenia. Phone: +386 1 522 8450; Fax: +386 1 522 2237; E-mail: marina.hodolic@kclj.si

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Background. Fluorocholine(18F) (FCH) was introduced at the beginning of April 2010 in France, Slovenia and three other EU member states for the localisation of bone metastases of prostate cancer with PET. The aim of the study was to compare the evolution of diagnostic imaging in patients with prostate cancer using a new radiopharmaceutical FCH, observed in France and in Slovenia, and to quantify the consequence of the results of new imaging modality on the detection rate of abnormal metastases and recurrences of prostate cancer.

Patients and methods. In two centres (France/Slovenia), a survey of the number of nuclear medicine examinations in patients with prostate cancer was performed, covering 5 quarters of the year since the introduction of FCH. For each examination, the clinical and biological circumstances were recorded, as well as the detection of bone or soft tissue foci.

Results. Six hundred and eighty-eight nuclear medicine examinations were performed impatients with prostate cancer. Nuclear medicine examinations were performed for therapy monitoring and follow-up in 23% of cases. The number of FCH PET/CT grew rapidly between the 1st and 5th period of the observation (+220%), while the number of bone scintigraphies (BS) and fluoride(18F) PET/CTs decreased (-42% and -23% respectively). Fluorodeoxyglucose(18F) (FDG) PET/CT remained limited to few cases of castrate-resistant or metastatic prostate cancer in Paris. The proportion of negative results was significantly lower with FCH PET/CT (14%) than with BS (49%) or fluoride(18F) PET/CT (54%). For bone metastases, the detection rate was similar, but FCH PET/CT was performed on average at lower prostate-specific antigen (PSA) levels and was less frequently doubtful (4% *vs.* 28% for BS). FCH PET/CT also showed foci in prostatic bed (53% of cases) or in soft tissue (35% of cases).

Conclusions. A rapid development of FCH PET/CT was observed in both centres and led to a higher detection rate of prostate cancer lesions.

Key words: prostate cancer; PET/CT; fluorocholine (FCH); fluoride(18F); bone scintigraphy; indication of imaging

Introduction

Among nuclear medicine diagnostic procedures, four are currently routinely used in patients with prostate cancer: bone scintigraphy (BS); fluoride(18F) PET/CT; fluorodeoxyglucose(18F) (FDG) PET/CT; fluorocholine(18F) (FCH) PET/CT. There is a clear difference between BS and

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TABLE 1. The two centres participating in the survey

Centre	Type	BS may be completed with	FNa PET/CT	FDG PET/CT	FCH PET/CT
France, Paris	Public university hospital	SPECT	since April 2008	since July 2004	since September 2004
Slovenia, Ljubljana	Public university hospital	SPECT/CT	Not available	since December 2009	since April 2010

BS = bone scintigraphy; FCH = fluorocholine(18F); FDG = fluorodeoxyglucose(18F); FNa = fluoride(18F); SPECT = single photon emission computed tomography

fluoride(18F) PET/CT which are suited only for the detection of bone metastasis, and FCH and FDG PET/CT which can also detect primary tumour and soft tissue lesions.

In France bisphosphonates (99mTc) were registered in 1992, FDG in 1998, fluoride(18F) in 2008 and FCH (IasoCholine, IASON, Graz, Austria) become available in 2010. We published a survey that showed the shift in the prescription of nuclear medicine imaging favouring FCH PET/CT at Hospital Tenon in Paris, after its registration.[1] All those radiopharmaceuticals have marketing authorisation and are available for the routine use also in five other EU member states: Austria, France, Germany, Poland and Slovenia.

The aim of the present article is to compare the evolution of diagnostic imaging in patients with prostate cancer using a new radiopharmaceutical FCH observed in France (Paris, Hospital Tenon), with evolution of corresponding imaging in an Central European country (Slovenia, University Medical Centre Ljubljana), and to quantify the consequence of the results of new imaging modality on the detection rate of metastases and recurrence of prostate cancer.

Patients and methods

Centres and data collection

Covering a period from 2nd April 2010 to 1st July 2011 (both included), *i.e.* 5 quarters, in two nuclear medicine centres (Table 1), the data base includes: the age of the patient; the type of nuclear medicine examination; the indication: initial staging, follow-up during or just after treatment, restaging (of a known recurrence), or occult biological recurrence; the total number of previous nuclear medicine

TABLE 2. Evolution of the number of examinations per quarter in Paris

	1st quarter	2nd quarter	3rd quarter	4th quarter	5th quarter	Total 1st-5th quarters
BS	20 (28%)	20 (22%)	24 (26%)	25 (28%)	14 (16%)	103
FNa PET/CT	35 (49%)	31 (34%)	39 (42%)	17 (19%)	24 (29%)	146
FDG PET/CT	8 (11%)	6 (7%)	6 (6%)	7 (8%)	7 (8%)	34
FCH PET/CT	8 (11%)	33 (37%)	24 (26%)	41 (46%)	39 (46%)	145
Total (100%)	71	90	93	90	84	428

BS = bone scintigraphy; FNa = fluoride(18F); FCH = fluorocholine(18F); FDG = fluorodeoxyglucose(18F)

TABLE 3. Evolution of the number of examinations per quarter in Ljubljana

	1st quarter	2nd quarter	3rd quarter	4th quarter	5th quarter	Total 1st-5th quarters
BS	6 (21%)	8 (19%)	6 (9%)	8 (13%)	1 (2%)	29
FDG PET/CT	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1
FCH PET/CT	23 (79%)	35 (81%)	58 (89%)	54 (87%)	60 (98%)	230
Total (100%)	29	43	65	62	61	260

BS = bone scintigraphy; FCH = fluorocholine(18F); FDG = fluorodeoxyglucose(18F)

examinations; a quotation of the result of each examination performed by two independent nuclear medicine specialists experienced in the 4 types of examinations (S.B. and M.V.) from the images and the report: negative, doubt for bone metastasis, highly evocative of bone metastasis, focus (foci) in the prostatic bed, doubtful soft tissue focus or foci, highly evocative of soft tissue metastasis. For one abnormal examination, several categories could thus be quoted.

In some cases, there were also available: the serum prostate-specific antigen (PSA) levels (ng/mL) at the time of the nuclear medicine examination (502 cases); the initial Gleason score (361 cases); and both: PSA level and Gleason score (299 cases). The investigators followed recommendations of the Helsinki Declaration. The study protocol was approved by the ethic committees of both participating centres.

Data processing and statistics

The number of examinations performed in patients with prostate cancer disease was determined for each of the 4 nuclear medicine examinations, for each quarter and for each centre. The comparison of the 1st and 5th quarter is of particular interest; since they correspond to the same months (April to June) of 2 consecutive years (2010 and 2011) avoiding the consequences of an influence of the season (feasts, vacations…) on the number of prescribed nuclear medicine examinations. Those proportions were compared using chi-square test.

Differences in age, serum PSA levels, and Gleason score between the patients, according to the prescribed nuclear medicine examination, were tested by Kruskal-Wallis test. In case only two alternatives exist, the Mann-Whitney test was used. In patients who benefited from several nuclear medicine examinations during the survey period, the number, the type and the sequence of the prescribed examinations were reported and analysed.

Results

Evolution of the prescription of nuclear medicine examinations

Overall, 688 nuclear medicine examinations were performed in 577 patients with prostate cancer during the survey period. In Paris, the most frequently prescribed examination was fluoride(18F) PET/CT (147 cases), very close to FCH PET/CT (145 cases), then BS (103 cases) and finally FDG PET/CT (34 cases) mostly prescribed in case of advanced cancer, with frequent repetition in the same patient during the survey period. During the same period of time, a total of 951 BS and 3896 whole-body PET/CT were performed in this centre: prostate cancer was the indication of 103 out of 951 BS (10.8%) and in 326 out of 3896 PET/CT (8.4%). The ratio of BS in patients with prostate cancer disease decreased from 15% in the 1st quarter to 6% in the 5th quarter. Conversely, PET/CT examinations in patients with prostate cancer increased from 6% in the 1st quarter to 9% in the 5th quarter (Table 2).

In Ljubljana, fluoride(18F) PET/CT was not available and the most frequently prescribed examination in patients with prostate cancer was FCH PET/CT (230 cases), BS (29 cases) and FDG PET/CT (1 case). During the same period of time, a total of 1757 BS and 2069 PET/CT were performed in this centre: prostate cancer was the indication in 29 out of 1757 BS (1.7%) and in 213 out of 2069 PET/CT (10.3%) (Table 3).

Tables 2 and 3 illustrate the evolution of the prescribed nuclear medicine examination during the 5 successive quarters in each centre. The chi-square test is very significant ($p << 0.001$): there was an increase in the proportion of FCH PET/CT with time, and a decrease in the proportion of BS in both centres and also of fluoride(18F) PET/CT in Paris.

Multiple nuclear medicine examinations in the same patient during the survey period

Sixty-seven patients had multiple nuclear medicine examinations, ranging between 2 and 11 examinations per patient (in Ljubljana, a maximum of 2 examinations were performed for one single patient during the 5 quarters).

The main prescription patterns were:

a) 2 or 3 examinations of the same type in the mentioned interval: BS in 2 patients, fluoride(18F) PET/CT in 3 patients, FDG PET/CT in 1 patient, FCH PET/CT in 8 patients.
b) 2 examinations of different type within less than one month: fluoride(18F) PET/CT and FCH PET/CT in 3 patients, fluoride(18F) PET/CT and FDG PET/CT in 1 patient and, most frequently in Ljubljana, BS and then FCH PET/CT in 19 patients, the reverse in only 1 patient.
c) a shift to another type of examination prescribed on the next visit, after several months: fluoride(18F) PET/CT to FCH PET/CT in 4 pa-

TABLE 4. Indication of the nuclear medicine examination

Indication	Initial	Follow-up	Restaging	Occult recurrence	All indications
BS	60	26	22	24	132
FNa PET/CT	77	27	18	24	146
FDG PET/CT	2	17	14	2	35
FCH PET/CT	97	85	54	139	375
All examinations	236	155	108	189	688

BS = bone scintigraphy; FCH = fluorocholine(18F); FDG = fluorodeoxyglucose(18F); FNa = fluoride(18F); SPECT = single photon emission computed tomography

TABLE 5. Examination-based interpretation. For both "bone" and "soft tissue" "doubt" was only quoted if no focus evocative of malignancy was observed. % correspond to the frequency of this interpretation for each modality; since fluorodeoxyglucose(18F) (FDG) PET/CT and fluorocholine(18F) (FCH) PET/CT can detect foci in the prostatic bed, the soft tissue and the skeleton, the total is greater than 100%

Interpretation	Number of examinations	Negative	Doubt bone	Bone metastasis	Prostate focus	Doubt soft tissue	Malignant soft tissue
BS	132	65 (49%)	37 (28%)	30 (23%)	0	0	0
FNa PET/CT	146	79 (54%)	32 (22%)	35 (24%)	0	0	1 (1%)
FDG PET/CT	35	2 (3%)	1 (3%)	29 (83%)	1 (3%)	3 (9%)	8 (23%)
FCH PET/CT	375	52 (14%)	15 (4%)	86 (23%)	198 (53%)	21 (6%)	132 (35%)

BS = bone scintigraphy; FCH = fluorocholine(18F); FDG = fluorodeoxyglucose(18F); FNa = fluoride(18F)

tients, fluoride(18F) PET/CT to FDG PET/CT in 1 patient, FCH PET/CT to FDG PET/CT in 2 patients, BS to FCH PET/CT in 13 patients, BS to fluoride(18F) PET/CT in 1 patient.

d) at least 3 different types of examination repeated within the survey period in 8 patients.

Clinical context

Mean age of patients included in the study was 68.4 years (range 45-97 years). As expected, there was a significant difference in age according to the indication of the nuclear medicine examination. The patients being referred for initial staging being younger (mean age 67.2 years) and the patients referred for occult recurrence older (mean age 69.8 years) (p=0.01).

The choice of the nuclear medicine examination was in relation with the indication (p <<0.001) (Table 4). BS and fluoride(18F) PET/CT were performed more frequently for the initial staging, while FCH PET/CT was performed in almost half of the cases for an occult recurrence. As already mentioned, FDG PET/CT was mostly used for therapy follow-up or restaging of advanced castration-resistant forms.

In accordance, the number of previous nuclear medicine examinations performed in the patient and recorded by the centre was significantly greater when FDG PET/CT was requested. The mean number of previous examinations was 0.4 when BS was prescribed, 0.8 when fluoride(18F) PET/CT was prescribed, 0.7 when FCH PET/CT was prescribed *vs*. 4.8 for FDG PET/CT.

Biological context

A significant relation was observed between the PSA serum levels and the type of the prescribed nuclear medicine examination (p<<0.001). The mean PSA level was 26 ng/ml when FCH PET/CT was prescribed, 24 ng/ml in case of FDG PET/CT, 74 ng/ml in case of fluoride(18F) PET/CT and 175 ng/ml when the patient was referred for BS. The difference in PSA levels according to the indication did not reach the level of significance. The initial Gleason score of the patients referred for FDG PET/CT (mean 8.4) was significantly greater than

that of patients referred for all other examinations (mean 7.4 for BS, 7.6 for fluoride(18F) PET/CT and 7.3 for FCH PET/CT); it was also higher in patients referred for the treatment follow-up (mean 7.8) or restaging (mean 7.8) than in case of initial staging (mean 7.4) or occult recurrence (mean 7.2).

Nuclear medicine examination report: normal, positive, doubtful

Table 5 illustrates the result of the report summarized on an examination-based manner, according to the findings and the type of nuclear medicine examination. BS or fluoride(18F) PET/CT was interpreted as normal in around one half of cases, without difference in the distribution of the "positive" and "doubtful" conclusions (on a per-examination level) between those two modalities. In one patient, a large lymph node took-up fluoride(18F).

FDG PET/CT results favoured bone metastases in 85% of patients and less frequently reported soft tissue foci evocative of malignancy. This does not mean that FDG is better than fluoride(18F) or FCH to detect bone metastases but, in accordance with previous results, that FDG PET/CT was prescribed in patients with advanced forms of the disease, mostly castration-resistant and metastatic to the skeleton, for restaging or chemotherapy monitoring.

FCH PET/CT was abnormal in 86% of patients and doubtful in a small minority of the examinations. It showed the primary tumour or a local recurrence in the prostatic bed in about half of the patients (Figure 1), foci suspicious for soft tissue malignancy in about one third, and also foci evocative of bone metastases, in a proportion of patients (23%) similar to that of BS or fluoride(18F) PET/CT ($p>0.9$), but with significantly less doubtful cases ($p< 0.001$) (Figure 2).

Reporting can also be analysed according to the indication of nuclear medicine imaging. As already mentioned, FDG PET/CT was most frequently prescribed for restaging and follow-up of response to treatment, in patients whose advanced prostate cancer was already known to be metastatic. In this context, the metastatic spread, in particular to the skeleton, was visible on FDG PET/CT in 97% of cases.

In the search for bone metastases, no difference in the frequency of detection was found according to the indication with BS while fluoride(18F) PET/CT and FCH PET/CT showed more frequently suspicious bone foci when performed for restaging or treatment follow-up, probably in relation with already known metastatic dissemination in those patients. The frequency of detection of suspicious bone foci in patients with a Gleason score less than or equal to 7, was 5% for BS, 8% for fluoride(18F) and 12% for FCH, in patients with a Gleason score greater than or equal to 8, the corresponding values were 35%, 23%, and 32% (the difference was significant for BS and FCH PET/CT).

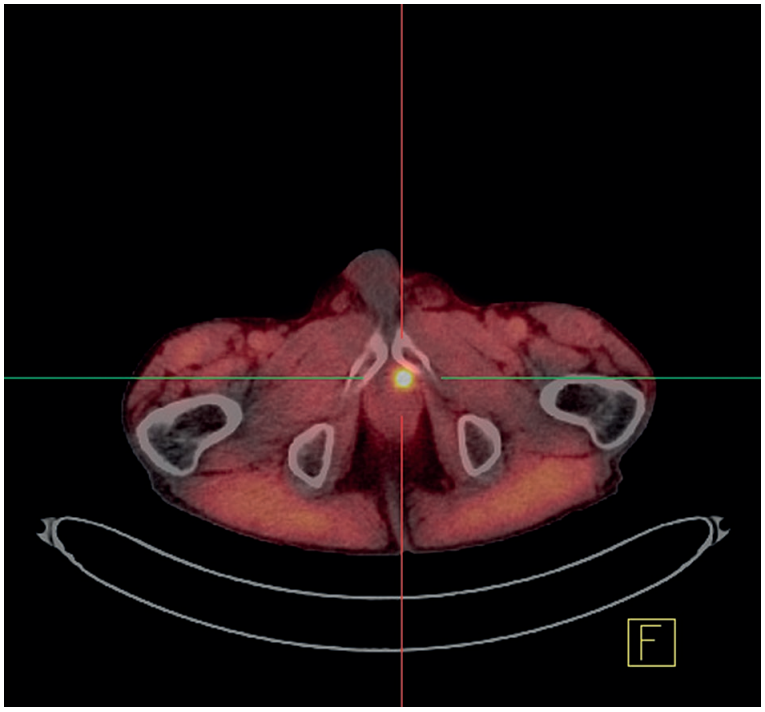

FIGURE 1. FCH PET/CT: Local recurrence of prostate cancer after radical prostatectomy (Gleason score 8, [PSA] 0.2 ng/ml).

Searching for malignant deposits in soft tissue, FCH PET/CT was more frequently positive in patients referred for restaging or occult recurrence than at initial staging ($p<0.01$). The detection rate of suspicious soft tissue foci was 27% in patients with a Gleason score less than or equal to 7, *vs*. 31% in patients with a Gleason score greater than or equal to 8 ($p > 0.6$).

In our centres, some examinations were performed at initial staging in patients who did not fulfil accepted criteria to refer patients at initial staging to nuclear medicine imaging, *i.e*. PSA levels less than or equal to 10 ng/ml and Gleason score less than 8. They corresponded to 36 of the 132 examinations (27%) performed for initial staging in patients whose PSA serum levels and Gleason score were mentioned on the prescription.

In case of biochemical recurrence following prostatectomy, the NCCN Guidelines mention a

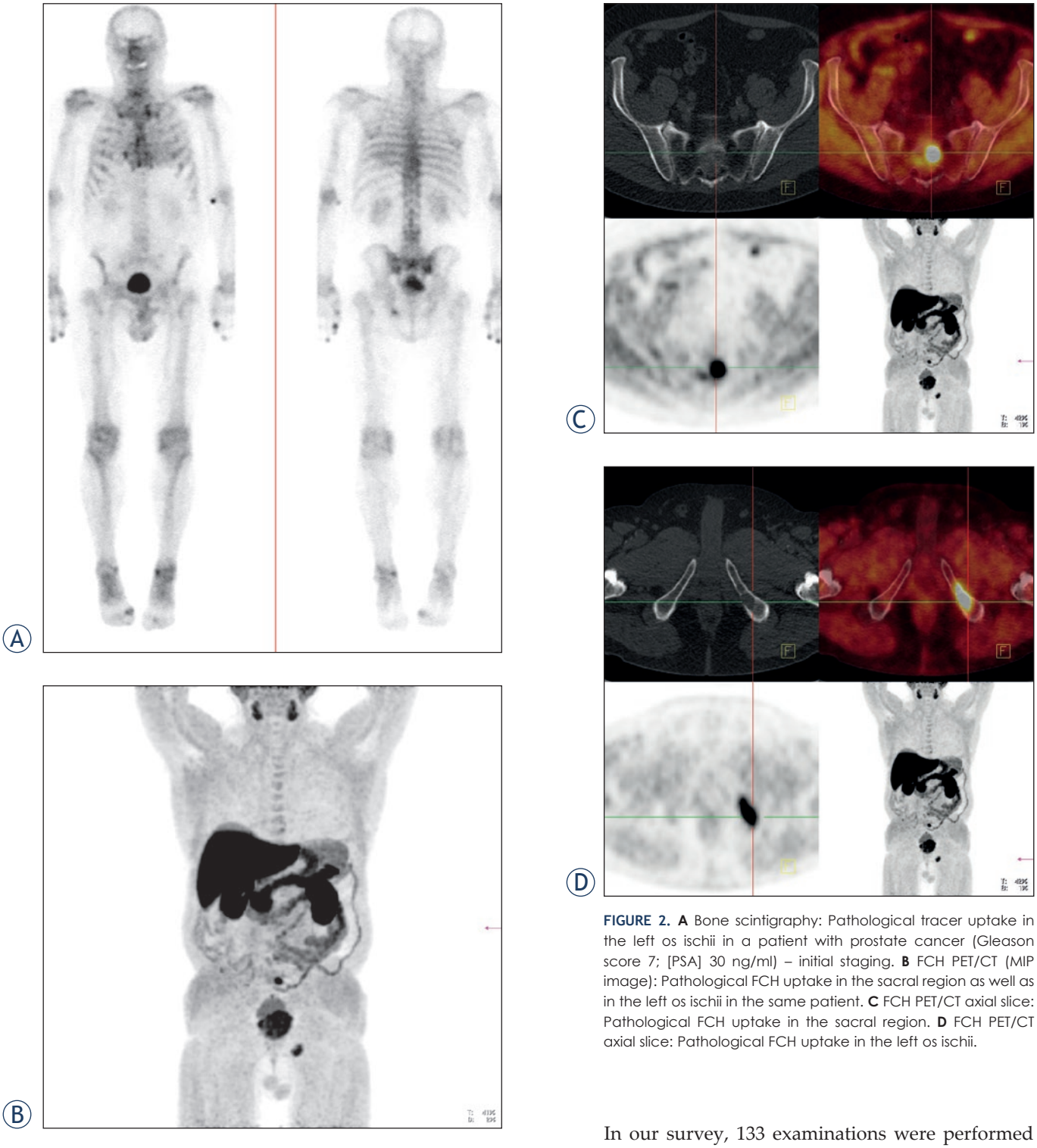

FIGURE 2. **A** Bone scintigraphy: Pathological tracer uptake in the left os ischii in a patient with prostate cancer (Gleason score 7; [PSA] 30 ng/ml) – initial staging. **B** FCH PET/CT (MIP image): Pathological FCH uptake in the sacral region as well as in the left os ischii in the same patient. **C** FCH PET/CT axial slice: Pathological FCH uptake in the sacral region. **D** FCH PET/CT axial slice: Pathological FCH uptake in the left os ischii.

potential indication for BS without precise target PSA value. NCCN Guidelines also recommends BS in case of post-irradiation recurrence in patients who are considered candidates for local therapy, with PSA less than 10 ng/ml among other criteria.[2]

In our survey, 133 examinations were performed for restaging or detection of occult recurrence in patients with PSA levels less than 10 ng/ml. Foci suspicious to correspond to malignant tissue out of the prostatic bed were reported in 1 out of 10 BS, 2 out of 15 fluoride(18F) PET/CT, 1 out of 1 FDG PET/CT and 50 out of 117 FCH PET/CT. This very significant superiority of FCH PET/CT over bone nu-

clear medicine imaging ($p<0.01$) is due to its ability to detect soft tissue lesions as well as bone lesions. In those patients, FCH PET/CT also showed foci in the prostatic bed suspicious for local recurrence in 41 cases (35%). In this context of recurrent disease, FCH PET/CT was prescribed in 23 patients with PSA levels < 2 ng/ml and initial Gleason score less than or equal to 7: its detection rate (including local recurrence) was still 35%.

Discussion

As its first result, this dual centre study confirms, in two independent nuclear medicine centres, the rapid rise in the demand for FCH PET/CT, as soon as FCH was registered.[1] At the same time, there was a marked decline in the prescription of BS in patients with prostate cancer. This shift was associated with a rise of the total number of prostate cancer patients referred for nuclear medicine examinations. The transfer of prescription to FCH PET/CT was more progressive in Paris than in Ljubljana. Bone PET/CT with fluoride(18F) has been available in Paris for one year and a half when FCH was registered, yielding images with PET quality and a superior resolution as compared to BS or bone single photon emission computed tomography (SPECT). Even for the most informed prescribers, the introduction of FCH meant two successive shifts in a limited period of time. Another reason can be the relation with the environment. The Paris area has 11.7 millions inhabitants and 42 nuclear medicine centres, 20 of which are equipped with PET/CT, which means a rather large resource for the prescriber, while Slovenia has 2 million inhabitants, 7 nuclear medicine centres and 2 PET/CT centres (FCH is being performed in one), which probably enables a more rapid diffusion of new PET imaging modalities.

The other aim of this survey was to record the detection of abnormal foci by the available nuclear medicine examinations, but not to compare their performance according to a standard of truth. Actually most patients only had one examination, and head to head comparison of results, according to the imaging modality, is not possible. Nevertheless, it is of importance to check how this concordant and rapid evolution in Paris and Ljubljana is based on evidence and matches results obtained in other centres.

The initial shift from BS to bone PET/CT with fluoride(18F), which has been observed in Paris[1], is in agreement with the results of the comparative study of Even-Sapir *et al*., in 44 patients with a high-risk prostate cancer.[3] Fluoride(18F) PET/CT was statistically more sensitive and more specific than planar BS or bone SPECT ($p < 0.05$). In our survey, the majority of fluoride(18F) PET/CT has been performed to search for bone metastases at initial staging, to profit from the better sensitivity. The advantage of fluoride(18F) PET/CT over BS and bone SPECT was not so obvious when examining reporting of examinations (Table 5) because fluoride(18F) PET/CT mostly results in the detection of a greater number of bone lesions as compared to BS, while the analysis of our results was based on a per-patient level rather than a per-lesion level. The further shift from fluoride(18F) to FCH as the PET/CT tracer to detect bone metastases is evaluated by the comparative studies from the team in Linz in co-operation with our team in Paris.[4] In this study, there was no significant difference in sensitivity between the two PET tracers, but FCH was significantly more specific on a lesion-based analysis. In the present survey, the use of FCH instead of BS, bone SPECT or fluoride(18F) PET/CT resulted in a similar proportion of examinations interpreted as positive for bone metastases, and in a decrease in the frequency of doubtful reports: in contrast with bisphosponate (99mTc) or fluoride(18F), FCH is not taken-up by non-inflammatory degenerative changes in the skeleton and its interpretation is more straightforward.[5]

Concerning the detection of lesions in the prostatic bed, locoregional lymph nodes and distant soft tissue, FCH is in competition with FDG. FDG has a low diagnostic performance in the general population of prostate cancer patients, but may be of interest in case of aggressive or castration-resistant prostate cancer. The analysis of the US national oncologic PET registry for the first 2 years of data by Hillner *et al*. revealed that, from 40,863 PET scans, prostate cancer was the most frequent indication corresponding to 5,309 FDG examinations, with change in management in 35% of cases.[6] However, also FCH is taken-up by androgen-independent prostate cancer, as showed as early as 2002 by Price *et al*. in 9 patients[7] and confirmed recently by Mc Carthy *et al*., in 26 patients.[8] In the present survey, FDG PET/CT was performed, in Paris only, in a very limited number of patients with a high Gleason score, to restage a known recurrence and to monitor therapy of metastatic forms, when restaging FCH PET/CT was positive. The prescription of FDG PET/CT in prostate cancer was not increasing with time, in contrast with that of FCH PET/CT.

The utility of FCH PET/CT to detect recurrent prostate cancer has been demonstrated by several teams since 2005[9], a special attention being paid to the rate of positive examinations according to PSA levels[10-14] or PSA doubling time or velocity[15,16], or initial Gleason score.[11] In our survey, 51% of the FCH PET/CT was performed for restaging a known recurrence or localising an occult biological recurrence. The reported relation between the frequency of positivity and PSA levels and the initial Gleason score has been observed in our series. However, FCH PET/CT detected suspicious foci in 35% of patients with PSA levels < 2 ng/mL and initial Gleason score less than or equal to 7. According to Pelosi *et al*., its detection rate was still 20% when PSA levels were < 1 ng/ml.[13] Even though FCH is for the moment only registered for the detection of bone metastases, it is also able to detect local recurrences (Figure 1) and locoregional lymph node metastases.

The utility of FCH PET/CT in the initial staging of prostate cancer has been addressed by Beheshti *et al*.[17] In this context, FCH PET/CT has limited value in the detection of malignant lymph nodes especially when smaller than 5 mm, but it led to changes in the therapeutic management of 20% of prostate cancer patients at a high risk for extracapsular disease, suggesting that it will be helpful in triaging care of this type of patient cohort. Patient-based sensitivity was 73% and specificity 88% in 210 intermediate or high-risk patients showing FCH PET/CT to be effective to detect N+ patients.[18] In our survey, 26% of the FCH PET/CT were performed at initial staging and not only visualised the primary cancer but also detected suspicious foci in soft tissue or in the skeleton in 31% of patients (Table 5). A recent study confirmed that, at staging, when PSA levels (> 20 ng/l) and/or Gleason score (8-10) are high, both FCH and fluoride(18F) PET/CT were effective and impacted on the treatment plan for 20% of the patients.[19] Should the classical criteria recommended for performing BS, *i.e*. PSA levels greater than or equal to 10 ng/ml or Gleason score of at least 8, also apply to PET/CT?[20] In our series, its yield was actually rather low when those criteria were not met: 2 cases of extraprostatic foci in 14 examinations. In the survey of Lavery *et al*. "overuse" of BS in patients who did not fulfil somewhat less though criteria (a Gleason score of 7 was accepted for indication) occurred in 241 of 667 preoperative imaging examinations (36%); BS were read as positive in 21 cases (9%) which all corresponded to false-positive results.[21] When the criteria used by Lavery *et al*.[21] were applied to examinations performed in our series at initial staging, only 20% of BS, 15% of fluoride(18F) PET/CT and 7% FCH PET/CT should not have been performed, but their yield was even lower than with "classical" criteria: positivity was reported in none of the BS, 1 fluoride(18F) PET/CT and 1 FCH PET/CT. Thus, in staging prostate cancer, the overuse of nuclear medicine imaging was less frequent in Paris and Ljubljana than the overuse of BS in New York, but our survey confirms that its yield is low when the criteria are not fulfilled, even by using FCH PET/CT which is more expensive than BS.

Another interesting result of the present survey was the rather frequent indication of nuclear medicine examinations in the follow-up of therapy: 23% of the examinations. In this indication, FCH PET/CT has an important advantage over BS and fluoride(18F) PET/CT which are limited to the monitoring of bone lesions. Even for monitoring the metabolic response of bone metastases to therapy, FCH has the advantage to show the viable prostate cancer tissue while BS and fluoride(18F) PET/CT show the reaction of the normal cortical bone to the insult by the metastatic tissue. This difference in the mechanism of functional imaging explains the "bone flare phenomenon" observed on BS at the beginning of an active hormone therapy, which has even been proposed as a criterion to improve both sensitivity and specificity of BS in prostate cancer.[22] In the evaluation of new therapeutic agents such as abiraterone, the effect of BS flare on the patient management and interpretation of results is clearly "confounding".[23] Nevertheless, NCCN recommends that patients treated with abiraterone or cabazitaxel with prednisone, must be monitored closely, in particular with BS, for evidence of progression.[2] We foresee from the present survey that the application of FCH PET/CT to treatment monitoring will develop when this examination will become more widely available.

Conclusions

In two PET centres of public hospitals of two EU member states, with a rather different context, the introduction of FCH PET/CT led to a rapid increase in its use, with a concomitant decrease in the number of nuclear medicine examinations devoted to the detection of bone metastases, but with an increase in the overall part of prostate cancer in nuclear medicine diagnostic practice: +24% in Paris and +100% in Ljubljana within one year. This shift for FCH PET/CT resulted in a greater proportion

of positive examinations. Given the trend that was observed in our survey, it seems likely that FCH PET/CT will become the first line nuclear medicine examination in patients with prostate cancer disease. As prostate cancer is a frequent malignancy and the number of PET/CT machines is not sufficient in France and in Slovenia, more evidence-based criteria for its indication will be needed. It appears important that the referring physician mentions the initial Gleason score, the current PSA serum level, the recent evaluation of PSA level and all the therapeutic modalities. In our survey, the PSA levels and the Gleason score were available in only 43% of the prescriptions. According to our results, the criteria for referring patients at initial staging to BS appear to be suited for fluoride(18F) or FCH PET/CT. In contrast, the criteria for referring patients to BS in case of recurrent prostate cancer cannot apply to FCH PET/CT, which is more sensitive and specific and is also able to detect local recurrence and soft tissue invasion. The kinetics of variation of PSA levels may offer the best criteria in this context. FCH still lacks registration in the detection of prostate cancer in soft tissue as well as for therapy monitoring. It is unclear whether FDG will still have a role to play in the restaging and therapy monitoring of advanced forms of prostate cancer if FCH would be registered in those settings.

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4.4. The ability of 18F-choline PET/CT to identify local recurrence of prostate cancer.

Evangelista L, Cimitan M, Hodolič M, Baseric T, Fettich J, Borsatti E.

Abdom Imaging. 2015 Oct;40(8):3230.; IF: 2.189

The aim of the study:

The aim of this study was to determine when ^{18}F-FCH PET/CT can truly identify the presence of local prostate cancer recurrence.

Conclusion of the study:

Although PET/CT with ^{18}F-FCH has some limitations for the evaluation of prostatic gland/fossa, due to the physiological biodistribution of the radiopharmaceutical agent, in 70–90% of patients with a PSA level >2 ng/mL, independently from the Gleason Score, a focal ^{18}F-FCH uptake could be compatible with local recurrence.

The ability of 18F-choline PET/CT to identify local recurrence of prostate cancer

Laura Evangelista, Marino Cimitan, Marina Hodolič, Tanja Baseric, Jure Fettich & Eugenio Borsatti

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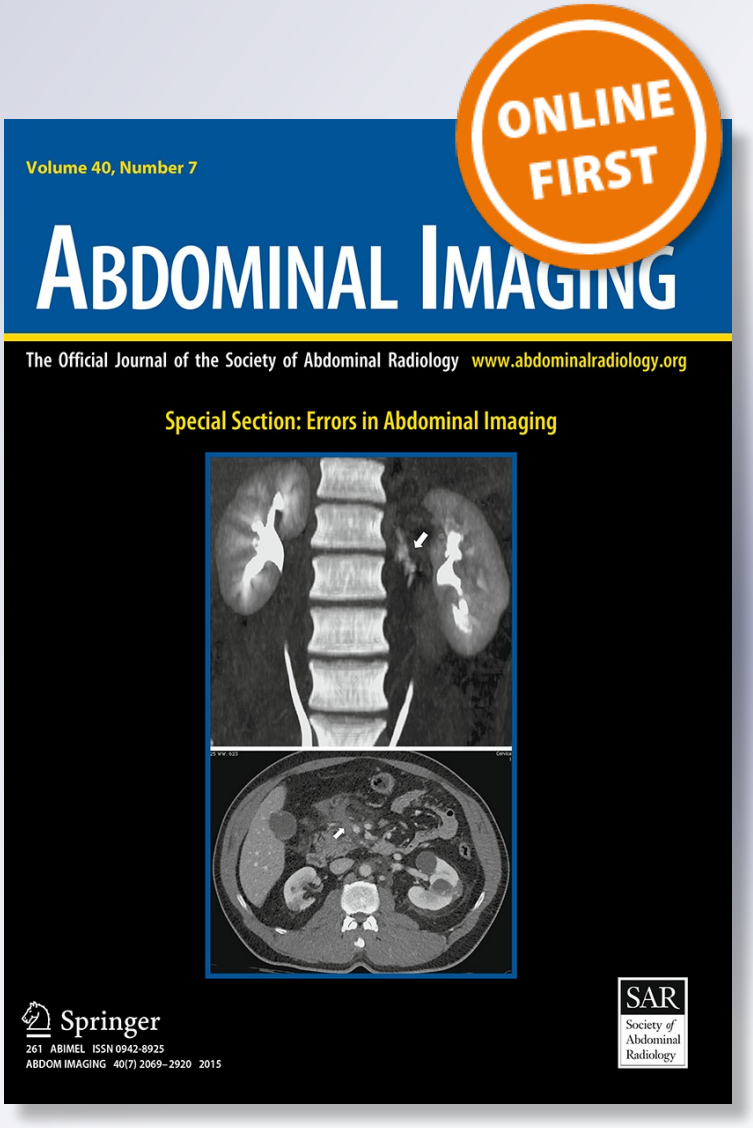

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The ability of 18F-choline PET/CT to identify local recurrence of prostate cancer

Laura Evangelista,[1] Marino Cimitan,[2] Marina Hodolič,[3] Tanja Baseric,[2] Jure Fettich,[4] Eugenio Borsatti[2]

[1]Radiotherapy and Nuclear Medicine Unit, Veneto Institute of Oncology IOV – IRCCS, Via Gattamelata, 64, 35128 Padua, Italy
[2]Nuclear Medicine Unit, IRCCS National Cancer Institute (CRO), Aviano, PN, Italy
[3]Nuclear Medicine Research Department, IASON, Graz, Austria
[4]Nuclear Medicine Department, University Medical Center Ljubljana, Ljubljana, Slovenia

Abstract

Purpose: To determine when 18F-choline PET/CT can truly identify local recurrence of prostate cancer.
Methods: 1031 patients from 3 European centers underwent ^{18}F-choline PET/CT (FCH PET/CT) for recurrent disease; 131 subjects (12.7%) showed a positive FCH uptake in the prostatic gland or prostatic fossa. Median age was 72 years (range 48–87 years), and the median PSA level at the time of FCH PET/CT scan was 4.41 ng/mL (0.22–18.13 ng/mL). 45 patients (34.4%) had a Gleason score (GS) >7, and the residual subjects had a GS ≤ 7. The assessment of true or false-positive FCH PET/CT findings was made by magnetic resonance imaging ($n = 34$) and/or biopsy in 75/131 cases. A χ^2 test and a Z Kolmogorov–Smirnov test were used to assess the correlation between clinical variables (age, PSA, GS, type of therapy) and FCH PET/CT findings.
Results: FCH PET/CT resulted truly positive (TP) for recurrent disease in the prostatic gland/fossa in 59/75 patients (79%) and falsely positive (FP) in 16 subjects (21%). The median value of PSA at the time of FCH PET/CT scan was higher in TP as compared to FP, although not statistically significant (4.76 vs. 3.04 ng/mL $p > 0.05$). Similarly, median age, GS categories, and the type of therapy were similar between the two groups ($p > 0.05$). However, when matching GS categories and PSA values, we found that the number of patients with TP findings were higher in the case of a PSA >2 ng/mL, independently from the GS (ranging between 74% and 92%). Conversely, FP rate ranged between 50% and 65% in patients with a PSA ≤ 2 ng/mL, especially in the case of GS ≤ 7, whereas FP was around 25% in those with a GS >7 and PSA >2 ng/mL.
Conclusions: FCH PET/CT has a limited role in evaluation of prostatic gland/fossa recurrence, due to the physiological biodistribution of the radiopharmaceutical agent. However, in 70–90% of patients with a PSA >2 ng/mL, independently from GS, a focal FCH uptake is compatible with a true local recurrence.

Key words: Prostate cancer recurrence—18F-choline PET/CT—False positive—True positive—Salvage treatments

From 27% to 53% of all, patients who undergo radical prostatectomy (RP) or external beam radiation therapy (RT) as the first-line treatment of prostate cancer (PCa) develop a biochemical recurrence [1]. Regarding local disease relapse after surgery, about 50% high-risk patients (those with wide positive margins and/or pT3) and approximately 10% of those with low risk (negative margins and pT2) will develop a local relapse within 15 years from surgery [2]. After RP, the most common sites of local recurrence are vesical–urethral anastomosis and peri-anastomotic tissues [3, 4]. Other sites include the anterior and the posterior bladder neck and, less frequently, the retrovesical space (posterior to the bladder neck). Conversely, after RT, morphological changes in the prostate include inflammation, glandular atrophy, fibrosis, and shrinkage [5, 6].

A large number of studies have shown that magnetic resonance imaging (MRI) is a powerful tool for early detection of local recurrence after surgery [7–12] and

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Correspondence to: Laura Evangelista; *email:* laura.evangelista@ioveneto.it

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external beam radiation therapy (EBRT) [13–17]. However, the introduction of Choline PET/CT, labeled with ^{11}C or ^{18}F, has deeply changed the management of patients with biochemical recurrence. In fact, Choline PET/CT is able to detect the recurrence of disease with high sensitivity (82%) [18], thus, guaranteeing the restaging of disease in a single session. Nevertheless, the detection rate and the sensitivity of Choline PET/CT for the local recurrence of disease, particularly ^{18}F-Choline (FCH), are significantly lower than MRI [19].

The aim of this study was to determine when FCH PET/CT can truly identify the presence of local prostate cancer recurrence, and it was carried out in a cohort of patients who showed a significant uptake of FCH only in the prostate gland or prostatic fossa.

Materials and methods

Patients

Between October 2004 and June 2013, 1031 men underwent FCH PET/CT scan, in three different centers, for biochemical recurrence of PCa and after potentially curative treatment: RP or EBRT (PSA ≥0.2 ng/mL in the case of RP and a PSA level above the previous PSA nadir measured at 3 months after EBRT). The median time between the first treatment and the biochemical relapse was 34 months (3–88 months). FCH PET/CT was performed within 2–3 months from biochemical recurrence. In this study, we retrospectively evaluated patients according to predefined inclusion criteria: (1) Gleason score (GS) (of biopsy in case of no surgery or of surgical specimen), (2) record of current and past therapies (surgery, radiotherapy and/or systemic therapy), (3) serum PSA level (ng/mL) at the time of the FCH PET/CT scan, and (4) a positive FCH uptake in prostatic gland or prostatic fossa. Exclusion criteria were (1) a significant FCH uptake in lymph nodes (i.e., the presence of focal FCH uptake corresponding to abdominal-pelvic lymph nodes, including lymph nodes <1 cm in size) and (2) a significant FCH uptake in the distant organs (such as in bone, lung, and other common metastatic sites). According to institutional policies, all patients had given their informed consent before undergoing a FCH PET/CT scan and for subsequent, anonymous analysis of data. The study was performed in accordance with the Declaration of Helsinki.

FCH PET/CT imaging

[18F]fluorocholine as [18F]fluoromethylcholine ([18F]fluoromethyldimethyl-2-hydroxyethylammonium [FCH]) was provided by IASON Labormedizin GesmbH & Co. KG (Feldkirchner Straße 4, A-8054 Graz-Seiersberg, Austria). [18F]fluoride is produced in an 18O(p,n)18F reaction by the bombardment of 1.7 mL [18O]water with a 16-MeV proton beam using a GE PET trace cyclotron. The synthesis of [18F]fluorocholine consists of two steps. In the first step, [18F] bromofluoromethane is produced by the nucleophilic substitution of dibromomethane with [18F]fluoride. Subsequently, [18F]bromofluoromethane is converted online to [18F]fluoromethyl triflate. In the second step, dimethylaminoethanol is alkylated with [18F]fluoromethyl triflate to [18F]fluoromethylcholine. The production of [18F] fluorocholine is performed in a fully automated synthesis module of the ARGOS Zyklotron Company. Before synthesis, the module is tested by an automated leak check. The radiochemical purity of [18F] fluorocholine by high-pressure liquid chromatography was $>95\%$ ([18F]fluoromethyl triflate $<5\%$). The integrated PET/CT systems employed at the three centers were a Discovery LS scanner (GE Healthcare, Milwaukee, USA) in Aviano, a Biograph 16 HT PET/CT scanner (Siemens Medical Solutions, IL, USA) in Padua, and a Biograph mCT PET/CT scanner in Ljubljana (Siemens Medical Solution, IL, USA). FCH PET/CT included a delayed whole-body PET scan (6–8 beds, 2–3 min per bed position) performed 45–60 min after the i.v. administration of 3.0–3.5 MBq/kg of FCH (IASOcholine, IASON GmbH, Graz, Austria) and a co-registered low-dose CT whole-body scan (140 kV, 80–120 mA) without contrast enhancement. In each institution, two specialists in nuclear medicine independently reviewed the scans, according to visual assessment. In particular, local relapse was recorded in the presence of clear focal FCH uptake in the prostatic bed.

FCH PET/CT diagnostic performance

Positive FCH PET/CT findings were compared with the results of biopsy, salvage surgery performed after PET/CT, and with MRI. Follow-up duration ranged between 1 and 12 months. Positive FCH PET/CT findings were considered true positive (TP) when any of the following criteria was met: (1) confirmation on histology, in case of salvage surgical approach; (2) confirmation on peri-urethral anastomosis biopsy; and (3) confirmation on MRI either at baseline or during follow-up.

Statistical analysis

Continuous data are presented as median and range, and categorical data as numbers and percentages. A Kolmogorov–Smirnov test was used to assess the correlation between continuous clinical variables and FCH PET/CT findings. The differences between categorical data were assessed using Yates-corrected χ^2 test. A univariate logistic regression analysis was performed to identify the independent predictors of TP and FP findings at PET/CT. Two-tailed p values <0.05 were considered statistically significant. Statistical analysis was performed with SPSS software for Windows (Chicago, IL).

Table 1. Characteristics of study population

	FCH uptake in prostate gland (n = 83)	FCH uptake in prostatic fossae (n = 48)	P value
Median age, years	73 (5.21)	69 (56–86)	0.059*
Median PSA pre-PET (ng/mL)	4.8 (0.25–18.13)	3.6 (0.22–14.6)	0.142*
PSA categories, n (%)			0.232**
1≤ ng/mL	6 (7.2)	8 (16.7)	
1> PSA ≤2 ng/mL	10 (12.1)	6 (12.5)	
≥2 ng/mL	67 (80.7)	34 (70.8)	
GS, n (%)			0.614**
≤6	26 (31.3)	16 (33.3)	
=7	26 (31.3)	18 (37.5)	
≥7	31 (37.4)	14 (29.2)	
Therapy, n (%)			<0.0001**
RP ± LAD (alone)	–	24 (50)	
RP + EBRT (±ADT)	–	7 (14.6)	
EBRT (±ADT)	28 (33.7)	–	
ADT alone	31 (37.3)	–	
NA	24 (28.9)	17 (35.4)	
Ongoing ADT			0.135**
No	43 (51.8)	27 (56.3)	
Yes	22 (26.5)	6 (12.5)	
NA	18 (21.7)	15 (31.3)	
Site of FCH PET/CT			0.982
Prostatic gland	26 (44)	7 (43.7)	
Prostatic fossae	33 (56)	9 (56.3)	

GS Gleason score, *RP* radical prostatectomy, *LAD* lymphadenectomy dissection, *EBRT* external beam radiotherapy, *ADT* androgen deprivation therapy, *NA* not available
* Kolmogorov–Smirnov test; ** χ^2 test

Results

From the 1031 subjects who underwent FCH PET/CT, 131 patients (12.7%) showed a positive FCH exclusively in the prostatic gland or fossa (n = 83; 63.3% in the prostatic gland and n = 48; 36.7% in the prostatic fossa). Median age was 72 years (range 48–87 years), and the median PSA level at the time of FCH PET/CT scan was 4.41 ng/mL (0.22–18.13 ng/mL). Moreover, 45 patients (34.4%) had a GS >7, and the residual subjects had a GS ≤7. Table 1 reports the correlations between clinical data and the site of FCH PET/CT uptake. As shown, no differences between the site of FCH uptake and clinical variables were found. However, in patients with a PSA ≤1 ng/mL, the detection rates of recurrent prostate cancer in the gland and in the fossa were 7.2% vs. 16.7%, respectively. Moreover, the detection of recurrent local disease appeared lower in patients under androgen deprivation therapy (ADT) than their counterpart (21.4% vs. 53.4%).

The correlations among FCH PET/CT findings, MRI, and/or histology were available in 75 cases (57%). In particular, 34 subjects had MRI examination. FCH PET/CT resulted TP in 59 patients (79%) and FP in 16 subjects (21%) (Table 2). The number of patients with true-positive PET/CT findings was 43 and 28, respectively, for histology and MRI. Conversely, the number of false positives was 10 and 6 patients, respectively, for histology and MRI. The median value of PSA at the time of PET/CT scan was higher in TP as compared to FP, although not statistically significant (4.76 vs. 3.04 ng/mL $p > 0.05$). Similarly, median age, GS categories, and the type of therapy were similar between the two groups ($p > 0.05$). However, when matching GS categories and PSA values, we found that the rates of TP were higher in patients with a PSA >2 ng/mL independently from GS (ranging between 74% and 92%). Conversely, the rates of FP ranged between 50% and 65% in patients with a PSA ≤ 2 ng/mL, especially in those with a GS ≤ 7 (n = 7/11; 63.6%), whereas FP findings were around 25% in those with a GS >7 and PSA >2 ng/mL (Table 3). Figures 1 and 2 present examples of a true-positive and false-positive FCH PET/CT in the prostatic fossa, respectively.

From the univariate analysis, none of the clinical parameters correlated with TP or FP results at FCH PET/CT, although, as shown in Table 4, the odds of FP findings in patients who were treated with RP and adjuvant RT were higher (OR 3.695; IC 95% 0.837–15.703) than those of patients treated with RP alone. Similarly, the odds of TP findings were higher in patients who were treated by ADT alone (OR 2.069; IC 95% 0.218–19.629) as compared to the other subset of patients.

Discussion

Time to PSA relapse, pathological stage, and GS are the main factors related to the likelihood of local vs. distant relapse. In general, PSA detectable after 1 year, negative

Table 2. Correlation between clinical variables and FCH PET/CT findings

	True-positive finding (n = 59)	False-positive finding (n = 16)	p value
Median age, years	72 (54–86)	69 (59–82)	0.688*
Median PSA pre-PET (ng/mL)	4.76 (0.25–18.13)	3.04 (2.35–3.74)	0.852*
PSA categories, n (%)			0.444**
1≤ ng/mL	6 (10.2)	3 (18.8)	
1> PSA ≤2 ng/mL	7 (11.9)	3 (18.8)	
≥2 ng/mL	46 (78)	10 (62.5)	
GS, n (%)			0.689**
≤6	16 (27)	3 (18.8)	
=7	20 (34)	5 (31.3)	
≥7	23 (39)	8 (49.9)	
Therapy, n (%)			0.427**
RP ± LAD (alone)	8 (13.6)	4 (25)	
RP + EBRT (±ADT)	4 (6.8)	1 (6.3)	
EBRT (±ADT)	12 (20.3)	5 (31.3)	
HT alone	6 (10.2)	6 (37.4)	
NA	29 (49.1)	0	
Ongoing ADT			0.086**
No	25 (42.3)	10 (62.5)	
Yes	9 (15.4)	4 (25)	
NA	25 (42.3)	2 (12.5)	

GS Gleason score, *RP* radical prostatectomy, *LAD* lymphadenectomy dissection, *EBRT* external beam radiotherapy, *ADT* androgen deprivation therapy, *NA* not available
* Kolmogorov–Smirnov test; ** χ^2 test

Table 3. Correlation between Gleason score/PSA categories and FCH PET/CT findings

	N pts	True-positive FCH PET/CT finding	False-positive FCH PET/CT finding	p value
GS ≤6 and PSA <1 ng/mL	3	3 (100)	0	0.382
GS ≤6 and 1> PSA ≤2 ng/mL	4	2 (50)	2 (50)	
GS ≤6 and PSA >2 ng/mL	12	11 (91.7)	1 (8.3)	
GS = 7 and PSA <1 ng/mL	3	1 (33.3)	2 (66.7)	
GS = 7 and 1> PSA ≤2 ng/mL	1	1 (33.3)	0	
GS = 7 and PSA >2 ng/mL	21	18 (85.7)	3 (14.3)	
GS >7 and PSA <1 ng/mL	3	2 (66.7)	1 (33.3)	
GS >7 and 1> PSA ≤2 ng/mL	5	4 (80)	1 (33.3)	
GS >7 and PSA >2 ng/mL	23	17 (73.9)	6 (26.1)	

GS Gleason score, *PSA* prostatic specific antigen

lymph nodes, no seminal vesicle invasion, positive margins, and GS <7 are all factors related to a higher risk of local relapse, while PSA detectable before 1 year, positive lymph nodes, seminal vesicle invasion, and GS >6 are related to systemic relapse. However, in clinical practice, it is not so easy to identify the origin of PSA. As suggested by Paparo et al. [1], the combination of multi parametric magnetic resonance imaging (mpMRI) and Choline PET/CT provides a comprehensive assessment for the restaging of patients with biochemical recurrence after RP and RT, thus allowing local recurrence to be distinguished from metastatic disease.

From our results, it emerged that the detection rate of FCH PET/CT for local recurrent disease, in a population of more than 1000 people, is at least 13%. From the analysis of published literature, the detection rate of FCH PET/CT in prostatic bed ranged between 17% and 100% (see Table 5; Ref. [19–27]). Unfortunately, few data on PSA levels are available to evaluate the correlation between biochemical recurrence and FCH PET/CT detection rate. In addition, we found that FCH PET/CT detection of local recurrence seems higher for the prostate gland as compared to prostatic fossa, probably related to our older patient population who were mainly treated by non-invasive approaches (brachytherapy or EBRT) as primary treatment, due to the presence of comorbidities (high Charlson Comorbidity index). However, the numbers of FP and TP findings were similar for both patients with FCH uptake in prostate gland and those with FCH uptake in prostatic fossa.

Picchio et al. [28] reported that false-positive findings could occur in the prostatectomy bed, although false-negative results are the greatest concern at this anatomical location. As reported by Richter et al. [29], ^{11}C-choline would be more useful than FCH PET for the detection of primary PCa and recurrent disease in prostatic fossa according to its physiological elimination. As largely discussed in the literature, 11C-Choline has the

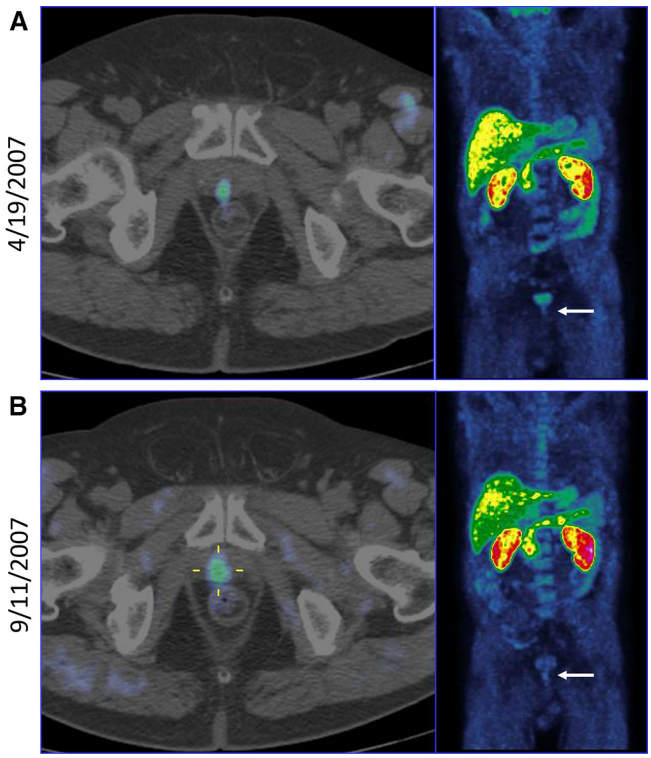

Fig. 1. A patient with suspected local recurrence after radical prostatectomy (GS = 7). **A** Focal uptake of FCH in the vesical–urethral anastomosis (PSA level was 2.4 ng/mL); **B** increase in focal FCH uptake after 7 months from the previous scan (PSA level was: 4.25 ng/mL) that confirmed the local recurrence of disease.

advantage of detecting prostate recurrence due to its physiological elimination, mainly by the intestinal tract rather than urinary one. On the contrary, FCH presents a variable urinary excretion with high accumulation in the bladder that can compromise the evaluation of the prostatic region. However, to date, comparative data are still missing.

As Cimitan et al. [30] demonstrated, delayed FCH PET/CT images (such as after 60 min) could reduce the rate of false-positive lymph node uptake. Recently, Chondroggianis et al. [31, 32] reported that the inclusion of early static images can improve the detection of local recurrence of prostate cancer, thus reducing the rate of FN and FP findings. Alonso et al. [33] investigated 64 prostate cancer patients with PSA relapse under ADT by 68Ga-DOTATATE PET/CT and 11C-Choline PET/CT. The authors found five false-positive lesions for both tracers, which were located in the prostate bed ($n = 1$) and regional lymph nodes ($n = 4$), respectively. Pathology revealed non-specific inflammatory lesions in all cases. Furthermore, in 2010, Le et al. described a case of active inflammation by FCH PET/CT in a patient with pulmonary infection, thus confirming that active infection is choline avid [34].

Unfortunately, none of the clinical parameters that we have evaluated in this setting can be useful to predict TP or FP FCH PET/CT. In our study, FCH PET/CT was able to identify true recurrence of prostate cancer in prostatic gland/fossa in 59/75 (79%) patients with available standard of reference (i.e., histology or MRI). As shown in Table 2, higher PSA values seem to be linked to a TP FCH uptake, although this result was not statistically significant ($p = 0.852$). Moreover, we found that the rates of TP FCH PET/CT for local recurrence were higher in patients with a PSA >2 ng/mL independently from GS. Conversely, the rates of FP ranged between 50% and 65% in patients with a PSA ≤ 2 ng/mL, particularly in 63.6% of those with a GS ≤ 7. At univariate analysis, we found that the odds of FP findings in patients who were treated by RP and adjuvant RT were 3.695 higher than those of patients treated with RP alone. This result can be associated with an increase in inflammation and/or a different anatomical conformation that can be associated with urinary residual.

As reported in the literature, after local primary treatments, patients who showed a confined recurrence of disease in prostate gland (in case of a previous EBRT) or in prostatic fossa (in case of RP) can benefit from salvage RP or pulse dose-rate brachytherapy with Ir-192 and salvage EBRT, respectively [35, 36]. Moreover, local therapies can be indicated after neo-adjuvant ADT [37], because men given neo-adjuvant hormone therapy prior to EBRT, showed significant improvements in clinical disease-free survival as well as overall survival [38]. Breeuwsma et al. [39] reported that in a cohort of 70 patients undergoing 11C-Choline PET/CT after EBRT, a significant FCH uptake in the prostatic gland was found in 41/57 (72%) patients with a positive PET scan. In this subgroup of patients, PSAdt and PSAvel were significantly higher than those with lymph node or distant metastases. Alongi et al. [40] analyzed 15 patients who underwent salvage EBRT due to a biochemical recurrence after high intensity focused ultrasound (HIFU). In these selected patients, 11C-Choline showed a positive intraprostatic-alone failure, thus being able to give information about the target definition in salvage EBRT, although it would still be considered an experimental procedure. D'Angelillo et al. [20] evaluated the utility of FCH dynamic PET imaging for the definition of recurrences in patients previously treated by RP and who were candidates for EBRT. In the analysis of 60 patients, the authors found that FCH PET/CT was able to recognize a local recurrence in all patients and also recorded a nodal disease in five subjects with low median PSA levels (median: 0.9 ng/mL; 0.2–11.7). Therefore, the identification of clinical data that are linked to a positive FCH uptake in prostatic bed could be useful to determine salvage treatments.

The main limitation of the present study is the absence of PSA kinetic data. As largely reported in the

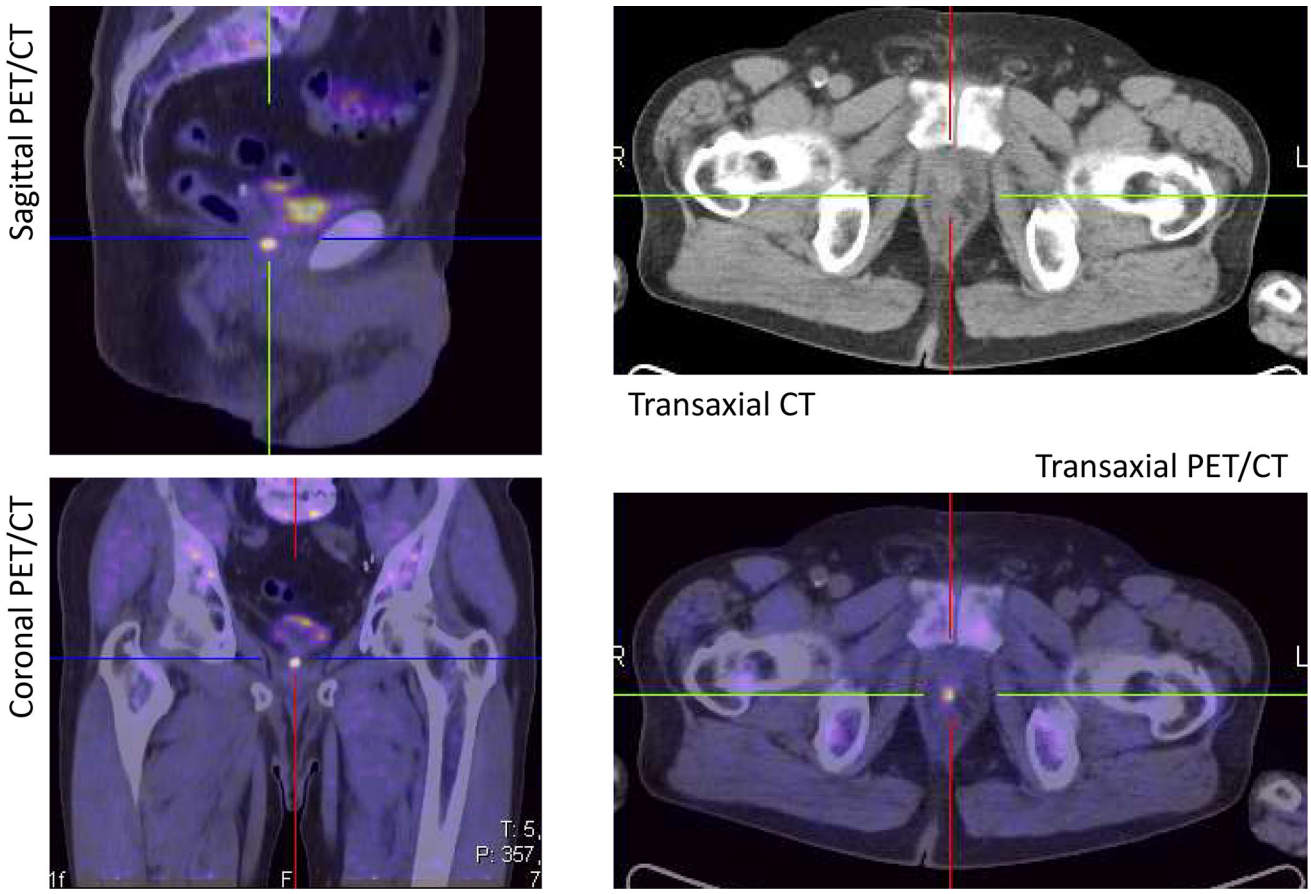

Fig. 2. A 78-year-old patient with a focal FCH uptake in prostatic fossa after robotic radical prostatectomy, in proximity of urethra (GS = 7; PSA level 0.7 ng/mL) at PET/CT scan. The suspicion was not confirmed by biopsy.

literature, a PSA velocity <0.75 ng/mL/year and a PSA doubling time >6 months are related to higher risk of local relapse, while a PSA velocity >0.75 ng/mL/year and a PSA doubling time <6 months are related to systemic relapse [41]. Nevertheless, pathological stage and GS are the main factors related to the likelihood of local vs. distant relapse. Therefore, for the retrospective nature of the present study, we considered only two out of the four predictive parameters that often correspond to clinical practice. The lack of dynamic or early PET acquisitions represents another important limitation to the present study. As recently demonstrated by Chondroggianis et al. [31, 32] and later reported in a recent revision by Evangelista et al. [42], the prostatic region uptake is better visualized in the early phase than in the late images. In fact, an early static or dynamic pelvic acquisition allows studying the prostate region before physiological urinary excretion of FCH, thus identifying with more accuracy, the presence of prostatic fossa recurrence. However, dual phase acquisition of PET/CT is time consuming and increases the number of false-positive findings of local recurrence especially in older patients who are mainly treated by non-invasive approaches. Thus, in clinical practice, a whole-body late imaging is often preferred. Other limitations are the lack of data on patient outcome and that the study was based on a retrospective analysis of the data.

In conclusion, from the present study emerged that, although PET/CT with FCH has some limitations for the evaluation of prostatic gland/fossa, due to the physiological biodistribution of the radiopharmaceutical agent, in 70–90% of patients with a PSA level >2 ng/mL, independently from the GS, a focal FCH uptake could be compatible with local recurrence. Therefore, a careful lecture of FCH PET/CT images, especially in the pelvis, also in whole-body examination is recommended for avoiding the presence of a true recurrence of prostatic bed, in patients with already treated prostate cancer. A prospective comparative study between MRI and PET/CT with FCH by including a large number of patients, stratified for age, GS, PSA level, PSA kinetic values, and type of treatments is mandatory in order to assess the

Table 4. Univariate analysis

	True positive at FCH PET/CT			False positive at FCH PET/CT		
	OR	IC 95%	*p* value	OR	IC 95%	*p* value
Age	1.015	0.936–1.099	0.723	0.986	0.910–1.068	0.723
PSA pre-PET/CT	1.036	0.890–1.206	0.648	0.965	0.829–1.124	0.648
GS categories						
GS ≤6	Reference	Reference	Reference	Reference	Reference	Reference
GS = 7	1.855	0.426–8.027	0.411	0.539	0.124–2350	0.411
GS >7	1.391	0.392–4.944	0.610	0.719	0.202–2554	0.610
PSA categories						
PSA ≤1 ng/mL	Reference	Reference	Reference	Reference	Reference	Reference
1> PSA ≤2 ng/mL	0.435	0.093–2.039	0.291	2.300	0.490–10.787	0.291
PSA >2 ng/mL	0.597	0.511–2.309	0.380	1.971	0.433–8.974	0.380
Therapy						
RP ± LAD (alone)	Reference	Reference	Reference	Reference	Reference	Reference
RP + EBRT (±ADT)	0.276	0.664–1.195	0.085	3.625	0.837–15.703	0.085
EBRT (±ADT)	0	–	–	0	–	–
HT alone	2.069	0.218–19.629	0.527	0.483	0.051–4.586	0.527
NA	0.207	0.045–0.946	0.042	4.833	1.057–22.091	0.042
ADT ongoing						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	0.200	0.040–1.007	0.051	5.000	0.993–25.170	0.051
NA	0.180	0.028–1.15	0.071	5.556	0.864–35.706	0.071

GS Gleason score, *RP* radical prostatectomy, *LAD* lymphadenectomy dissection, *EBRT* external beam radiotherapy, *ADT* androgen deprivation therapy, *NA* not available

Table 5. Detection rate of local recurrence of disease by FCH PET/CT in patients with prostate cancer

Authors, reference	N of pts	Detection Rate in prostatic fossae	PSA levels
D'Angellillo et al. [20]	60	60 (100%)	0.9 (0.2–11.7)
Piccardo et al. [21]	21	4 (19%)	No data
Beheshti et al. [22]	250	95 (38%)	6.6 ± 2.8 (ADT ongoing) 5.9 ± 2.0 (no ADT)
Panebianco et al. [19]	76	63 (83%)	No data
Henninger et al. [23]	35	17 (49%)	No data
Schillaci al [24]	49	33 (67%)	5.35 ± 5.04
Husarik et al. [25]	68	19 (28%)	No data
Pelosi et al. [26]	24	4 (17%)	No data
Vees et al. [27]	11	5 (45%)	No data

ADT androgen deprivation therapy

correct management of patients with suspicion for prostatic bed recurrence.

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4.5. Gleason score at diagnosis predicts the rate of detection of ^{18}F-choline PET/CT performed when biochemical evidence indicates recurrence of prostate cancer: experience with 1,000 patients.

Cimitan M, Evangelista L, Hodolič M, Mariani G, Baseric T, Bodanza V, Saladini G, Volterrani D, Cervino AR, Gregianin M, Puccini G, Guidoccio F, Fettich J, Borsatti E.

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The Aim of the study:

To explore the ability of the initial Gleason score to predict the rate of detection of recurrent prostate cancer with ^{18}F-choline PET/CT in a large cohort of patients (1000 patients).

Conclusion of the study:

For suspected prostate cancer recurrence, a high GS at diagnosis can be associated with positive ^{18}F-choline PET/CT scan results, regardless of the serum PSA level at the time of imaging. Therefore, the GS can be considered a robust predictive factor for positive ^{18}F-choline PET/CT results, even at a very early stage of biochemical failure of prostate cancer, that is, when the PSA level is less than 1 ng/mL.

Gleason Score at Diagnosis Predicts the Rate of Detection of ^{18}F-Choline PET/CT Performed When Biochemical Evidence Indicates Recurrence of Prostate Cancer: Experience with 1,000 Patients

Marino Cimitan[1], Laura Evangelista[2], Marina Hodolič[3], Giuliano Mariani[4], Tanja Baseric[1], Valentina Bodanza[1], Giorgio Saladini[2], Duccio Volterrani[4], Anna Rita Cervino[2], Michele Gregianin[2], Giulia Puccini[4], Federica Guidoccio[4], Jure Fettich[3], and Eugenio Borsatti[1]

[1]Nuclear Medicine Unit, IRCCS National Cancer Institute (CRO), Aviano, Italy; [2]Radiotherapy and Nuclear Medicine Unit, Veneto Institute of Oncology, IRCCS, Padua, Italy; [3]Nuclear Medicine Department, University Medical Center Ljubljana, Ljubljana, Slovenia; and [4]Regional Center of Nuclear Medicine, University of Pisa, Pisa, Italy

The objective of this study was to explore the ability of the initial Gleason score (GS) to predict the rate of detection of recurrent prostate cancer (PCa) with ^{18}F-choline PET/CT in a large cohort of patients. **Methods:** Data from 1,000 patients who had undergone ^{18}F-choline PET/CT because of biochemical evidence of relapse of PCa between 2004 and 2013 were retrieved from databases at 4 centers. Continuous data were compared by the Student *t* test or ANOVA, and categoric variables were compared by the χ^2 test. Univariable and multivariable analyses were performed by logistic regression. **Results:** The GS at diagnosis was less than or equal to 6 in 257 patients, 7 in 347 patients, and greater than 7 in 396 patients. The results of 645 PET/CT scans were positive for PCa recurrence. Eighty-one percent of the positive PET/CT results were found in patients with a PSA level of greater than or equal to 2 ng/mL, 43% were found in patients with a PSA level of 1–2 ng/mL, and 31% were found in patients with a PSA level of less than or equal to 1 ng/mL; 78.8% of patients with positive PET/CT results had a GS of greater than 7. The results of ^{18}F-choline PET/CT scans were negative in 300 patients; 44% had a GS of less than or equal to 6, 35% had a GS of 7, and 17% had a GS of greater than 7. PET/CT results were rated as doubtful in only 5.5% of patients (median PSA, 1.8 ng/mL). When the GS was greater than 7, the rates of detection of ^{18}F-choline PET/CT were 51%, 65%, and 91% for a PSA level of less than 1 ng/mL, 1–2 ng/mL, and greater than 2 ng/mL, respectively. In univariable and multivariable analyses, both a GS of 7 and a GS of greater than 7 were independent predictors for positive ^{18}F-choline PET/CT results (odds ratios, 0.226 and 0.330, respectively; *P* values for both, <0.001). **Conclusion:** A high GS at diagnosis is a strong predictive factor for positive ^{18}F-choline PET/CT scan results for recurrent PCa, even when the PSA level is low (i.e., $\leq$1 ng/mL).

Key Words: ^{18}F-choline PET; Gleason score; prostate cancer; PSA; restaging

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For correspondence or reprints contact: Laura Evangelista, Radiotherapy and Nuclear Medicine Unit, Veneto Institute of Oncology, IRCCS, Via Gattamelata 64, 35128 Padua, Italy.
E-mail: laura.evangelista@ioveneto.it
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Prostate cancer (PCa) remains the leading cancer in North American and European men, with annual age-adjusted incidence rates of 85.6 and 59.3 per 100,000, respectively (*1*). Despite highly successful surgery and radiotherapy treatments, PCa relapses in up to 20%–40% of patients within 10 y of potentially curative local therapy (*2–4*). This observation suggests that PCa metastasizes relatively early in the course of the disease, probably as a result of genetic instability, including loss of metastasis suppressor genes (*5–7*).

PET/CT with ^{11}C- or ^{18}F-choline has emerged as a powerful tool for detecting recurrent disease in PCa patients, with a pooled sensitivity of 85.6% (95% confidence interval, 82.9%–88.1%) (*8,9*). The diagnostic performance of radiolabeled choline PET increases with increasing prostate-specific antigen (PSA) levels, reaching greater than 80% sensitivity in patients with a PSA level of greater than 2–3 ng/mL (*9*). Moreover, the sensitivity of radiolabeled choline PET is higher in patients with a higher PSA velocity (the rate at which PSA level increases from year to year) or a shorter PSA doubling time (*9,10*). However, the role of variables other than the PSA level, such as the Gleason score (GS) at diagnosis, in predicting positive radiolabeled choline imaging results remains unclear. In this regard, GS is a well-established predictive risk factor for recurrence (*11*), but its value in predicting positive radiolabeled choline PET/CT results has been reported to be less robust than that of the trigger PSA (the PSA level before ^{18}F/^{11}C-choline PET/CT) (*12,13*). However, most patients evaluated in previous reports, such as those by Giovacchini et al. (*12*) and Castellucci et al. (*13*), had a low GS (6 or lower). This limitation is important from a clinical point of view. The purpose of the present study was to assess the ability of the initial GS to predict the rate of detection of recurrent PCa with ^{18}F-choline PET/CT in a large cohort of patients.

MATERIALS AND METHODS

Patients

This was a retrospective study based on patients' files from 4 nuclear medicine centers. Between October 2004 and June 2013, 1,359 men underwent ^{18}F-choline PET/CT scans because of biochemical evidence of recurrence of PCa after potentially curative treatment (a PSA level of $\geq$0.2 ng/mL in cases of radical prostatectomy and a PSA level above the previous PSA nadir measured at 3 mo after external-beam radiotherapy). Patients were included in this retrospective review if they met predefined

inclusion criteria, including the availability of clinical information, such as GS (for the biopsy in cases of no surgery or for the surgical specimen), records of current and past therapies (surgery, radiotherapy, or systemic therapy), and serum PSA level at the time of the PET/CT scan. Moreover, if available, PSA velocity was calculated with the formula (PSA2 − PSA1)/Δ time, where PSA2 corresponds to the PSA level at the time of PET imaging and PSA1 corresponds to the PSA level before a Δ time from PSA2.

According to institutional policies, all patients had given their informed consent for undergoing an ^{18}F-choline PET/CT scan and for subsequent analysis of data in an anonymized manner.

^{18}F-Choline PET/CT Imaging

The integrated PET/CT systems used at the 4 centers were a Discovery LS scanner (GE Healthcare) in Aviano, Italy; a Biograph 16 HT PET/CT scanner (Siemens Medical Solutions) in Padua, Italy; a Biograph mCT PET/CT scanner (Siemens Medical Solutions) in Ljubljana, Slovenia; and a Discovery ST8 scanner (GE Healthcare) in Pisa, Italy. ^{18}F-choline PET/CT included a delayed whole-body PET scan (6–8 bed positions; 2–3 min per bed position) performed 45–60 min after the intravenous administration of ^{18}F-choline (IASOcholine; IASON GmbH) at 3.0–3.5 MBq/kg and a coregistered low-dose CT whole-body scan (140 kV; 80–120 mA) without contrast enhancement.

At each institution, 2 specialists in nuclear medicine independently reviewed the scans by visual assessment. In particular, local relapse (LR) was recorded in the presence of clear focal ^{18}F-choline uptake in the prostate bed; lymph nodes were considered to have positive results (N+) in the presence of focal ^{18}F-choline uptake corresponding to that in abdominal–pelvic lymph nodes (including lymph nodes of <1 cm). However, weak ^{18}F-choline uptake at the inguinal and mediastinal lymph nodes was not considered a pathologic finding but rather was related to prevailing reactive lymphadenitis (*14,15*). Focal ^{18}F-choline uptake in the skeleton or in soft tissue other than lymph nodes indicated distant metastases (M+).

Doubtful recurrent disease was defined as the presence of mild ^{18}F-choline uptake in the skeleton without structural changes in the corresponding coregistered CT images; similarly, local disease was rated as doubtful when ^{18}F-choline uptake in the prostate bed was weak and irregular. Doubtful interpretations were resolved by consensus between the 2 interpreters.

^{18}F-Choline PET/CT Diagnostic Performance

Positive ^{18}F-choline PET/CT findings were compared with the results of biopsy, surgery performed after PET/CT, and conventional imaging studies (such as CT, MR imaging, or follow-up ^{18}F-choline PET/CT). Follow-up duration ranged from 1 to 12 mo. Positive ^{18}F-choline PET/CT findings were considered true-positive when any of the following 5 criteria were met: confirmation on histology or confirmation on periurethral anastomosis biopsy; increase in number of pathologic ^{18}F-choline uptake sites or increase in uptake intensity on follow-up PET/CT studies; confirmation on conventional imaging either at baseline or during follow-up; disappearance or considerable reduction of ^{18}F-choline uptake on follow-up PET/CT scans after local or systemic treatment; or a decrease in the PSA level after local or systemic treatment. Negative ^{18}F-choline PET/CT findings were considered true-negative in the absence of evidence of disease on periurethral anastomosis biopsy, conventional imaging, or PET/CT during follow-up. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated.

Statistical Analysis

Continuous data are presented as median and interquartile range (IQR), and categoric data are presented as numbers and percentages. Associations for paired samples were assessed with the *t* test or the Mann–Whitney test for nonnormal data variables, as verified with the Shapiro–Wilk test. An ANOVA was used for comparing 3 or more variables. Comparisons of dichotomized variables were performed with the χ^2 test or the Fisher exact test. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated by standard methods. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of the rate of detection of ^{18}F-choline PET/CT. Variables were selected with entry and retention set at a significance level of 0.1. Receiver operating characteristic (ROC) analysis was performed by evaluating the area under the ROC curve to assess PSA level and GS as predictors of positive PET/CT findings. Two-tailed *P* values of less than 0.05 were considered statistically significant. Statistical analysis was performed with SPSS software for Windows (SPSS).

RESULTS

On the basis of the criteria described earlier, a total of 1,000 patients were included in the study (Table 1). In accordance with National Comprehensive Cancer Network guidelines (version 2.2014; www.nccn.org/professionals/physician_gls/f_guidelines.asp), we classified patients as being at low risk (T1 or T2; GS of ≤6; PSA level of <10 ng/mL), intermediate risk (T2b or T2c; GS of 7; PSA level of 10–20 ng/mL), high risk (T3a; GS of 8–10; PSA level of >20 ng/mL), or very high risk (T3b or T4) or as having metastatic disease (any T and N1; any T, any N, and M1). On the basis of these classifications, 29 patients (2.9%) were at low risk, 59 (5.9%) were at intermediate risk, 55 (5.5%) were at high risk, 91 (9.1%) were at very high risk, and 73 (7.3%) had metastatic disease. Histologic data (TNM) were available for 307 patients. At the time of PET/CT, the median PSA level was 3.30 ng/mL (IQR, 1.15–11.0). Concerning the GS at diagnosis, 257 patients (25.7%) had a GS of less than or equal to 6, 347 (34.7%) had a GS of 7, and 396 (39.6%) had a GS of greater than 7. Patients with a GS of less than or equal to 6 were at low to intermediate risk (n = 44; 59.5%). Conversely, 41% of this subset of patients was at high risk or had metastatic disease. As expected, patients with a GS of greater than 7 were at high to very high risk. Most patients with a GS of greater than 7 had received more aggressive treatments (such as a combination of surgery and hormonal therapy, a combination of radiotherapy and hormonal therapy, or combinations of both) than patients with a GS of less than or equal to 7. At the time of PET/CT scanning, 257 patients were receiving hormonal therapy; 21% had a GS of less than or equal to 6, 26% had a GS of 7, and 53% had a GS of greater than 7.

^{18}F-Choline PET/CT Results

^{18}F-choline PET/CT detected PCa recurrence in 645 of the 1,000 patients, with the following distribution: LR in 275 patients, N+ in 303, and M+ in 335. Moreover, 85 patients had both LR and N+ findings, 136 had both N+ and M+ findings, and 44 had LR and N+ and M+ findings.

Data were available to assess the diagnostic performance of ^{18}F-choline PET/CT in 731 of the 1,000 patients. ^{18}F-choline PET/CT findings were validated with histologic criteria in 26 patients (35.6%) and with imaging and clinical or biochemical criteria in the remaining 705 patients. Accordingly, there were 367 true-positive findings, 307 true-negative findings, 78 false-positive findings, and 9 false-negative findings. Thus, the sensitivity was 97.6%, the specificity was 79.7%, the positive predictive value was 82.5%, the negative predictive value was 97.2%, and the accuracy was 88.6%.

The median PSA level was significantly higher in patients with positive scan results than in those with negative scan results (6.65 vs. 1.20 ng/mL; P = 0.035). Conversely, the statistical significance was lost when the doubtful cases were included in the

TABLE 1
Main Characteristics of the Patients

Characteristic	Value
Age (y)*	69.68 ± 7.67
Center	
CRO	626 (62.6)
Medical Center Ljubljana	79 (7.9)
IOV	227 (22.7)
University of Pisa	68 (6.8)
GS	
≤6	257 (25.7)
7	347 (34.7)
>7	396 (39.6)
Actual GS	
2	2 (0.2)
3	4 (0.4)
4	9 (0.9)
5	43 (4.3)
6	199 (19.9)
7	347 (34.7)
8	223 (22.3)
9	155 (15.5)
10	18 (1.8)
Primary treatment	
Surgery alone	353 (35.3)
Surgery and adjuvant EBRT (with or without HT)	167 (16.7)
EBRT (with or without HT)	152 (15.2)
HT alone	121 (12.1)
NA	207 (20.7)
PSA level, in ng/mL†	3.30 (1.15–11.0)

*Reported as mean ± SD.
†Reported as median (IQR).
CRO = IRCCS National Cancer Institute; IOV = Veneto Institute of Oncology; EBRT = external beam radiotherapy; HT = hormone therapy; NA = not available.
Values are reported as number of patients followed by percentage in parentheses unless otherwise indicated.

statistical analysis (median PSA level, 1.8 ng/mL; $P = 0.0.73$) (Table 2). The median PSA level was significantly higher in patients with N+ disease (2.47 ng/mL [IQR, 0.98–6.87]) than in those who did not have N+ disease (8.04 ng/mL [IQR, 2.55–21.7]) and significantly higher in patients with M+ disease (2.27 ng/mL [IQR, 1–6.07]) than in those who did not have M+ disease (8.11 ng/mL [IQR, 2.96–25]).

As expected, increasing PSA levels were associated with increasing PET/CT positivity rates: 31% of patients with a serum PSA level of less than or equal to 1 ng/mL had positive scan results, 43% of patients with a serum PSA level between 1 and 2 ng/mL had positive scan results, and 78.8% of patients with a serum PSA level of greater than or equal to 2 ng/mL had positive scan results. Similarly, when the ^{18}F-choline PET/CT results were stratified according to the GS at diagnosis, the scan results were positive in 49.2% of patients with a GS of less than or equal to 6, 59.4% of patients with a GS of 7, and 79% of patients with a GS of greater than 7. A PSA level of less than or equal to 1 ng/mL was associated with positive ^{18}F-choline PET/CT results at local sites, at lymph nodes, and at distant metastases in 14.1%, 22.4%, and 28.2% of patients with a GS of greater than 7, respectively. On the contrary, a PSA level of greater than 2 ng/mL was associated with distant metastases in 51.7% of the same group of patients. Both of these findings can be useful in clinical practice for determining the best choice of treatment. Table 3 shows the correlations of the clinical characteristics of the study population and PET/CT findings. Moreover, the median value for PSA velocity, available in 505 patients, was significantly higher in patients with positive PET/CT scan results than in those with negative PET/CT scan results (7.04 vs. 1.16 ng/mL/y; $P < 0.001$) and was significantly higher in patients with a GS of greater than 7 than in those with a GS of less than or equal to 7 (4.86 vs. 2.20 ng/mL/y; $P < 0.001$).

^{18}F-Choline Detection Rate Based on GS Combined with PSA Levels

The combination of the GS at diagnosis with the serum PSA level at the time of ^{18}F-choline PET/CT scanning had better discriminating power for positive scan results than either variable alone. In particular, when the serum PSA level at the time of the scan was less than 1 ng/mL, PCa recurrence was detected by ^{18}F-choline PET/CT in 51%, 27%, and 10% of patients with a GS of greater than 7, a GS of 7, and a GS of less than or equal to 6, respectively. When the serum PSA level was between 1 and 2 ng/mL, ^{18}F-choline PET/CT detected PCa recurrence in 65%, 36%, and 29% of patients with a GS of greater than 7, a GS of 7, and a GS of less than or equal to 6, respectively. Finally, when the serum PSA level was greater than 2 ng/mL, PCa recurrence was detected by ^{18}F-choline PET/CT in 91%, 75%, and 72% of patients with a GS of greater than 7, a GS of 7, and a GS of less than or equal to 6, respectively (Fig. 1). For patients undergoing hormonal therapy at the time of the ^{18}F-choline PET/CT scan, recurrent disease was detected in 64%, 74%, and 87.5% of patients with a GS of less than or equal to 6, a GS of 7, and a GS of greater than 7, respectively (Supplemental Table 1) (supplemental materials are available at http://jnm.snmjournals.org).

ROC Analysis

ROC analysis revealed that a GS of 7 was correlated with positive ^{18}F-choline PET/CT results at a sensitivity and a specificity of 80.3% and 62.3%, respectively; the corresponding values for the correlation of a PSA level of 2 ng/mL with positive ^{18}F-choline PET/CT results were 79.5% and 67.0%, respectively. The corresponding area under the curve values were 0.826 for the serum PSA level and 0.655 for the GS, respectively (both with P values of <0.001) (Fig. 2).

Univariate and Multivariate Analyses

Univariate analysis (Table 3) revealed that clinical and demographic data as well as therapy-related variables were significantly correlated with positive PET/CT scan results (all P values were <0.005). However, multivariate analysis revealed that only older age, a GS of greater than or equal to 7, systemic chemotherapy, and a serum PSA level of greater than or equal to 1 ng/mL were identified as independent predictors of positive ^{18}F-choline PET/CT results in patients with biochemical evidence of recurrence. Similarly, a GS of greater than or equal to 7 and a serum PSA level

TABLE 2
Correlations Between Clinical Characteristics of Patients and PET/CT Findings

Characteristic	Negative PET/CT	Positive PET/CT	Doubtful PET/CT	*P*
n	300	645	55	
PSA level, in ng/mL*	1.20 (0.58–2.35)	6.65 (2.56–17.47)	1.8 (0.85–3.9)	0.073†
PSA range				
<1 ng/mL	127 (42.3)	66 (10.2)	18 (32.7)	<0.001‡
≥1 but <2 ng/mL	74 (24.7)	66 (10.2)	13 (23.6)	
≥2 ng/mL	99 (33)	513 (79.5)	24 (43.6)	
GS				
≤6	113 (37.7)	127 (19.7)	17 (30.9)	<0.001‡
7	120 (40)	206 (31.9)	21 (38.2)	
>7	67 (22.3)	312 (48.4)	17 (30.9)	
Type of therapy				
RP alone	161 (53.7)	162 (25.1)	30 (54.5)	<0.001‡
RP and adjuvant EBRT (with or without HT)	50 (16.7)	107 (16.6)	10 (18.2)	
EBRT (with or without HT)	35 (11.7)	113 (17.5)	4 (7.3)	
HT alone	10 (3.3)	109 (16.9)	2 (3.6)	
NA	44 (14.7)	154 (23.9)	9 (16.4)	

*Reported as median (IQR).
†ANOVA.
‡χ^2 test.
RP = radical prostatectomy; EBRT = external-beam radiotherapy; HT = hormone therapy; NA = not available.
Values are reported as number of patients followed by percentage in parentheses unless otherwise indicated.

of greater than or equal to 1 ng/mL were identified as independent predictive variables for the detection of lymph node and distant metastases by ^{18}F-choline PET/CT (all *P* values were <0.001). Conversely, no logistic relationship was found between the GS and LR detection ($P = 0.645$ and $P = 0.231$ for a GS of 7 and a GS of >7, respectively).

DISCUSSION

Imaging of PCa recurrence in patients with biochemical evidence of relapse of the disease remains challenging. Predominantly morphologic imaging modalities, such as CT and MR imaging, have low to moderate sensitivities for the early detection of lymph node metastases (widely ranging at 30%–80%) (*16,17*)

TABLE 3
Univariate and Multivariate Analyses

Parameter	Univariable			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.035	1.016–1.054	<0.001	1.025	1.003–1.048	<0.05
GS ≤ 6						
GS = 7	0.241	0.167–0.348	<0.001	0.226	0.145–0.3351	<0.001
GS > 7	0.369	0.261–0.521	<0.001	0.330	0.216–0.503	<0.001
Surgery (yes vs. no)	1.463	0.885–2.416	0.138			
EBRT (yes vs. no)	0.466	0.303–0.717	<0.05	2.221	0.342–14.41	0.403
HT (yes vs. no)	0.357	0.225–0.567	<0.001			1.00
Ongoing HT (yes vs. no)	0.490	0.313–0.978	<0.005			1.00
Chemotherapy (yes vs. no)	0.488	0.321–0.742	<0.05	0.203	0.074–0.560	<0.05
PSA of <1						
PSA ≥1 but <2	0.100	0.069–0.145	<0.001	0.092	0.060–0.141	<0.001
PSA of ≥2	0.172	0.116–0.256	<0.001	0.206	0.134–0.316	<0.001

OR = odds ratio; CI = confidence interval; EBRT = external-beam radiotherapy; HT = hormonal therapy.

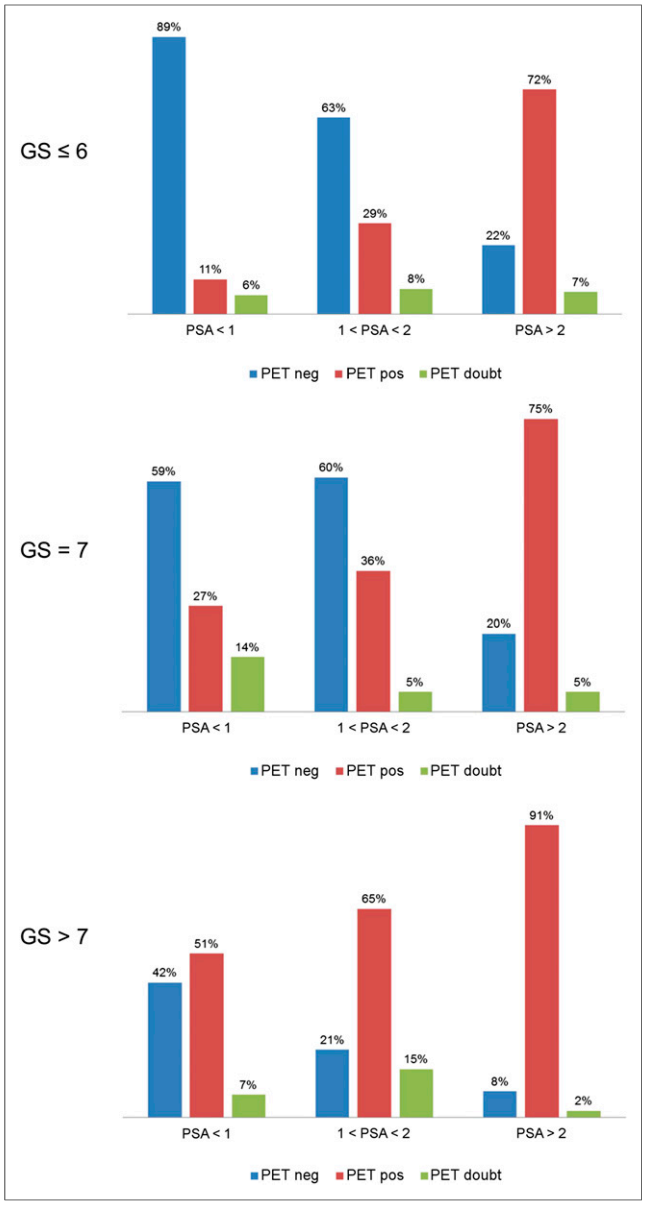
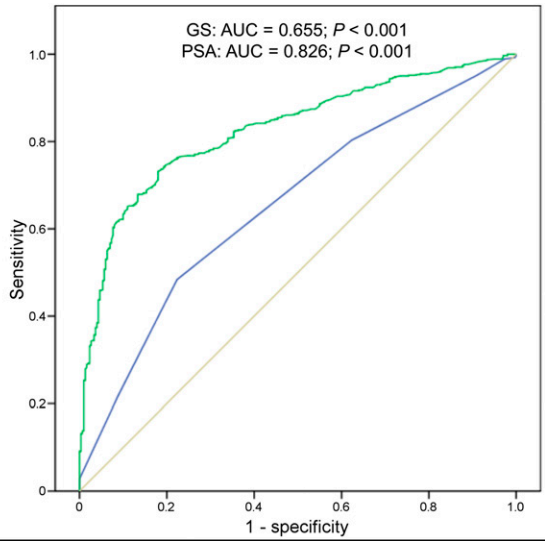


FIGURE 1. Distributions of Gleason scores and PSA cutoff values. doubt = doubtful; neg = negative; pos = positive.

and local cancer recurrence (25%–54%) (*18,19*). With regard to radionuclide imaging, bone scintigraphy is recommended for assessing patients at a high risk of PCa because of a PSA level of greater than 20 ng/mL or symptomatic patients (i.e., with bone pain or pathologic fracture) because metastatic disease may occur even when PSA is undetectable (*20,21*). On the other hand, PET with ^{18}F-FDG is generally not recommended for detecting metastatic lesions, likely because of the low glucose metabolic rates (resulting in low tracer uptake) that often characterize PCa; this pattern is linked to the frequently low level of expression of glucose transporters on cell membranes in this type of cancer (*22–24*). Nevertheless, the sensitivity of ^{18}F-FDG PET for the detection of PCa metastases is higher in patients with a GS of greater than 7, a high serum PSA level, and high PSA velocity (*4,25*).

The introduction of radiolabeled choline for clinical use has heralded a turning point in the role of PET imaging for patients with PCa, with overall higher sensitivity than ^{18}F-FDG PET imaging (*26*). After the initial experience with ^{11}C-choline (which requires the availability of an in-house cyclotron and radiochemistry or radiopharmacy facility), most centers have now shifted to the use of the more widely available ^{18}F-choline. In fact, ^{18}F-choline is characterized by a high diagnostic accuracy similar to that of ^{11}C-choline, particularly for patients with a higher serum PSA level, higher PSA velocity, or shorter PSA doubling times (*9*). As recently reported by Evangelista et al. (*9*), the pooled sensitivity of ^{18}F-choline PET/CT was 91.8% (range, 64.3%–100%). The sensitivity observed in the present study (97.6%) is at the upper end of this range. Nevertheless, as in most investigations published on this topic, clinical follow-up and conventional instrument examinations were used to confirm the ^{18}F/^{11}C-choline PET findings, making these studies primarily observational.

At variance with the established role of serum PSA in estimating the probability of ^{18}F-choline PET/CT detection of recurrences of PCa, the role of the GS in predicting positive scan results at the time of biochemical relapse (i.e., at diagnosis) remains questionable. Several reports (*27–29*) confirmed the high value of the GS, which is the most commonly used grading system for PCa and which provides highly meaningful prognostic information (*12,13*), for predicting the clinical outcomes of PCa patients after no treatment, treatment with radical prostatectomy (with or without pelvic lymph node dissection), or treatment with radiation therapy. For patients receiving neoadjuvant or adjuvant hormonal therapy, the GS was an independent predictor of biochemical failure (*30*). In a study of 100 consecutive cases, it was



	Value	Sensitivity	Specificity
Gleason Score	6	95.2%	42.2%
	7	80.3%	62.3%
	8	68.4%	87.6%
PSA	1.00 ng/mL	89.8%	43.3%
	1.50 ng/mL	84.2%	59.7%
	2.00 ng/mL	79.5%	67.0%
	5.00 ng/mL	58.4%	92.7%

FIGURE 2. ROC analysis. Values of 1.5 ng/mL for serum PSA and 7 for Gleason score (GS) were defined as best cutoff values for predicting positive ^{18}F-choline PET/CT scan. AUC = area under the curve.

found that when the serum PSA level was less than 4 ng/mL, ^{18}F-choline PET/CT was positive in 54% of patients with a GS of greater than 7 but only 8% of those with a GS of less than or equal to 7 (*31*); these findings are consistent with those of a prior similar report (*9*). Castellucci et al. (*13*) explored the role of ^{11}C-choline PET/CT in detecting recurrent disease in 102 patients with a lower trigger PSA level (1.5 ng/mL). Using both univariate and multivariate analyses, they found that only the PSA doubling time and lymph node status, not the initial GS, were significant and independent predictors of positive scan results; however, most of their patients (91/102, or 89%) had a GS of less than or equal to 7. Similarly, for 358 patients who had biochemical evidence of recurrence of PCa and underwent ^{11}C-choline PET/CT, Giovacchini et al. (*12*) found that the GS was a less robust predictor of positive scan results than the trigger PSA; however, most of the patients (257/358, or 72%) in this series also had a GS of less than or equal to 7.

In the present study, we investigated the role of the GS at diagnosis in predicting positive ^{18}F-choline PET/CT results in a large population that we stratified at different levels of PSA: less than 1 ng/mL, 1–2 ng/mL, and greater than 2 ng/mL. All of the scans were performed with a delayed PET protocol acquisition, and strict interpretation criteria for positive results were adopted. This comprehensive analysis showed that most patients with a serum PSA level of greater than or equal to 1 ng/mL (n = 579) had positive ^{18}F-choline PET/CT scan results. Moreover, the rates of detection of recurrent PCa were especially high in patients with more aggressive tumors at diagnosis, that is, 59.4% and 79% in patients with a GS of 7 and a GS of greater than 7, respectively. Multivariate analysis revealed that both a GS of 7 and a GS of greater than 7 appeared to be independent predictors of positive ^{18}F-choline PET/CT results in patients with biochemical failure of PCa (odds ratios, 0.226 and 0.330, respectively; P values for both, $<$0.001).

In contrast to prior studies, the present analysis involved stratification of patients into subgroups with low risk, intermediate risk, and high risk of recurrence according to the GS at diagnosis, that is, a GS of less than or equal to 6, a GS of 7, and a GS of greater than 7, respectively. In prior studies (*9,12,13*), patients were generally grouped together regardless of the GS-based risk of recurrence and almost exclusively on the basis of PSA-related parameters. In particular, regardless of the GS, the rates of detection of PCa recurrence with ^{18}F/^{11}C-choline PET/CT were reported to range widely, from 7.6% to 36% for a PSA level of less than 1 ng/mL (*9,12*) and from 43% to 100% for a PSA level of less than or equal to 2 ng/mL (*9–11,16*). In the present study, the rate of detection of ^{18}F-choline PET/CT when the PSA level was less than 2 ng/mL was 13.2% in the overall patient population; however, it exhibited a rising trend when it was associated with the GS, that is, 13.6% for a GS of less than or equal to 6, 30.3% for a GS of 7, and 56.1% for a GS of greater than 7. As a consequence of this trend, most patients with a GS of greater than 7 and a PSA level of greater than or equal to 2 ng/mL had positive ^{18}F-choline PET/CT scan results (n = 238, or 91.8%); nevertheless, 56.1% of patients with a GS of greater than 7 and a PSA level of less than 2 ng/mL also had positive ^{18}F-choline PET/CT scan results. Therefore, the probability of positive ^{18}F-choline PET/CT scan results is greater than 50% in patients with a GS of greater than or equal to 7, even with a relatively low PSA level ($<$1 ng/mL). Conversely, a similar rate of positive ^{18}F-choline PET/CT scan results can be found in patients with a GS of less than or equal to 6 only when the PSA level is greater than 1 ng/mL. ROC analysis confirmed that a GS of 7 was the optimal cutoff, with a high sensitivity (80.3%) for predicting the detection of PCa recurrence with ^{18}F-choline PET/CT; this sensitivity was similar to that in patients with a PSA level of greater than 2 ng/mL (79.5%). Taken together, these observations can serve as the basis for selecting patients for ^{18}F-choline PET/CT scans because of suspected PCa recurrence.

As extensively reported in the literature (*9*), a PSA level of greater than 1 ng/mL is one of the strongest predictors of positive radiolabeled choline PET or PET/CT in patients with suspected disease relapse. We found that PSA thresholds at 1 ng/mL and 1.5 ng/mL had good sensitivity (89.8% and 84.2%, respectively) in the ROC analysis but low specificity (Fig. 2). Nevertheless, this type of analysis is somewhat problematic if the standard of reference is not histopathology in all patients. Therefore, the results of the present study emphasize the notion that the selection of patients for ^{18}F-choline PET/CT scans should not be limited to the PSA level because a high initial GS can be associated with positive PET/CT scans even when the serum PSA level is less than 1 ng/mL.

A potential limitation of this study is that for most patients, the kinetic pattern of serum PSA was not available for analysis. In this regard, Partin et al. demonstrated that the combination of PSA velocity, GS, and lymph node status was helpful for distinguishing local recurrence from distant metastases in patients who had undergone radical prostatectomy (*31*). Also, a more recent reappraisal indicated that PSA alone is not an accurate indicator of tumor recurrence and that multiple diagnostic tests are necessary to stage disease recurrence (*9*). Finally, although the retrospective nature of the present study in principle could have introduced some bias, to our knowledge, this was the first analysis of the role of ^{18}F-choline PET/CT in a large population of patients with suspected recurrent PCa.

CONCLUSION

For suspected PCa recurrence, a high GS at diagnosis can be associated with positive ^{18}F-choline PET/CT scan results, regardless of the serum PSA level at the time of imaging. Therefore, the GS can be considered a robust predictive factor for positive ^{18}F-choline PET/CT results, even at a very early stage of biochemical failure of PCa, that is, when the PSA level is less than 1 ng/mL.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. No potential conflict of interest relevant to this article was reported.

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Gleason Score at Diagnosis Predicts the Rate of Detection of ^{18}F-Choline PET/CT Performed When Biochemical Evidence Indicates Recurrence of Prostate Cancer: Experience with 1,000 Patients

Marino Cimitan, Laura Evangelista, Marina Hodolic, Giuliano Mariani, Tanja Baseric, Valentina Bodanza, Giorgio Saladini, Duccio Volterrani, Anna Rita Cervino, Michele Gregianin, Giulia Puccini, Federica Guidoccio, Jure Fettich and Eugenio Borsatti

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4.6. (18)F-FET and (18)F-FCH uptake in human glioblastoma T98G cell lines.

Persico MG, Buroni FE, Pasi F, Lodola L, Aprile C, Nano R, Hodolič M.

Radiol Oncol. 2016 Apr 19;50(2):153-8.;IF: 1.736

The Aim of the study:

Aim of this study was to evaluate ^{18}F-FCH and ^{18}F-FET uptake by human glioblastoma T98G cells.

Conclusion of the study:

^{18}F-FCH and ^{18}F-FET are candidates for neuro-oncological PET imaging. ^{18}F-FET could be the most useful oncological PET marker in the presence of reparative changes after therapy, where the higher affinity of ^{18}F-FCH to inflammatory cells makes it more difficult to discriminate between tumour persistence and non-neoplastic changes.

research article

^{18}F-FET and ^{18}F-FCH uptake in human glioblastoma T98G cell lines

Marco Giovanni Persico[1], Federica Eleonora Buroni[1], Francesca Pasi[2], Lorenzo Lodola[1], Carlo Aprile[1], Rosanna Nano[3], Marina Hodolic[4]

[1] Department of Oncohaematology, Nuclear Medicine Unit, IRCCS San Matteo Hospital Foundation, Pavia, Italy
[2] Department of Oncohaematology, Radiotherapy Unit, IRCCS San Matteo Hospital Foundation, Pavia, Italy
[3] Department of Biology and Biotecnology "Lazzaro Spallanzani", University of Pavia, Pavia, Italy
[4] Nuclear medicine research department, Iason, Graz, Austria

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Correspondence to: Lorenzo Lodola, Fondazione IRCCS Policlinico San Matteo, V. le Golgi 19, 27100 Pavia, Italy. Phone: +39 038 250 1666; Fax: +39 0382501669; E-mail: l.lodola@smatteo.pv.it

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M.G.P., F.E.B. and F.P. have contributed equally.

Background. Despite complex treatment of surgery, radiotherapy and chemotherapy, high grade gliomas often recur. Differentiation between post-treatment changes and recurrence is difficult. ^{18}F-methyl-choline (^{18}F-FCH) is frequently used in staging and detection of recurrent prostate cancer disease as well as some brain tumours; however accumulation in inflammatory tissue limits its specificity. The ^{18}F-ethyl-tyrosine (^{18}F-FET) shows a specific uptake in malignant cells, resulting from increased expression of amino acid transporters or diffusing through the disrupted blood-brain barrier. ^{18}F-FET exhibits lower uptake in machrophages and other inflammatory cells. Aim of this study was to evaluate ^{18}F-FCH and ^{18}F-FET uptake by human glioblastoma T98G cells.

Material and methods. Human glioblastoma T98G or human dermal fibroblasts cells, seeded at a density to obtain 2 x 10^5 cells per flask when radioactive tracers were administered, grew adherent to the plastic surface at 37°C in 5% CO_2 in complete medium. Equimolar amounts of radiopharmaceuticals were added to cells for different incubation times (20 to 120 minutes) for ^{18}F-FCH and ^{18}F-FET respectively. The cellular radiotracer uptake was determined with a gamma counter. All experiments were carried out in duplicate and repeated three times. The uptake measurements are expressed as the percentage of the administered dose of tracer per 2 x 10^5 cells. Data (expressed as mean values of % uptake of radiopharmaceuticals) were compared using parametric or non-parametric tests as appropriate. Differences were regarded as statistically significant when $p<0.05$.

Results. A significant uptake of ^{18}F-FCH was seen in T98G cells at 60, 90 and 120 minutes. The percentage uptake of ^{18}F-FET in comparison to ^{18}F-FCH was lower by a factor of more than 3, with different kinetic curves. ^{18}F-FET showed a more rapid initial uptake up to 40 minutes and ^{18}F-FCH showed a progressive rise reaching a maximum after 90 minutes.

Conclusions. ^{18}F-FCH and ^{18}F-FET are candidates for neuro-oncological PET imaging. ^{18}F-FET could be the most useful oncological PET marker in the presence of reparative changes after therapy, where the higher affinity of ^{18}F-FCH to inflammatory cells makes it more difficult to discriminate between tumour persistence and non-neoplastic changes. Additional studies on the influence of inflammatory tissue and radionecrotic cellular components on radiopharmaceutical uptake are necessary.

Key words:

Introduction

The human brain is made up of approximately 100 billion nerve cells. Already in 19th century there was a statement that nervous system is held together by specific cells called glia (in Greek language: glia=glue). More than insulating one neuron from another and prevent neuronal injury, glia

supply oxygen and nutrients to neurons, destroy pathogens and remove dead neurons. In the brain, glial cells are more numerous than nerve cells (ratio of app. 3:1).[1]

Approximately 30% of all brain tumours and app. 80% of malignant ones arise from glial cell (gliomas). Different oncogenes and genetic disorders are most commonly mentioned as causes of gliomas. Despite complex treatment of surgery, radiotherapy and chemotherapy, high grade gliomas almost always recur.[2,3] Before additional systemic or local therapies are performed, precise localization of recurrent tumour is essential. Differentiation between postsurgical, postradiotherapy changes and recurrent tumour is still a difficult diagnostic task.

Magnetic resonance imaging (MRI) is well established imaging modality for diagnosis of recurrent disease in patients with gliomas.[4-6] ^{18}F-fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography (PET) in brain tumours was the first application of this modality in oncology[7,8], however because of the high physiologic glucose uptake of normal brain tissue, ^{18}F-FDG did not gain widespread use in brain tumours imaging.[9,10]

PET imaging with [^{11}C]- and [^{18}F]-labelled choline derivates is frequently used in the staging and detection of recurrent prostate cancer disease due to the increased choline kinase expression in this malignancy. Moreover, choline kinase dysregulation can be frequently found, not only in prostate cancer cells but in a large panel of human tumours such as lung, colorectal, and brain tumours.[11-13] Following intravenous injection of choline derivatives in rats and mice, the brain uptake is less than 0.2% of the injected dose.[14] However, choline accumulation in inflammatory tissue limits the specificity of choline PET for tumour detection.[15]

In the last decades, radiolabelled amino acids are attracting increasing interest in nuclear medicine because amino acid tracers appear to be more specific for brain tumour imaging than tracers like [^{11}C]- and [^{18}F]-labelled choline derivates or 3,4-Dihydroxy-6-[18F]fluoro-l-phenylalanine (^{18}F-DOPA). Results on cellular uptake of O-(2-[18F] fluoroethyl)-l-tyrosine (^{18}F-FET) has been studied in vitro and in vivo already in the 1960's.[16] The uptake mechanism of ^{18}F-FET in malignantly transformed cells can either be active or probably result from increased expression of amino acid transporters or passive, whereby the accumulation is slightly higher in tumour tissue with a disrupted blood-brain barrier. In contrast to ^{18}F and ^{11}C-choline, ^{18}F-FET exhibits lower uptake in machrophages and other inflammatory cells.[17,18] Also ^{11}C-methionine, labelled amino acid for PET imaging of central nervous system tumours, showed very good results. But because of short half-life of ^{11}C (20.4 min), this tracer can be used just in the centres with on-site cyclotron. In the last years many articles supported statement that ^{18}F-FET PET/CT is valuable modality for individual treatment decision in patients with low grade gliomas.[19-24] The T98G cells are the most radio resistant cell line available derived from a human glioblastoma multiform tumour.[25] T98G are arrested in G1 phase under stationary phase conditions, so they also exhibit the transformed characteristics of anchorage independence and immortality.[26]

In our previous study[27], we compared the uptake of ^{18}F-FCH and ^{18}F-FDG by T98G cells and fibroblasts; also for evaluation its influence on cellular radiopharmaceutical uptake competition experiments with cold choline were performed.

Aim of this study was to evaluate ^{18}F-FCH and ^{18}F-FET uptake on T98G cell lines derived from a human glioblastoma multiforme tumour.

Material and methods

Cell lines

Human glioblastoma T98G cells were purchased from the European Collection of Cell Cultures (ECACC, Salisbury, UK) and cultured in Eagle's Minimum Essential Medium (EMEM, Euroclone SpA, MI, Italy) supplemented with 10% fetal bovine serum, 100 units/mL penicillin/streptomycin, 2 mM L-glutamine and 0.01% sodium pyruvate at 37°C in a humidified atmosphere of 5% CO_2 in air. Human dermal fibroblasts were used as non-pathological control cell types. Primary cultures of human dermal fibroblasts were derived from biopsies of healthy donors after obtaining informed consent. Primary cultures of fibroblasts were cultured in Dulbecco's modified Eagle's medium (DMEM, Euroclone SpA, MI, Italy) supplemented with 10% fetal bovine serum, 100 units/mL penicillin, 100 g/mL streptomycin, 2 mM L-glutamine at 37°C in a humidified atmosphere of 5% CO_2 in air. Stock cultures of both cell lines were maintained in exponential growth as monolayers in 25 cm^2 Corning plastic tissue-culture flasks (Sigma-Aldrich, St Louis, MO, USA).

Radioactive tracer incubation

^{18}F-FCH and ^{18}F-FET were obtained from IASON GmbH (Graz-Seiersberg, Austria). Synthesis of ^{18}F-FCH was performed as follows: The precur-

sor was reacted with ^{18}F and the intermediate was evaporated via a solid phase cartridge. After the gas phase reaction, the product was trapped and purified by solid phase cartridges and passed through a sterilized filter, synthesis of ^{18}F-FET was performed as follows: The precursor (in acetonitrile) was reacted with ^{18}F. After ^{18}F incorporation, acetonitrile was removed under pressure, and hydrolysis was carried out with 1 M HCl. The final solution was neutralized and purified by solid phase cartridges and passed through a sterilized filter.

Cells, seeded at a density to obtain 2 x 10^5 cells per flask when radioactive tracers were administered, grew adherent to the plastic surface at 37°C in 5% CO_2 in complete medium. Radioactive tracer experiments were performed 20-22 hours post-seeding in order to use the cells in the exponential phase of growth. The medium was renewed before performing studies. Cells were incubated at 37°C with 100 kBq (100 µL) equimolar amounts of ^{18}F-FCH or ^{18}F-FET, added in 2 mL of medium in each flask for varying incubation times (20, 40, 60, 90, 120 min for ^{18}F-FCH; 20, 40, 60, 80, 100, 120 min for ^{18}F-FET) under 5% CO_2 gaseous conditions. For experiments with ^{18}F-FCH and ^{18}F-FET, radiotracer incubation was done in complete medium. Control samples underwent the same procedure as other samples, but they were incubated with 100 µL of saline instead of a radiotracer.

Cell kinetic studies and uptake evaluation

The cellular radiotracer uptake was determined with a 3 x 3'' NaI(Tl) pinhole 16 x 40 mm gamma counter (Raytest, Straubenhardt, Germany). All measurements were carried out under the same counting position along with a standardized source to verify the counter's performance and the data were corrected for background and decay. Total radioactivity was counted when the radiotracer was added to the medium in each flask (time 0). After 20, 40, 60, 90, 120 min for ^{18}F-FCH and 20, 40, 60, 80, 100, 120 min for ^{18}F-FET from time 0, the medium was harvested, the cells were rapidly washed three times with 1 mL of phosphate-buffered saline (PBS) and radiopharmaceutical uptake for each sample was assessed. All experiments were carried out in duplicate and repeated three times. The uptake measurements are expressed as the percentage of the administered dose of tracer per 2 x 10^5 cells after correction for negative control uptake (flasks containing no cells with complete medium and incubated with radiopharmaceutical).

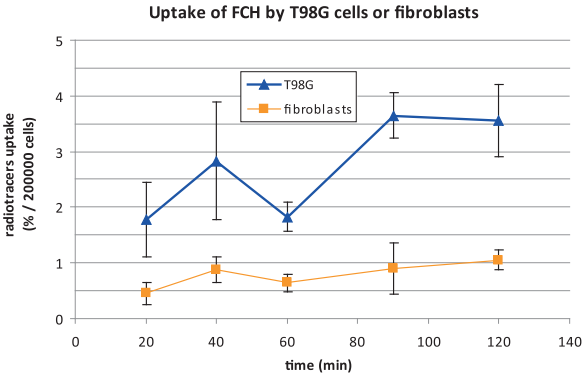

FIGURE 1. Uptake of ^{18}F-methyl-choline (^{18}F-FCH) by T98G cells and human dermal fibroblasts.

Cell viability assay

At the end of quantitative gamma spectrometry, adherent cells were harvested with 1% trypsin-EDTA solution and supernatants with adherent cells were counted with Burker's chamber. Trypan Blue dye assay was performed to assess cell viability as standard protocol.

Statistical analysis

In vitro binding experiments were conducted in duplicate and repeated three times. Data (expressed as mean values of % uptake of radiopharmaceuticals) were compared using parametric or non-parametric tests as appropriate. Differences were regarded as statistically significant when $p<0.05$. All values are expressed as mean values with confidence interval CI 95% and report the uptake of radiotracers as a function of the incubation period. All values are shown as a percentage of the administered dose per 200,000 cells (mean ± CI 95%). Therefore, if error bars on the Y axis do not overlap, the two points are considered significantly different.

Results

Radiopharmaceuticals binding assay

A significant uptake of ^{18}F-FCH was seen in T98G cells after 60 minutes, with a percentage of uptake of 1.8 ± 0.3%, 3.6 ± 0.4% and 3.6 ± 0.6% at 60, 90 and 120 min respectively. Human dermal fibroblasts did not seem to accumulate ^{18}F-FCH specifically; at each incubation time the percentage of the administered dose in the cells was lower than 1%. Human dermal fibroblast uptake was significantly lower than in the T98G cell uptake in all incubation times (Figure 1).

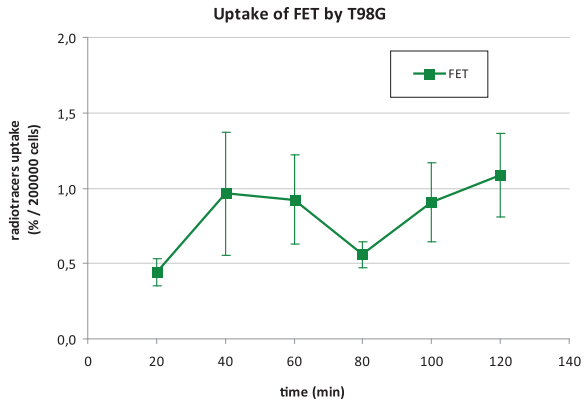

FIGURE 2. Uptake of ^{18}F-ethyl-tyrosine (^{18}F-FET) by T98G cells.

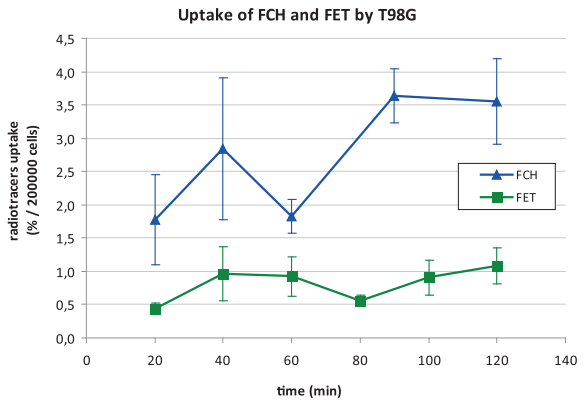

FIGURE 3. Uptake of ^{18}F-methyl-choline (^{18}F-FCH) and ^{18}F-ethyl-tyrosine (^{18}F-FET) by T98G cells.

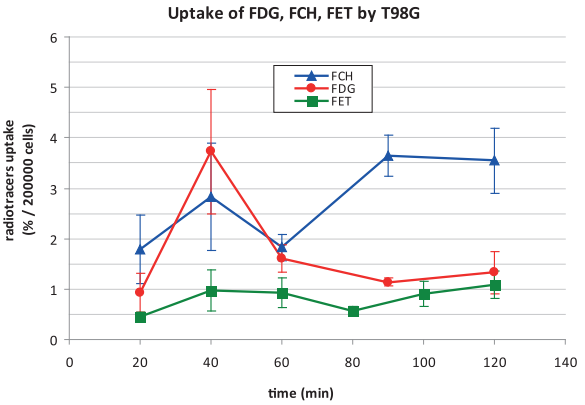

FIGURE 4. Uptake of ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{18}F-methyl-choline (^{18}F-FCH) and ^{18}F-ethyl-tyrosine (^{18}F-FET) by T98G cells.

Figure 2 shows the kinetic uptake of ^{18}F-FET by T98G cells. Despite the trend represented by the curve, the uptake is quite low in terms of radiotracer uptake (% / 200000 cells).

Figure 3 shows that the uptake by T98G cells is increased for ^{18}F-FCH in comparison to ^{18}F-FET. The trend of the two kinetic curves are quite different: the uptake by T98G cells is increased for ^{18}F-FCH over ^{18}F-FET and the accumulation kinetic is not superimposable (see discussion).

Figure 4 illustrates the comparison of ^{18}F-FDG (data derived from our previous study[27], ^{18}F-FCH and ^{18}F-FET uptake in T98G cells. At 40 min and at the following time points there is not overlapping of the confidence bars for ^{18}F-FDG and ^{18}F-FET, and the ^{18}F-FET uptake is always lower than ^{18}F-FDG. ^{18}F-FCH uptake at time points after 60 min, is higher in comparison to the other radiopharmaceuticals.

As a negative control, flasks containing medium without cells were incubated under the same conditions and did not show a significant uptake of radiotracers.

Cell viability

Exposure to the gaseous mixture was maintained throughout the experiment and the cells' viability was calculated to be approximately 90% under all experimental conditions (data not shown).

Discussion

Our research data on T98G human glioblastoma cell lines underscores the affinity of ^{18}F-FET for neoplastic tissue, confirming its potential as a viable oncological PET marker. However, two aspects need to be discussed.

The percentage uptake of ^{18}F-FET in comparison to ^{18}F-FCH was lower by a factor of more than 3. Furthermore, both tracers showed a lower uptake of radioactivity under 60 minutes in comparison to values previously reported for ^{18}F-FDG.[2]

A thorough literature search did not find any studies with direct comparisons between ^{18}F-FCH and ^{18}F-FET uptake in glioma cell cultures. However, papers related to in vivo uptake in experimental rat gliomas indicate a higher accumulation of ^{18}F-FET in terms of Standard Uptake Value (SUV) as seen in both transplanted C6[28] or F98 glioma models[29,30] in comparison to radio-labelled choline. Despite the different amounts of ^{18}F-FCH and ^{18}F-FET taken up by the same cell culture, the in vitro kinetic uptake is quite similar. ^{18}F-FET did show a more rapid initial uptake up to 40 minutes and ^{18}F-FCH showed a more progressive, continuous rise reaching a maximum activity plateau after

90 minutes. Several factors render the comparison between our results and data found in the literature difficult, due to the differing characteristics of our T98G cells and other experimental cell lines. In particular, the accumulation kinetics of ^{18}F-FET in T98G cells is quite different from that described in the 9L cancer cell line, where a wash-out is observable after 60 min of incubation.[31] This phenomenon is less evident in F98 cell culture, with an initially fast uptake, peaking at 10 min, and followed by a nearly constant or slow wash-out rate during the incubation period of 60 min.[32] On the other hand, Habermeier *et al*. described a progressive accumulation of non-radioactive FET in a NL229 human glioblastoma line up to 4 hours.[33]

Both Hebermaier *et al*.[33] and Heiss *et al*.[34] tested the release of FET. Heiss *et al*.[34] demonstrated a quick efflux of ^{18}F-FET from porcine SW707 colon cancer cells, only 7% of the original activity remained in the experimental cells after 6 min incubation time, when the culture medium was replaced with a new tracer-free medium. Different results were reported by Habermeier *et al*.[33] demonstrating that, although ^{18}F-FET is not incorporated into proteins, an intracellular metabolism could lead to another impermeable derivative trapped within the glioma cells. This would suggest an asymmetry of intra- and extracellular recognition by LAT1. The ^{18}F-FCH kinetic pattern in our study was quite similar to that seen in 9L glioma cells[35], both in the normoxic or hypoxic conditions, reaching maximum activity at 120 minutes. Bansal *et al*.[35] reported a negligible washout of ^{18}F-FCH of about 13% after 2 hours in the release experiments because this radiopharmaceutical remains trapped in the cells as phospho-FCH. This demonstrates the slow rate of dephosphorylation. Conversely, apparent discrepancies between our in vitro observations and the in vivo glioma rat model emerged, both in terms of relative uptake and tracer kinetics. These mismatches could be explained by different causes, including radiotracer accumulation detected by the external imaging device or direct measurement of the pathological specimen, which provides information not only of the true tumour uptake but also of the inflammatory cells. In this setting, ^{18}F-FET accumulates predominantly in the tumour rather than in inflammatory cells, differing from ^{11}C-MET and suggesting that different subtypes of the L system are involved.[36] Contrarily, ^{18}F-FCH accumulation has been demonstrated in brain radiation injuries and in murine atherosclerotic plaques - probably mediated by macrophages - as well as in a turpentine-induced sterile abscess.[37,38] In a rat model of acute brain injury (cryolesion and proton-induced necrosis) ^{18}F-FET uptake was mainly due to the disruption of the blood-brain-barrier while ^{18}F-FCH was additionally taken up by inflammatory cells.[39] Similarly, a comparison of ^{18}F-FCH and ^{18}F-FET in a rat glioma radionecrosis indicated ^{18}F-FET as the superior discriminant between viable tumour and inflammatory changes[30], although evidence of increased ^{18}F-FET uptake in perilesional reactive astrogliosis after radiotherapy could lead to an overestimation of tumor size.[40]

Conclusions

The in vitro model used in these experiments allows direct comparison of different radiopharmaceuticals as potential candidates for neuro-oncological PET imaging. The results obtained indicate a superiority of ^{18}F-FCH in terms of absolute uptake and in obtaining an optimal target to non-target ratio in the brain, whereas the major limitation of ^{18}F-FDG is its physiological parenchymal uptake. However, a direct translation to clinical application is hampered by certain conflicting results reported in the literature. ^{18}F-FET could be more useful in the presence of reparative changes after therapy, where the higher affinity of ^{18}F-FCH to inflammatory cells makes it more difficult to discriminate between tumour persistence and non-neoplastic changes. Additional studies on the influence of inflammatory tissue and radionecrotic cellular components on radiopharmaceutical uptake will be necessary to elucidate these topics.

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4.7. Metastatic prostate cancer proven by 18F-FCH PET/CT staging scan in patient with normal PSA but high PSA doubling time.

Hodolič M, Maffione AM, Fettich J, Gubina B, Cimitan M, Rubello D.

Clin Nucl Med. 2013 Sep;38(9):739-40.; IF: 2.857

Case report:

A 59-year-old man presented with frequent urination. Six months ago, his prostate-specific antigen (PSA) was 1.56 ng/mL; currently it is 3.5 ng/mL (PSAdt = 6 months; PSAve = 0.19 ng/mL/months). Biopsy revealed aggressive prostate cancer (Gleason score 5 + 5). Staging with ^{18}F-FCH PET/CT demonstrated lymph node metastasis. After 6 months of hormonal therapy with goserelin, PSA decreased to 0.38 ng/mL. A ^{18}F-FCH PET/CT restaging scan demonstrated a global reduction of ^{18}F-FCH lesion uptake with disappearance of some mediastinal and iliac pelvic lymph node activity.

Conclusion:

PSA doubling time may be an important predictor for prostate cancer spreading. It should be taken into account by a urologist for referring patients to ^{18}F-FCH PET/CT scan in case of biochemical relapse after radical prostatectomy, as well as for initial staging of patients with prostate cancer disease.

Metastatic Prostate Cancer Proven by ^{18}F-FCH PET/CT Staging Scan in Patient With Normal PSA but High PSA Doubling Time

Marina Hodolič, MD, Anna Margherita Maffione, MD,† Jure Fettich, MD,* Borut Gubina, MD,‡ Marino Cimitan, MD,§ and Domenico Rubello, MD†*

Abstract: A 59-year-old man presented with frequent urination. Six months ago, his prostate-specific antigen (PSA) was 1.56 ng/mL; currently it is 3.5 ng/mL (PSA doubling time = 6 months; PSA velocity = 0.19 ng/mL/mo). Biopsy revealed aggressive prostate cancer (Gleason score 5 + 5). Staging with ^{18}F-fluorocholine PET/CT (^{18}F-FCH PET/CT) demonstrated lymph node metastasis. After 6 months of hormonal therapy with goserelin, PSA decreased to 0.38 ng/mL. A ^{18}F-FCH PET/CT restaging scan demonstrated a global reduction of ^{18}F-FCH lesion uptake with disappearance of some mediastinal and iliac pelvic lymph node activity.

Key Words: prostate cancer, PSA doubling time, fluorocholine PET/CT, staging

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From the *Department of Nuclear Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia; †Department of Nuclear Medicine, PET/CT Centre, Santa Maria della Misericordia Hospital Rovigo, Rovigo, Italy; ‡Department of Urology, University Medical Centre Ljubljana, Ljubljana, Slovenia; and §Department of Nuclear Medicine, National Cancer Institute CRO IRCCS, Aviano, Italy.

Conflicts of interest and sources of funding: none declared.
M.H. and A.M.M. contributed equally to the manuscript.

Reprints: Anna Margherita Maffione, MD, Santa Maria della Misericordia Hospital Rovigo, Via Tre Martiri 140, 45100 Rovigo, Italy. E-mail: maffione.anna@azisanrovigo.it.

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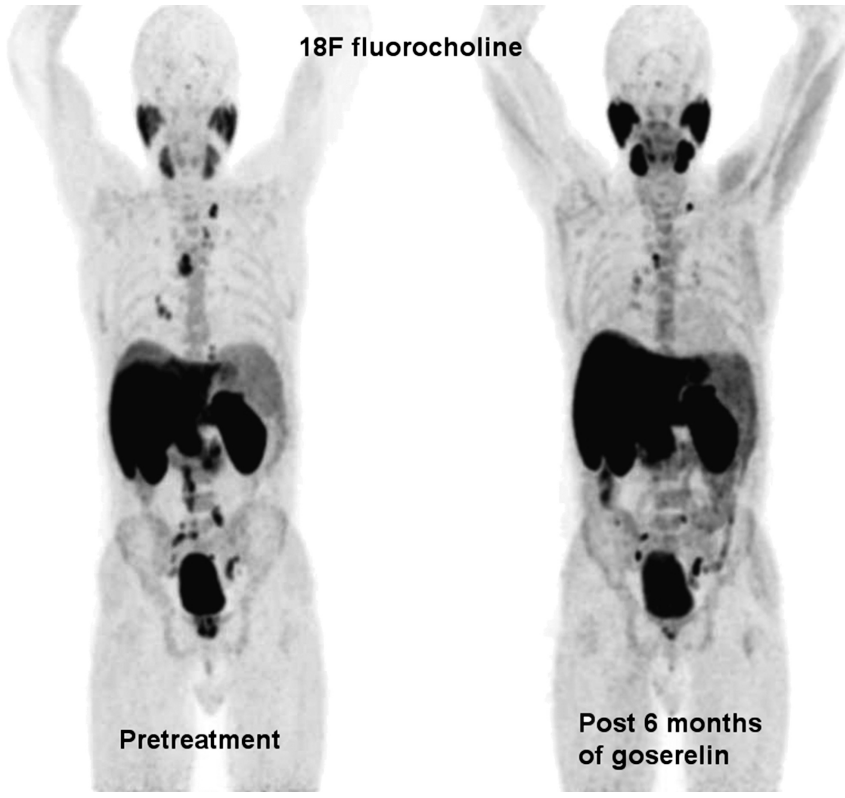

FIGURE 1. A 59-year-old man was referred to a urologist in December 2011 because of frequent urination (approximately twice per hour). On digitorectal examination, the prostate was enlarged with hard structures bilaterally, predominantly on the right side. Routine blood examination revealed PSA 3.5 ng/mL. Previous PSA level, on May 2011, was 1.56 ng/mL (PSA doubling time = 6 months; PSA velocity = 0.19 ng/mL/mo). Ultrasound showed a hypoechogenic prostate gland, mostly in the right lobe, with prostate volume 38 mL. Prostate adenocarcinoma with Gleason score 10 (5 + 5) was pathologically proven (positive 8/8 specimens). A staging ^{18}F-FCH PET/CT scan was then performed by means of a Siemens Biograph mCT PET/CT scanner. The patient fasted for 10 hours prior to the scan and ^{18}F-FCH (IASOcholine) was injected i.v. (250 MBq, according to the weight of the patient). The patient rested for approximately 1 hour. Whole-body acquisition was performed, 2 minutes per bed position, from the base of the skull to midthigh (9 bed positions). Whole-body images were presented in the usual transaxial, coronal, and sagittal planes. Increased ^{18}F-FCH uptake within the prostate gland and multiple paraaortic and iliac lymph nodes was observed, as well as at the left laterocervical, lung hilar, and mediastinal lymph nodes. Hormonal therapy with goserelin was subsequently started. In June 2012, PSA level decreased to 0.38 ng/mL. After 6 months of hormonal therapy, ^{18}F-FCH PET/CT restaging scan was performed. Global reduction of ^{18}F-FCH uptake within lesions and disappearance of some mediastinal and iliac pelvic lymph nodes were assessed. PET/CT may become a routine imaging procedure in patients with prostate cancer disease: for staging of prostate cancer disease (in patients with biopsy-proven prostate cancer), for localizing recurrence of prostate cancer disease (in case of biochemical relapse) as well as for follow-up of patients with prostate cancer disease on hormonal treatment.[1,2] Development of both local and metastatic disease have been shown to occur with normal PSA levels. This happens almost exclusively in patients with poorly differentiated prostate tumors.[3–5] PSA doubling time may be an important predictor for prostate cancer spreading. It should be taken into account by a urologist for referring patients to ^{18}F-FCH PET/CT scan in case of biochemical relapse after radical prostatectomy,[6–8] as well as for initial staging of patients with prostate cancer disease.

4.8 Unusual F-18 choline uptake in penile metastasis from prostate cancer.

Hodolič M, Fettich J, Cimitan M, Kragelj B, Goldsmith SJ.

Clin Nucl Med. 2012 Apr;37(4):e89-90.; IF: 2.955

Case report:

We present a prostate cancer patient with unusual ^{18}F-FCH uptake in a penile metastasis from prostate cancer. Metastasis from prostate adenocarcinoma to the bulbus and corpus of penis was identified with ^{18}F-FCH during follow-up, 3 years after the initial diagnosis.

Conclusion:

Despite rich vascularization and vascular communication between the penis and the prostate, metastatic involvement of the penis is relatively infrequent. The powerful imaging modality ^{18}F-FCH PET/CT improves assessment of clinically silent sites of recurrence.

Unusual F-18 Choline Uptake in Penile Metastasis From Prostate Cancer

Marina Hodolič, MD, PhD, Jure Fettich, MD, PhD,* Marino Cimitan, MD,† Borut Kragelj, MD,‡ and Stanley J. Goldsmith, MD§*

Abstract: Functional imaging of prostate carcinoma is important especially for restaging of the disease in the case of biochemical relapse. The powerful imaging modality F-18 choline PET/CT (FCH PET/CT) improves assessment of clinically silent sites of recurrence. Despite rich vascularization and vascular communication between the penis and the prostate, metastatic involvement of the penis is relatively infrequent. We present a prostate cancer patient with unusual FCH uptake in a penile metastasis from prostate cancer. Metastasis from prostate adenocarcinoma to the bulbus and corpus of penis was identified with FCH during follow-up, 3 years after the initial diagnosis.

Key Words: F-18 choline PET/CT, prostate cancer, penile metastasis

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From the *Department for Nuclear Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia; †Institute for Nuclear Medicine, National Cancer Institute CRO Aviano, Aviano, Italia; ‡Department for Radiotherapy, Onkološki Inštitut Ljubljana, Ljubljana, Slovenia; §Division of Nuclear Medicine and Molecular Imaging, New York-Presbyterian Hospital-Weill Cornell Medical Center, New York, NY.

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Reprints: Marina Hodolič, MD, PhD, Department for Nuclear Medicine, University Medical Centre Ljubljana, Zaloška cesta 7, 1525 Ljubljana, Slovenia. E-mail: marina.hodolic@kclj.si.

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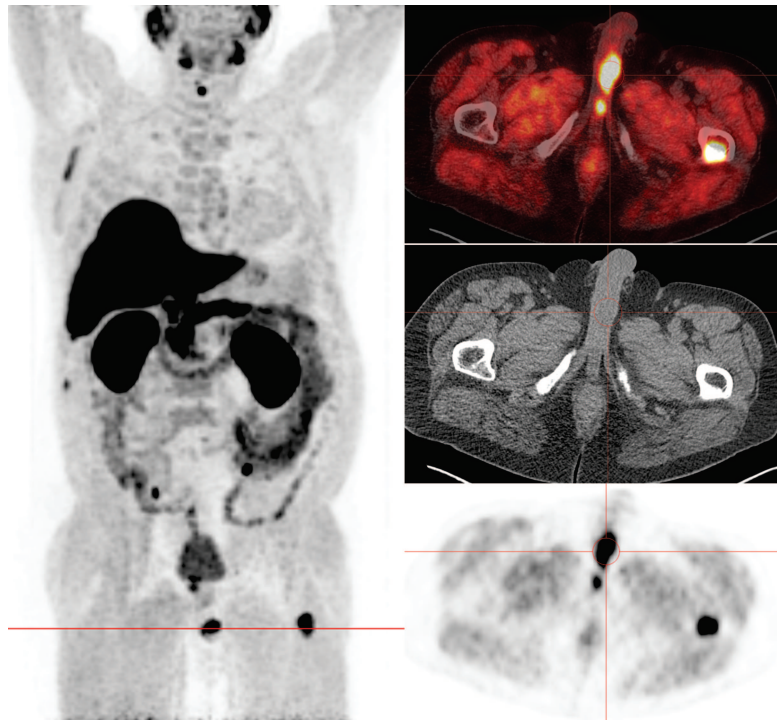

FIGURE 1. Biochemical recurrence occurs in 15% to 77% of patients during the first 5 years after surgery.[1,2] Local recurrence may invade rectum, bladder, and lower ureters. Moreover, prostate carcinoma may metastasize to other sites in the body. Lymph nodes and bone[3] represent the most common target; however, involvement of other organs, especially the penis, is very rare.[4–8] A 60-year-old man was evaluated in the assessment of suspected prostate cancer. Final diagnosis of adenocarcinoma of prostate was confirmed with a Gleason score of 7 (3 + 4). MRI showed enlarged right iliac lymph node. The patient underwent hormonal therapy and later on definitive radiation treatment. Because of a persistent increase in serum prostate specific antigen (PSA), which was suspicious for distant recurrence, the patient had F-18 choline PET/CT scan (FCH PET/CT). There was increased FCH uptake (IASOcholine) in the right lobe of prostate and in multiple skeletal sites, specifically cervical and thoracic spine, several ribs bilaterally, the left femur, and a few pelvic foci. Increased tracer uptake was seen in subcentimeter paravesical lymph node and in the bulbus and corpus of the penis. Pathologic FCH uptake in the penis was confirmed histopathologically as metastatic prostate cancer. Radiotherapy of penile secondaries as well as hormonal therapy was planned.

4.9. Incidental detection of Leydig cell tumor via fluorine-18-Choline PET/CT in a patient with recurrent prostate cancer disease.

Cimitan M, Hodolič M, Maffione AM, Borsatti E, Urso C, Colletti PM, Rubello D.

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Case report:

We report a case of a 62-year-old man with biochemical recurrence of prostate cancer disease, investigated by ^{18}F-FCH PET/CT. ^{18}F-FCH PET/CT demonstrated focal increased uptake of ^{18}F-FCH inside the right testis, suggestive for distant recurrent disease. On testis removal, a Leydig cell tumour of 2.5 cm in diameter was unexpectedly found.

Conclusion:

^{18}F-FCH PET/CT may demonstrate tumours other than prostate cancer.

Incidental Detection of Leydig Cell Tumor Via Fluorine-18-Choline PET/CT in a Patient With Recurrent Prostate Cancer Disease

Marino Cimitan, MD, Marina Hodolič, MD,† Anna Margherita Maffione, MD,‡ Eugenio Borsatti, MD,* Carmelo Urso, MD,§ Patrick M. Colletti, MD,¶ and Domenico Rubello, MD‡*

Abstract: We report a case of a 62-year-old man with biochemical recurrence of prostate cancer disease, investigated by fluorine-18-Choline (^{18}F-FCH) PET/CT. ^{18}F-FCH PET/CT demonstrated focal increased uptake of ^{18}F-FCH inside the right testis, suggestive for distant recurrent disease. On testis removal, a Leydig cell tumor of 2.5 cm in diameter was unexpectedly found. ^{18}F-FCH PET/CT may demonstrate tumors other than prostate cancer.

Key Words: fluorocholine, PET/CT, incidental findings, seminoma, Leydig cell tumor

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From the *Nuclear Medicine Unit, National Cancer Institute (IRCCS)—CRO Aviano, Milan, Italy; †Nuclear Medicine Department, University Medical Centre Ljubljana, Ljubljana, Slovenia; ‡Nuclear Medicine Department, Hospital S. M. della Misericordia of Rovigo, Rovigo, Italy; §Pathology Unit, Hospital S. M. Annunziata, Florence, Italy; and ¶Department of Radiology, University of Southern California, Los Angeles, CA.

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Reprints: Anna Margherita Maffione, MD, Santa Maria della Misericordia Hospital Rovigo, Via Tre Martiri 140, 45100 Rovigo, Italy. E-mail: maffione.anna@azisanrovigo.it.

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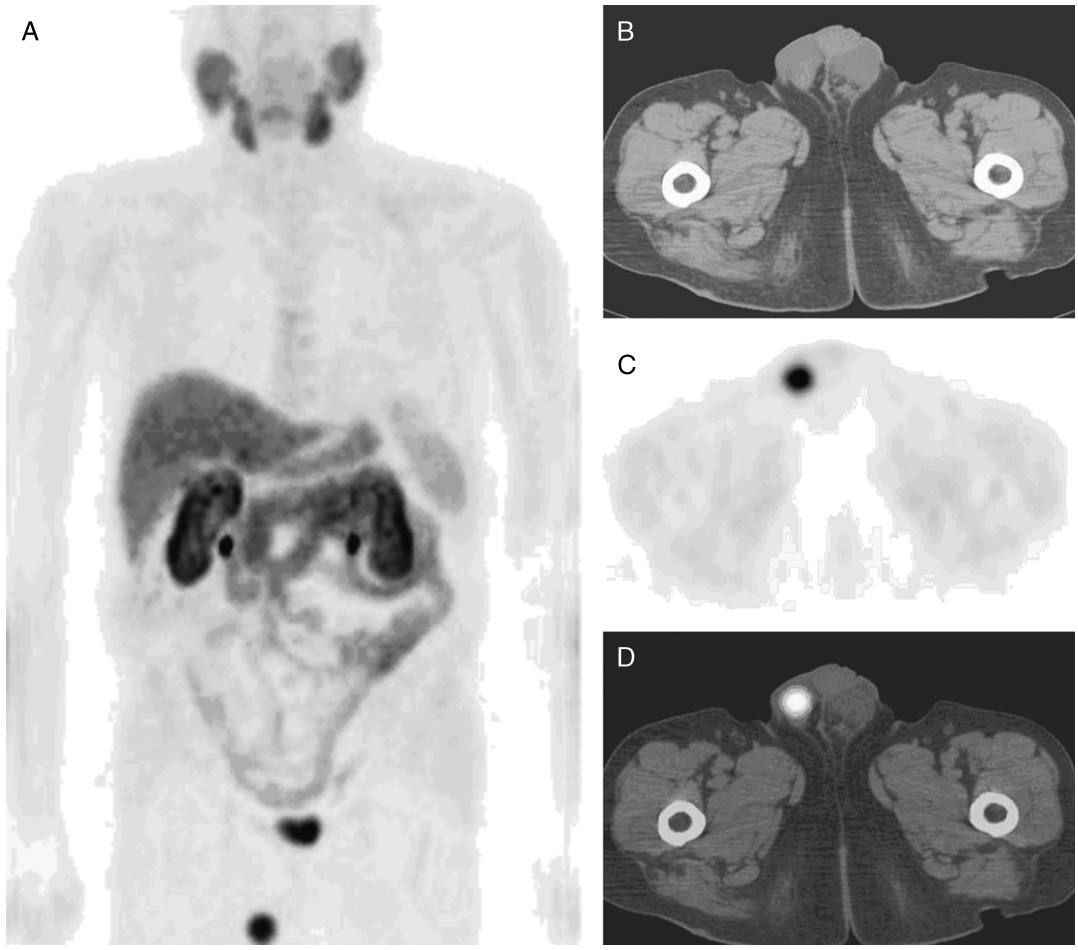

FIGURE 1. We report a case of a patient referred to fluorine-18-Choline (^{18}F-FCH) PET/CT for biochemical recurrence of prostate cancer showing a second non-prostate malignant tumor. Whole-body PET/CT was performed with a GE Discovery LS PET/CT scanner, 45–60 minutes after injection of 3.2 MBq/kg of IASOcholine (^{18}F-fluoromethylcholine) from IASON Graz, Austria. Fused PET/CT late images were analyzed. Semiquantitative maximum standardized uptake values (SUV) were calculated. Clinical data were interpreted with PET/CT data. From October 1993 to September 1994, a 62-year-old man has been followed for moderately increased serum PSA levels ranging from 9.9 to 13.1 ng/mL. In September 1994, he underwent prostate biopsy which revealed a well-differentiated prostate cancer (Gleason score 3 + 2). Radical prostatectomy confirmed a well-differentiated prostate tumor (Gleason score 2 + 2). After prostatectomy, serum PSA levels remained below 0.2 ng/mL for 5 years. Between September 1999 and June 2004, serum PSA level increased to 2.49 ng/mL, suspicious for prostate cancer recurrence. In July 2004, bone scan and CT were negative for bone and lymph node metastases, so the patient was referred to FCH PET/CT. PET/CT scans demonstrated a focal ^{18}F-FCH uptake (SUV_{max} 9.9) in the right testis (**A**, MIP; **B**, CT; **C**, ^{18}F-FCH PET; **D**, ^{18}F-FCH PET/CT) thought to be metastasis from prostate cancer. On testis removal, a Leydig cell tumor 2.5 cm in diameter was found. After orchiectomy, PSA increased to 4.44 ng/mL, but a further ^{18}F-FCH PET/CT in November 2005 did not show pathological findings consistent with prostate cancer relapse. The final conclusion was that PSA increased due to local recurrence of prostate cancer, and the patient was referred for local salvage radiotherapy. This patient had a low risk to develop distant recurrence because Gleason score was 2 + 2 and PSA relapsed 5 years after prostatectomy. However, the possibility that prostate cancer may spread in the testis and penis had been reported in the literature.[1,2]

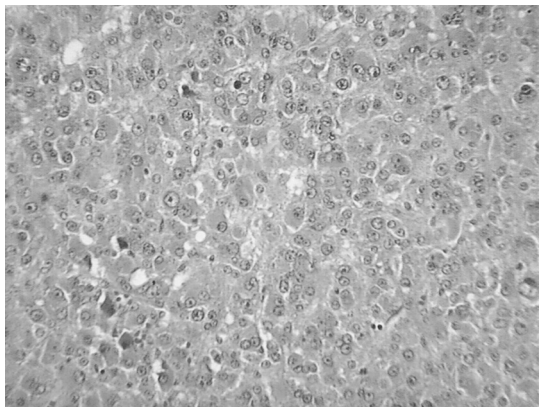

FIGURE 2. H&E pathologic specimen showed solid growth of cells with abundant cytoplasm and round or oval nuclei with evident nucleoli. Original magnification ×200. PET/CT using ^{18}F-FCH is increasingly used in the evaluation of patients with prostate cancer, mainly when biochemical recurrence occurs. The efficiency of ^{18}F-FCH PET/CT to detect recurrent prostate disease increases when relapsing PSA is more than 2 ng/mL or when PSA doubling time is less than 10 months.[3,4] Also, tumor disease should be considered when PSA relapses within 1 year, PSA doubling time is less than 6 months, and Gleason score is above 7.[5,6] ^{18}F-FCH has been studied in a variety of malignancies. In a recent systematic review article of ^{18}F-FCH[7] in the management of patients with tumors other than prostate cancer, comprising 52 studies and 1800 patients, ^{18}F-FCH PET/CT demonstrated uptake in brain tumors, head and neck tumors,[8] thoracic tumors (lung and mediastinal), hepatocellular carcinoma, gynecologic malignancies (including breast tumors), bladder and upper urinary tract tumors, and bone and soft-tissue tumors.

4.10. Early and Delayed 18F-FCH PET/CT Imaging in Parathyroid Adenomas.

Vellani C, Hodolič M, Chytiris S, Trifirò G, Rubello D, Colletti PM.

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Case report:

We report the case of a 43-year-old man with early ^{18}F-FCH uptake in a cystic parathyroid adenomas with delayed washout at 60 minutes negative on conventional nuclear medicine imaging modalities.

Conclusion:

^{18}F-FCH PET/CT is used predominantly in patients with prostate cancer and is under investigation in parathyroid adenomas.

Early and Delayed ^{18}F-FCH PET/CT Imaging in Parathyroid Adenomas

Cecilia Vellani, MD, Marina Hodolič, MD,†‡ Spyridon Chytiris, MD,§ Giuseppe Trifirò, MD,* Domenico Rubello, MD,|| and Patrick M. Colletti, MD#*

Abstract: Preoperative localization with ^{99m}Tc-sestaMIBI or ultrasound is a common prerequisite for successful minimally invasive parathyroid adenoma (PA) surgery. SPECT/CT with ^{99m}Tc-sestaMIBI and PET/CT with ^{18}F-FCH offer the possibility of attenuation correction and coregistration of functional and anatomical images providing more accurate PA localization. ^{18}F-FCH PET/CT is used predominantly in patients with prostate cancer and is under investigation in PA. We report the case of a 43-year-old man with early FCH uptake in a cystic PA with delayed washout at 60 minutes.

Key Words: CT, FCH, MIBI, PA, PET

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From the *Nuclear Medicine Unit, Fondazione Salvatore Maugeri, Pavia, Italy; †Nuclear Medicine Research Department, Graz, Austria; ‡Medical Faculty, Palacký University Olomouc, Czech Republic; §Internal Medicine & Endocrinology Unit, Fondazione Salvatore Maugeri, Pavia; ||Department of Nuclear Medicine, Rovigo Hospital, Rovigo, Italy; and #Department of Radiology, Division of Nuclear Medicine, University of Southern California, Los Angeles, CA.

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Correspondence to: Patrick M. Colletti, MD, Division of Nuclear Medicine, University of Southern California, Keck Medical Center of USC, 1500 San Pablo Street, 2nd Floor, Imaging, Los Angeles, CA 90033. E-mail: colletti@med.usc.edu.

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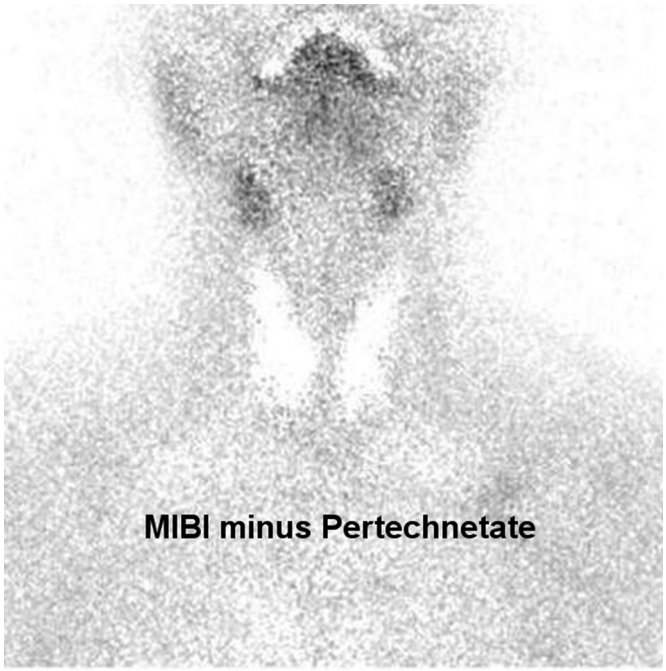

FIGURE 1. A 43-year-old man with recurring kidney stones and a parathyroid hormone level of 302.4 pg/mL (reference range, 11.5–78.4 pg/mL), calcium 11.0 mmol/L (reference range, 8.5–11 mmol/L), and phosphorus 2.2 mmol/L (reference range, 2.5–4.5 mmol/L) underwent neck ultrasound (US). The US results showed a hypertrophic parathyroid gland characterized by a relevant cystic involution measuring 20 × 10 × 15 mm located behind and laterally to the right thyroid lobe. This cystic component was probably the cause of the hourglass morphology presented by the parathyroid gland. Parathyroid imaging was performed with 72.3 MBq of ^{99m}Tc-pertechnetate followed by a scan at 120 minutes after administration of 483.3 MBq of ^{99m}Tc-sestaMIBI. SPECT/CT of the mediastinum was also performed 150 minutes after ^{99m}Tc-sestaMIBI admiration. The subtraction double-tracer (^{99m}Tc-pertechnetate and ^{99m}Tc-sestaMIBI) parathyroid scan did not show any abnormal uptake.

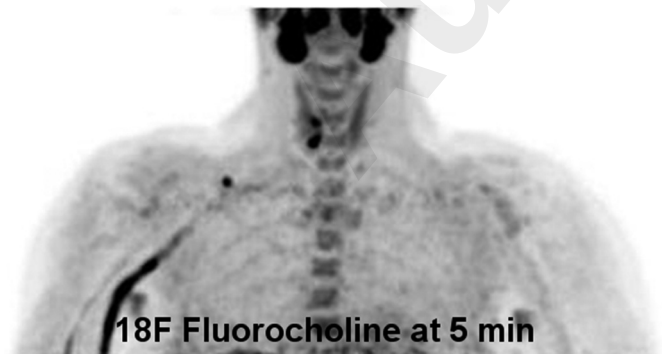

FIGURE 2. One week later, the patient received 160 MBq of FCH. Early (5 minutes after administration) and late (60 minutes after administration) FCH PET/CT scans were performed. Early FCH PET/CT showed intense focal tracer uptake in the cellular peripheral portion of the cystic parathyroid adenoma (PA) as described by US. Surprisingly, this uptake was not seen on the 1-hour FCH PET/CT examination (Fig. 3).

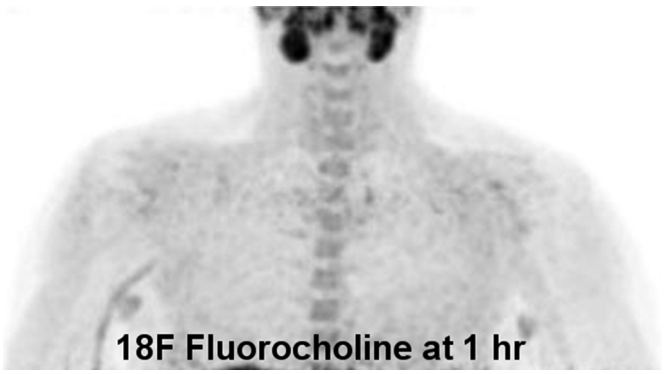

FIGURE 3. The patient underwent right parathyroidectomy and excision of the right thyroid lobe. After surgery, parathyroid hormone was normal at 22.1 pg/mL. Histopathologic findings confirmed the removal of a right PA. FCH PET/CT in a patient with PA.[1–4] This behavior could be explained by PA characteristics including a rich blood supply with rapid radiotracer uptake and washout.[2,5–8]

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5. Conclusions

After many years in which nuclear medicine's role in the evaluation and treatment of patients with prostate carcinoma was limited to nonspecific bone scintigraphy, there have been great strides toward development and clinical applications of PET imaging agents with excellent sensitivity and specificity.

Although prostate carcinoma was sometimes identified with ^{18}F-FDG PET, it was found not to be sufficient to detect all prostate cancer foci.

Currently, the most sensitive registered agent for the detection of intraprostatic tumour, lymph node, and bone involvement appears to be ^{18}F-FCH.

Since ^{18}F has a 2-hour half-life, ^{18}F-FCH can be prepared in regional centres and distributed similar to ^{18}F-FDG. ^{18}F-FCH is commercially available in Europe. A rapid development of ^{18}F-FCH PET/CT in European countries (such as Slovenia and France) led to a higher detection rate of prostate cancer lesions. In the United States, ^{11}C-Choline has been approved by the FDA on a site-by-site basis. Accurate knowledge of the normal biodistribution of ^{18}F-FCH is essential for the correct interpretation of PET/CT images. Delayed or dual-phase imaging after injection of ^{18}F-FCH may improve the performance of ^{18}F-FCH PET for localising malignant areas of the prostate.

^{18}F-FCH PET/CT may be considered a valuable imaging modality in patients with prostate cancer disease. Its main role is in restaging of patients with biochemical recurrence of prostate cancer disease after radical prostatectomy or external beam radiotherapy. Although PET/CT with ^{18}F-FCH has some limitations for the evaluation of prostatic gland/fossa, due to the physiological biodistribution of the radiopharmaceutical agent, in 70–90% of patients with a PSA level >2 ng/mL, independently from the Gleason Score, a focal ^{18}F-FCH uptake could be compatible with local recurrence. For suspected prostate cancer recurrence, a high Gleason score at diagnosis can be associated with positive ^{18}F-FCH PET/CT scan results, regardless of the serum PSA level at the time of imaging. Therefore, the Gleason Score can be considered a robust predictive factor for positive ^{18}F-FCH PET/CT results, even at a very early stage of biochemical failure of prostate cancer, that is, when the PSA level is less than 1 ng/mL. Additionally, PSA doubling time and PSA velocity can influence positivity of ^{18}F-FCH PET/CT. PSA doubling time may be an important predictor for prostate cancer spreading. It should be taken into account by urologist for referring patients to ^{18}F-FCH PET/CT scan. The influence of androgen deprivation therapy on choline uptake in patients with prostate cancer disease has not yet been precisely clarified.

At the same time, ^{18}F-FCH PET/CT is strengthening its position in the initial staging, biopsy target definition, radiotherapy planning as well as therapy monitoring of prostate cancer disease.

^{18}F-FCH PET/CT is used predominantly in patients with prostate cancer but also ^{18}F-FCH PET/CT may demonstrate tumours other than prostate cancer such as parathyroid adenomas, pituitary adenomas and meningeomas. We described incidental ^{18}F-FCH uptake in the head or in the neck, in 1.9% of the ^{18}F-FCH PET/CT performed for staging or restaging of prostate cancer. Such foci should be mentioned in the report, as hyperparathyroidism or meningioma may directly impact on management of a patient with prostate cancer. In case of parathyroid adenomas early ^{18}F-FCH PET/CT acquisition is crucial. In case of brain tumours another such as ^{18}F-FET should also be taken into account, especially because higher affinity of ^{18}F-FCH to inflammatory cells makes it more difficult to discriminate between tumour persistence and non-neoplastic changes. Additionally, we described ^{18}F-FCH uptake in Leydig cell tumour and penile metastases from prostate cancer.

Independently from our results, we must be aware that collaboration between nuclear medicine physicians, radiologists, urologists, oncologists and radiotherapists is crucial in our intention to help prostate cancer patients.

6. Literature

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