Three-phase ^{18}F-fluorocholine PET/CT in the evaluation of prostate cancer recurrence

3-Phasen-PET/CT mit ^{18}F-Fluorcholin zur Evaluation des Prostatakrebsrezidivs

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Keywords

^{18}F-fluorocholine, 3-phase PET/CT, prostate cancer recurrence, rising PSA

Summary

Aim: Contribution of 3-phase ^{18}F-fluorocholine PET/CT in suspected prostate cancer recurrence at early rise of PSA. **Patients, methods:** Retrospective analysis was performed in 47 patients after initial treatment with radiotherapy (n = 30) or surgery (n = 17). Following CT, 10 minutes list-mode PET acquisition was done over the prostate bed after injection of 300 MBq of ^{18}F-fluorocholine. Three timeframes of 3 minutes each were reconstructed for analysis. All patients underwent subsequent whole body PET/CT. Delayed pelvic PET/CT was obtained in 36 patients. PET/CT was interpreted visually by two observers and SUV_{max} determined for suspicious lesions. Biopsies were obtained from 13 patients. **Results:** Biopsies confirmed the presence of cancer in 11 of 13 patients with positive PET for a total of 15 local recurrences in which average SUV_{max} increased during 14 minutes post injection and marginally decreased in delayed scanning. Conversely inguinal lymph nodes with mild to moderate metabolic activity on PET showed a clearly different pattern with decreasing SUV_{max} on dynamic images. Three-phase PET/CT contributed to the diagnostic assessment of 10 of 47 patients with biological evidence of recurrence of cancer. It notably allowed the discrimination of confounding blood pool or urinary activity from suspicious hyperactivities. PET/CT was positive in all patients with PSA ≥ 2 ng/ml (n = 34) and in 4/13 patients presenting PSA values <2 ng/ml. **Conclusion:** ^{18}F-fluorocholine 3-phase PET/CT showed a progressively increasing SUV_{max} in biopsy confirmed cancer lesions up to 14 minutes 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.

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Schlüsselwörter

^{18}F-Fluorcholin, 3-Phasen PET/CT, Prostatakrebs-Rezidiv, PSA-Anstieg

Zusammenfassung

Ziel: Retrospektive Analyse der klinischen Wertigkeit einer 3-Phasen-Fluorcholin(FCH)-PET/CT bei 47 Patienten mit Verdacht auf frühes biochemisches Rezidiv eines Prostatakarzinoms. **Patienten, Methoden:** Die FCH-PET/CT wurde bei Patienten nach initialer Radiotherapie (n = 30) oder Chirurgie (n = 17) durchgeführt. Nach der CT wurden 300 MBq ^{18}F-Fluorcholin appliziert und eine 10 Minuten dynamische PET in List-Mode-Technik über dem Prostatabett aufgenommen. Für die Analyse wurden hieraus drei statische Zeitabschnitte zu je 3 Minuten rekonstruiert. Anschließend erfolgte die Aufnahme der Ganzkörper-PET. Bei 36 Patienten wurde eine zusätzliche Spätaufnahme des Beckens aufgenommen. Die Analyse der PET/CT erfolgte visuell und anhand der SUV_{max} für verdächtige Befunde. Bei 13 Patienten mit positiver FCH PET/CT der Prostataloge wurden Biopsien analysiert. **Ergebnisse:** Histologisch bestätigt wurden 15 Lokalrezidive (4 bilateral) bei 11 von 13 FCH-PET-positiven Patienten. In histologisch gesicherten Rezidiven stieg der SUV_{max} während der ersten 14 Minuten nach Injektion an und fiel anschließend leicht ab. Metabolisch aktive inguinale Lymphknoten zeigten im Gegensatz eine stetige Abnahme des SUV_{max}. Die Drei-Phasen-FCH-PET trug bei 10/47 Patienten entscheidend zur Diagnose bei, da sie die klare Abgrenzung von vaskulärer bzw. Harn-Aktivität gegenüber pathologischen Anreicherungen erlaubte. Bezüglich PSA war die FCH PET/CT bei allen Patienten ≥ 2ng/ml (n = 34) positiv und bei 4/13 <2ng/ml. **Schlussfolgerung:** Die Drei-Phasen-FCH-PET/CT zeigte bei histologisch bestätigten Rezidiven einen initial zunehmenden SUV_{max} während in benignen inguinalen Lymphknoten ein stetiger Abfall zu verzeichnen war. Weiter erwies sie sich als sehr nützlich, um Lokalrezidive von vaskulärer bzw. Urinaktivität zu unterscheiden.

Evaluation of biochemical recurrence of prostate cancer after radical surgery remains a major challenge (10). Recurrence of cancer can be suspected at the earliest rise of PSA (36, 37). It has been shown that even very low PSA values of between 0.01 and 0.1 ng/ml post radical surgery represent a probability for further rise of PSA and tumor recurrence of 67% and that this probability rises to 90% or more at PSA > 0.1 ng/ml (11).

After first line radiotherapy (RT) the definition of biochemical recurrence remains even more challenging. An ASTRO consensus statement of 1997 required the measurement of three consecutive increases of PSA (7) for a definitive diagnosis. More recently, a retrospective analysis of 4800 patients showed that two consecutive PSA increases of at least 0.5 ng/ml each, or a PSA value ≥ 2 ng/ml above nadir would provide sensitivities and specificities for recurrence with values ranging between 64 and 78 % (16). Considering this still rather modest sensitivity and specificity of PSA values for recurrence, it is obvious that the development of reliable imaging techniques remains a high priority to precisely localize recurrences in order to allow for adequate choice of relapse treatment modality.

Endorectal MRI can provide valuable diagnostic information concerning local disease at initial presentation (8, 31). However, the interpretation of MRI after radiotherapy and surgery is difficult due to signal modifications by scar tissue. A higher specificity of MR spectroscopy compared to conventional endorectal MRI in the recurrence situations has been reported (6, 33), although its accuracy has not been clearly established yet. Promising results in the de-

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tection of recurrent prostate cancer have been obtained with different PET tracers (1, 5, 14, 17, 19, 22, 23, 26, 27, 29, 30, 32, 34, 35) such as

- ^{11}C-acetate,
- ^{11}C-choline,
- ^{18}F-fluorocholine and
- anti-^{18}F-FACBC (anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid).

Very recently, results of ^{11}C-choline PET/CT have been published by 5 different groups in recurrent prostate cancer (12, 13, 18, 25, 27). For patients with PSA levels below 2 ng/ml, these studies showed variable PET positivity rates of between 15 and 73%, the overall mean positivity rate being about 33%. Our evaluations and those of another group had shown similar results with ^{11}C-acetate or ^{18}F-fluorocholine in early detection of prostate cancer recurrence (1, 34). PET, in comparison with endorectal MRI and MR spectroscopy, has the advantage of being a whole body examination with the ability to detect also metastases.

^{18}F-fluorocholine has become widely available and is frequently used for evaluation of prostate cancer in patients with biochemical recurrence or in initial staging. However, no consensus exists as to which protocol of PET examination should be applied. A single phase whole body PET, started early after injection of ^{18}F-fluorocholine in order to evaluate the prostate bed before observation of urinary activity may be performed (29). Dual-phase pelvic evaluation performed by adding a late PET acquisition of the prostate bed has been reported as advantageous (5, 19). On the other hand, an earlier report had shown that dynamic PET of ^{11}C-choline showed an increasing uptake in cancer up to 12 to18 minutes after injection (32), suggesting that the early evaluation of the prostate bed could be suboptimal due to submaximal uptake of ^{18}F-fluorocholine in cancer lesions. However, the dynamic of ^{18}F-fluorocholine tumor uptake has not been well defined yet.

Considering that bladder activity from ^{18}F-fluorocholine is generally present at the expected time of maximal tumor uptake as was observed with ^{11}C-choline, we choose to acquire images in 3-phases over the pelvis to better assess the dynamic uptake of the tracer in the prostate. The initial dynamic sequence of images was then compared with findings observed on the subsequent uptake image obtained from whole body imaging. In the majority of the patients, the study was extended with a delayed image of the prostate bed to evaluate the dynamic of late tissue uptake and washout.

Patients, material, methods

This retrospective data analysis has been approved by the Ethical Committee of Geneva University Hospital and was performed in conformance with Swiss legislation regarding patient confidentiality and data protection. All patients provided their written informed consent to the use of ^{18}F-fluorocholine as an unregistered radiopharmaceutical that was authorized for each patient by the Swiss federal authorities (Swissmedic and Federal Office of Public Health, Section of Radioprotection).

Forty-seven patients (Tab. 1) were selected based on their suspected biochemical relapse of cancer after initial RT (n = 30) or radical surgery (n = 17). Initial combined hormone and radiation therapy had been performed in 19 patients and RT alone in 11 patients. Regarding the 17 patients treated initially by surgery, median time between surgery and their PET study was 5.6 years for 13 patients while only 4 patients had their PET study at three to eight months after surgery because of persistently elevated PSA. None of the patients was under hormonal therapy at PET study.

Tab. 1 Characteristics of 47 patients

		RT	surgery
number of patients		30	17
age (years)	mean range	72.3 52–87	66.5 47–74
initial stage	T1 T2 T3 T4 not available	n = 5 n = 5 n = 15 n = 2 n = 3	0 10 6 1 0
Gleason score summed	4–6 (low grade) 7 (intermediate grade) 8–9 (high grade)	n = 15 n = 12 n = 3	8 6 3
PSA at PET (ng/ml)	median range	5.2 1.4–30	1.35 0.4–37.7

^{18}F-fluorocholine, PET/CT scanning

^{18}F-fluorocholine (fluorocholinefluoromethyl-dimethyl-2-hydroxyethylammonium) was prepared according to GMP conditions at the Centre of Radiopharmacy, University Hospital of Zürich, Switzerland (9, 29). All patients received a standard activity of 300 MBq ^{18}F-fluorocholine.

PET studies were performed on two LSO-based PET/CT scanners, a Biograph 16 and a Biograph 64 (Siemens Medical Solutions, Erlangen, Germany). All patients were fasted for at least four hours before ^{18}F-fluorocholine PET study. After bladder voiding, patients underwent an initial CT scan from the mid thigh to skull performed under standard protocol (arms held above the head and flat breathing) using 120 kVp, 90 mAs, 16 × 1.5 collimation, pitch of 0.8 and 0.5 sec per rotation. Under these conditions, the mean effective radiation dose for an adult patient was estimated at 12 mSv, as calculated by the IMPACT CT patient dosimetry calculator (www.impactscan.org/ctdosimetry.htm).

After the CT scan, patients underwent a continuous list-mode PET acquisition of the pelvis during 10 minutes starting immediately at the time of tracer injection. The 10 min list mode data could be used for generating 2 × 5, 5 × 2 and 3 × 3 minutes time frames. We decided to use a partitioning in three image sets of three time intervals of 3 minutes each corresponding to 0–3, 3–6 and 6–9 minutes after injection. Following the list mode acquisition a standard whole-body PET study was performed from the mid thigh to the skull over 7 to 8 bed positions of 3 to 4 minutes each, depending on patient size and weight. An additional late image of 5 minutes of prostate bed was acquired in 36 patients (71%) immediately after whole-body PET (~40 minutes after tracer injection).

Following Fourier rebinning and model-based scatter correction, PET images were reconstructed using two-dimensional iter-

ative normalized attenuation-weighted ordered subsets expectation maximization (NAW-OSEM) (21). The CT-based attenuation map was used to correct emission data. The default reconstruction parameters of four iterations and eight subsets followed by a post-processing Gaussian filter (kernel size 5 mm, full-width at half-maximum) were applied.

PET/CT interpretation was performed by two experienced nuclear medicine physicians who graded the presence of recurrent tumor as positive, equivocal or negative. PET grading was performed according to the typical time course of activity in malignant and benign lesions. Positive lesion: focal hyperactivity above background persistent throughout the examination with a typical kinetic, as shown in this article, based on biopsy confirmed cancer lesions. Negative: Non focal activity equal or inferior to background and vanishing. Equivocal: Lesions not entering into the category of „positive" or „negative". Lymph node biopsies were not obtained, however, they were interpreted as mentioned here and for those considered negative, the indication for biopsy was not given.

Maximum standard uptake value (SUV_{max}) was calculated within regions of interest (ROIs) drawn over focal hyperactivity using standard formula (3). SUV_{max} values were evaluated since widely used in the literature and because they are not dependent on lesion size or operator. Since the two PET/CT used here are from the same provider (Siemens), had been installed simultaneously and that acquisition, treatment protocols and software evaluation were identical, images and SUV calculations were comparable. Furthermore, a Jaszack-phantom based calibration was carried out to ensure compatibility between both scanners. A radiologist interpreted CT for distant sites.

For the assessment and comparison of SUV_{max} time-activity in different tissues (cancer and inguinal lymph nodes) SUV_{max} values were normalized to the first dynamic frame recorded between 0 and 3 minutes after tracer injection by setting this SUV_{max} to 1.0 (100%). This normalization limits potential bias from partial volume effects particularly in small inguinal lymph nodes (28).

Tab. 2 PET results of 47 relapsed patients according to initial treatment and PSA value

	PSA	prostate or prostate bed		locoregional lymph nodes positive	distant sites positive	patients positive	total number of patients
		positive	equivocal				
RT n = 30	< 2	1*				1 (100%)	1
	≥ 2	26	3*	5	5	29 (100%)	29
surgery n = 17	< 2	1		2		3 (25%)	12
	≥ 2	2		1	3	5 (100%)	5
all		30	3**	8	8	38 (81%)	47

* numbers of patients; ** three patients with an equivocal PET result on the prostate bed had a positive PET result either in draining lymph nodes or distant sites

Biopsy and further imaging

Biopsies were performed in patients with local recurrence and no evidence of systemic extensions when salvage RT was indicated. Biopsy results were obtained for 13 patients at relapse after initial RT. Additional evaluation by bone scintigraphy was performed in 27 patients. The CT of PET/CT interpreted by the radiologist and PSA evolution served as reference for distant sites.

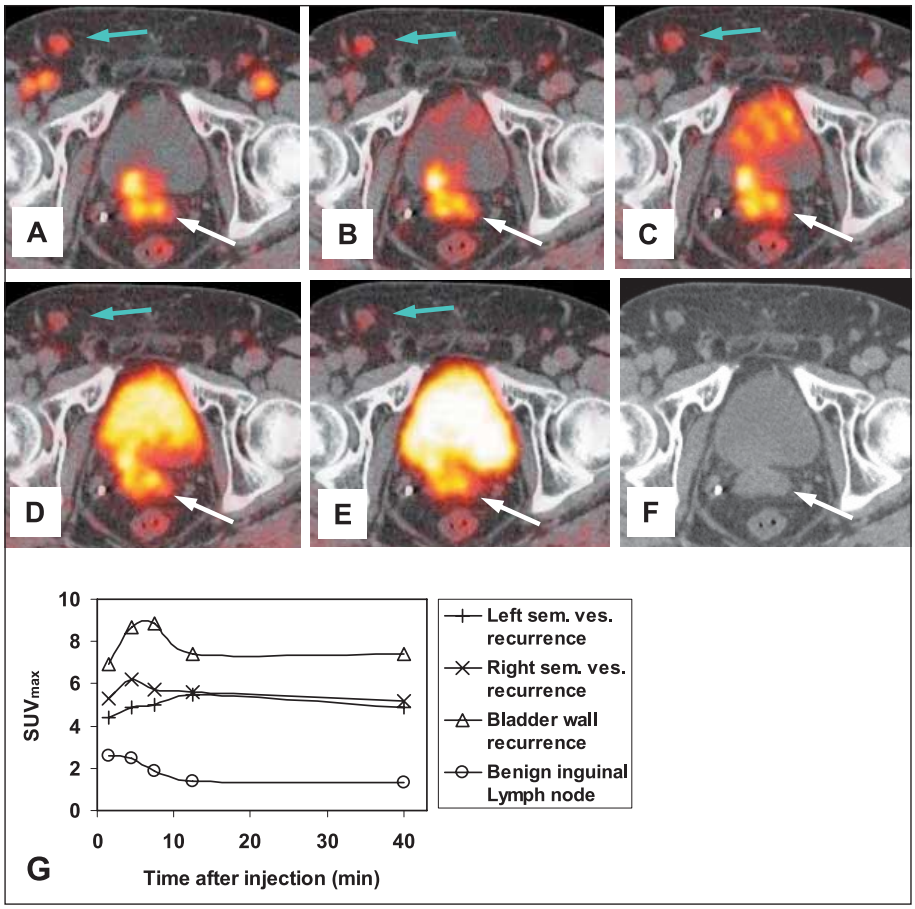

Fig. 1 Three-phase PET/CT display showing dynamic frames A (0–3 min), B (3–6 min) and C (6–9 min post injection), followed by whole body PET (D, 11–14 min p.i.) and delayed scanning (E, ~40 min p. i.), all fused to the initial CT (F). Sequential disappearance of vascular activity (frame A) and appearance of urinary activity (frame C) is observed. Note the differential uptake evolution in suspected cancer lesions (←) compared with the lymph node interpreted as benign (blue arrow) shown below graphically (G).

Statistics

The statistical correlation between positive and negative results of PET and histology were performed for relapsed patients after initial RT using the available results of right and left side prostate biopsies and PET. The inter-category variation kappa test was used for the correlation analysis of negative and positive results on each side (26 pairs from 13 patients). Unweighted direct proportional correlation kappa values were expressed as 0.01–0.59, 0.6–0.79 and 0.8–1.0 and rated (33), a kappa correlation value of 1 indicating perfect agreement between two observation series. The comparison of normalized SUV_{max} at different times post injection between prostate cancer recurrence and benign inguinal lymph nodes activity was performed with the linear regression analysis by means of multivariate linear regression. Since patients' characteristics could be associated with each collected sample, we performed this analysis accounting for the lack of independence between observations. It resulted in 15 clusters, each one representing a patient. An interaction term between the type of tissue (cancer and lymph nodes) and time was introduced in the regression model. This term evaluates the difference of SUV_{max} evolution over time according to the type of tissue. If statistically significant, this term means that as time passes, SUV_{max} evolves differently in cancer or lymph nodes. Analyses were performed using STATA release 10 (Stata Corporation, College Station, Texas). Values of $p < 0.05$ and $p < 0.005$ are considered significant and highly significant, respectively.

Results

This retrospective ^{18}F-fluorocholine PET analysis was performed in 47 patients 30 of whom had been treated initially with RT and 17 by surgery (Tab. 1). All patients except one with initial RT had PET at PSA values of 2 ng/ml or higher (Tab. 2). In contrast, 12 of 17 surgery patients presented PSA values at PET below 2 ng/ml. Metastases were relatively rarely diagnosed in these patients (Tab. 2), probably related to the early evaluation at an overall low PSA value.

Using the criteria of initially increasing and conserved SUV_{max} at late scanning for PET interpretation as cancer recurrence (Fig. 1), 30 of 47 patients where highly suspect of prostate or prostate bed recurrence. When analyzed according to initial treatment (Tab. 2), prostate cancer recurrence after RT was observed in 27 of 30 patients and equivocal in three others. In surgery patients, three local recurrences were diagnosed.

Three-phase PET interpretation of all patients with PSA values equal or higher than 2 ng/ml indicated at least one positive finding for recurrence of cancer. A large majority 28/34 (82%) were PET positive for local recurrence in prostate or prostate bed, while an additional three patients (8%) were equivocal (Tab. 2). In these patients, draining lymph nodes or distant sites were positive in six (18%) and eight patients (24%), respectively.

PET/CT results in patients with PSA value < 2ng/ml were positive in four of 13 patients (31%), two in the prostate bed and two in the draining lymph nodes (Tab. 3). This sensitivity is low. Furthermore, since only a low number of patients was analyzed at PSA < 2 ng/ml, the calculated percent positivity can only be indicative.

Cancer recurrence was confirmed by histology in 11/13 patients who underwent prostate biopsy (Fig. 2, Tab. 3). Histology was positive in needle biopsies in 10 patients. In the 11th patient (patient 26), needle biopsies were negative. However, subsequent surgery performed for urinary obstruction revealed cancer tissue in the surgical specimen. Overall, histology confirmed cancer recurrence in prostate either bilaterally in 4 patients or unilaterally in 7 patients adding to a total of 15 left and/or right-sided recurrences (Tab. 3). None of the 11 bone scintigraphies performed in these patients showed any evidence of bone metastasis.

Two of 13 patients (patients 40 and 57) with a bilateral positive PET after RT were cancer negative by histology. One of these patients (patient 40), having had repeatedly an increasing PSA (up to 3.4 ng/ml at PET), had a subsequent spontaneous PSA regression to 1 ng/ml which has to be considered as normal (5, 6) and PET a false positive. For patient 57, insufficient follow up after a negative biopsy does not allow to give a conclusive interpretation of PET. A third patient (patient 42) was PET positive on both left and right prostate, but biopsy was positive only in one of the three biopsies of the left side while three biopsies from the right side were negative.

patient	PET			biopsy	bone scintigraphy	PSA at PET (ng/ml)
	early	trunk	late			
12	r	r	not done	r	negative	5.1
16	l	l	l	l		7.0
19	r+l	r+l	not done	r+l		6.0
26	l	l	l	l		4.1
27						5.1
28					not done	2.5
31	r+l	r+l	r+l	r+l	negative	16
40*				negative		3.4
42				l		2.8
50				r+l		6.3
54						2.2
56	l	l	l	l	not done	3.0
57	r+l	r+l	r+l	negative	negative	2.8

*after a positive PET examination, PSA decreased from 3.4 ng/ml at PET to 1 ng/ml without any treatment, strongly suggestive of a false positive PET, possibly due to an inflammatory process; l (r): left (right side)

Tab. 3
Results of 13 patients in the post RT situation with suspected recurrence by PET are shown in comparison to histology. When positive, results are differentially given for right side (r), left (l) side. Right and left side positive results are indicated as r+l. Equivocal results are indicated as equiv. n.d.: not done. Early, indicates dynamic PET frames 1 to 3 recoded from 1st to 3rd, 3rd to 6th and 6th to 9th minutes after injection, respectively.

PET and histology showed a good correlation of left or right lobe localization in the 13 patients (Tab. 3) with a highly significant Kappa test ($p < 0.001$) and a correlation value κ of 0.55, rated as moderate. PET showed correlation with histology in 21 of 26 locations (81%, Tab. 2).

For 15 lesions from 11 patients with proven cancer recurrence (Tab. 3), temporal behavior of SUV_{max} values obtained from dynamic PET, the following whole body PET and delayed imaging (Fig. 3A) showed a progressive increase up to 14 minutes post injection and marginal decrease on delayed images. This pattern was confirmed by the normalized SUV_{max} curves of all patients (Fig. 3C).

Uptake of ^{18}F-fluorocholine above background level was observed in inguinal lymph nodes (Fig. 1) in five patients. In the absence of any evidence of cancer recurrence in primary draining lymph nodes (34■, 15) and a benign presentation in CT (small sized nodes, presence of fat tissue), the tracer uptake in such inguinal lymph nodes was considered to be due to non-specific inflammatory processes. Time-activity curves of SUV_{max} of inguinal lymph nodes showed a decreasing activity mostly over the initial dynamic timeframes (Fig. 3B), which is an opposite pattern from the one observed in cancer tissue (Fig. 3A). This pattern of SUV_{max} values in the dynamic scanning was also observed after normalizing the data to the first timeframe (Fig. 3C).

The different behavior of normalized SUV_{max} curves in proven cancer tissue and benign inguinal lymph nodes (Fig. 3C) showed a statistically highly significant difference ($p < 0.005$) when modeled by linear regression analysis. In this analysis, the adopted interactive term was relevant and showed an R-squared value of 0.5, indicating that 50% of the observed SUV_{max} variation in time was attributed to the type of tissue.

The added value of 3-phase imaging protocol was identified in 10 out of 47 patients (21%). Thus, for six patients (2 relapses post surgery and 4 post RT), a centralized hyperactivity either at prostate bed or bulbar level (Fig. 4) could be differentiated as urinary or persistent vascular activity. For 4 other patients (2 relapses post surgery and 2 post RT), tumor recurrence was only unequivocally identified on 3-phase images (Fig. 1 and 2), while being uncertain on a standard static whole body PET image. For the patient shown in Figure 2, three-phase imaging showed the presence of a suspect hyperactivity already in frames 1 to 3 before the observation of urinary activity in the bladder. SUV_{max} evolution in this lesion was typical for recurrent cancer and matched a second lesion in the right prostate (Fig. 2G).

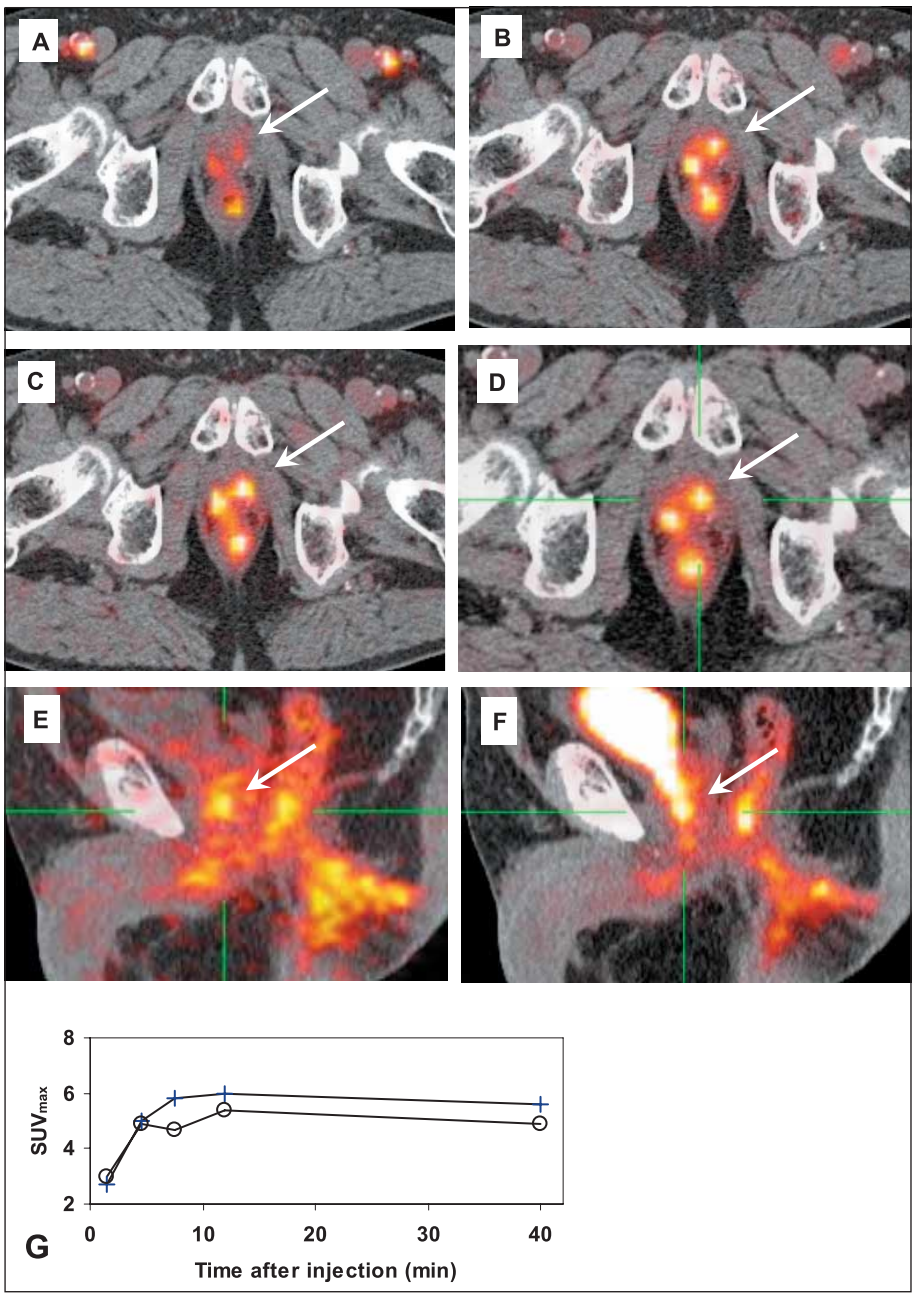

Fig. 2 Three-phase PET/CT showing on transverse sections (A – D, 0 to 14 min p.i.) and sagittal frames (E, 6 – 9 min p.i. and F, 11–14 min p.i.), the early appearance of a peri-urethral and right prostate focus of hyperactivity. SUV_{max} evolution over time (G), in the left-sided (+) and right prostate lesion (o) is similar and suspicious of cancer recurrence. Cross sections on transverse and sagittal PET indicate a focal hyperactivity in the left prostate that falls into the prolongation of the urethra (frame D and F) but is already present in the dynamic frames A to C and E in the absence of urinary activity, further supporting the diagnosis of recurrence. The left and right sided recurrence in this patient was confirmed subsequently by histology.

Discussion

We report our experience with a new 3-phase ^{18}F-fluorocholine PET/CT protocol that was adopted in view of the considerable variability of the protocols in the literature. Different significant observations were made, the first showing a different evolution of SUV_{max} curves in cancer lesions as compared to benign inguinal lymph nodes. The second observation concerned the variable time of blood pool peri-urethral activity decrease and the variable time of appearance of urinary bladder activity in individual patients, confounding with the identification of local cancer recurrences. Finally, it clearly appeared that our proposed three-phase imaging strategy allowed us to obtain a straightforward statement on presence or absence of cancer recurrence at prostate level in 10 of 47 patients where single phase imaging would not have been able to do so.

Three-phase PET in the 15 histological proven cancer recurrences showed an increasing SUV_{max} up to 14 minutes post injection. This pattern of ^{18}F-fluorocholine uptake is similar to the findings previously reported for ^{11}C-choline (32). Delayed PET performed in 9 of 11 patients with biopsy-proven prostate cancer confirmed the persistence of elevated SUV_{max}, with a minor tendency of late decrease. The latter result is only in partial agreement with previous observations of "dual phase" ^{18}F-fluorocholine PET, where delayed PET images showed an increasing SUV_{max} (19). A possible explanation might be that our patients had a dynamic PET followed by whole body PET allowing the determination of the highest SUV_{max} over time. In dual phase PET, however, early acquisition on the prostate bed is variably acquired in between a few minutes up to 15 minutes after injection (5, 19). At 5 minutes post injection, however, ^{18}F-fluorocholine uptake in tumor has not yet reached its peak.

Inguinal lymph nodes showing mild uptake of ^{18}F-fluorocholine were considered benign based on the fact that none of the pelvic and abdominal draining nodes in these patients were PET positive. Furthermore, CT morphological aspects were unequivocal making the presence of metastases in the inguinal nodes highly unlikely (15, 38). The time activity curve of SUV_{max} of these lymph nodes showed a coherent tendency of decrease, as was mentioned earlier for a few patients in a different study (24). The pattern in the early dynamic phase of benign inguinal lymph nodes was opposite to the one we observed in proven cancer lesions. Similar observations of decreasing SUV_{max} in benign inflammatory processes have been described for FDG PET (2). A good scanning time for optimal discrimination of benign lymph nodes and cancer with ^{18}F-Fluorocholine would lie between 10 to 15 minutes post injection, however, high urinary activity at that time can compromise PET interpretation. Clearly, when using ^{11}C-choline PET, urinary activity would not be an issue in these patients. Dynamic initial scanning after injection of ^{18}F-fluorocholine, however, can allow avoiding this difficulty.

Optimal timing of early imaging after ^{18}F-fluorocholine injection for the early detection of recurrence of prostate cancer remains a critical challenge (5). Our results show that the early phase dynamic scanning added highly valuable information by allowing a better discrimination of blood pool and urinary activity from recurrent cancer. Indeed, as shown for histological

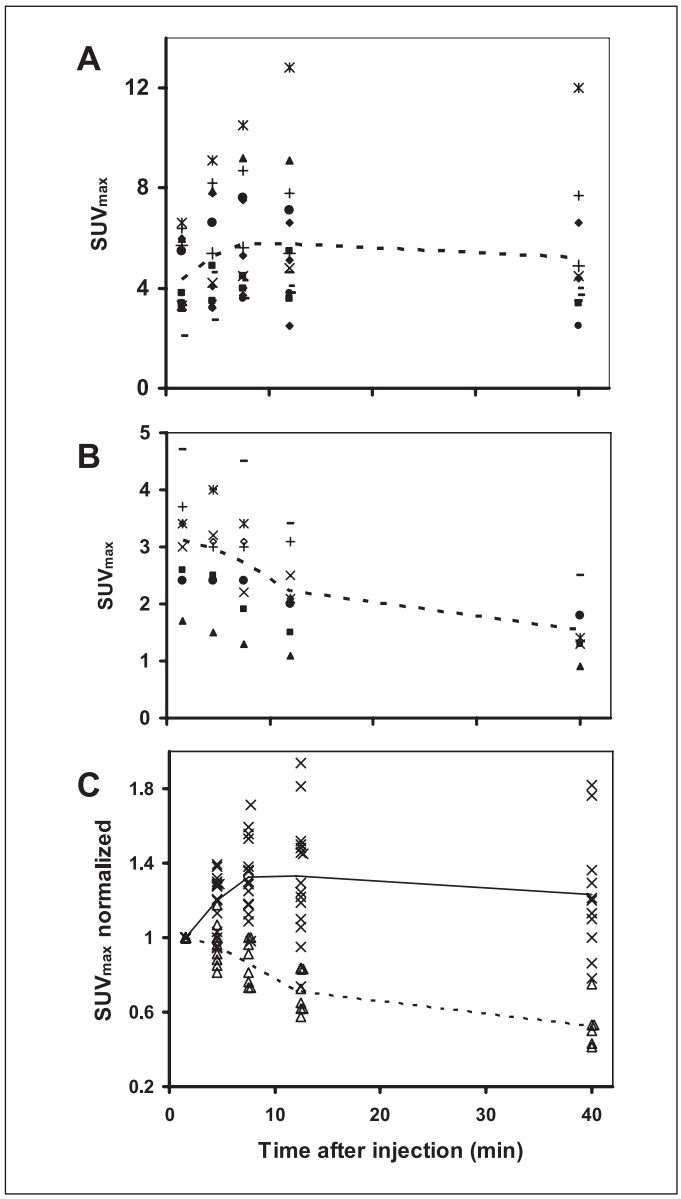

Fig. 3 Graph showing SUV_{max} evolution in histologically confirmed recurrent cancer (A, N = 15) and hyperactive inguinal lymph nodes interpreted as benign (B, N = 8). When SUV_{max} evolution was normalized (C) to the first dynamic frame for histologically confirmed cancer, (×, mean —) and reactive lymph nodes (Δ, mean ------), the results between the two tissues showed a clear different behavior over time ($p < 0.005$).

confirmed cancer lesions, uptake in tumor was very rapid and already significant in the first dynamic frame of 0 to 3 minutes post injection and further increased at 3 to 6 minutes post injection (Fig. 3A), while urinary activity appeared generally later. In the course of dynamic PET acquisition, bulbar or peri-urethral blood pool activity disappeared frequently late 6 to 9 minutes post injection when urinary bladder activity was present in the majority of patients. Dynamic initial ^{18}F-fluorocholine PET over 8 minutes followed by whole body PET was recently used in a study searching the identification of bone metastases from prostate cancer in comparison with ^{18}F-fluoride PET (4). Though not studied in that particular report (4), dynamic scanning was also used, according to these authors, with the aim to avoid difficulties in PET interpretation due to urinary activity.

In our patient population, the adopted protocol allowed furthermore to identify cancer lesions at peak uptake of ^{18}F-fluorocholine with an initially increasing time activity curve opposite to the pattern of rapidly decreasing activity observed in benign inguinal lymph nodes. In one patient, we observed a group of positive pelvic and peritoneal lymph nodes in the 3-phase PET bed position (Fig. 5). In these nodes of which one was enlarged on CT, an initial increasing SUV_{max} tends to confirm the value of 3-phase PET/CT for differentiating benign hyperactive lymph nodes from metastases.

Here, 3-phase PET proved to provide critical additional diagnostic criteria in a subgroup of 10 of 47 patients (21%) with suspected cancer recurrence. In the 10 patients, management could be adapted according to the more precise evaluation of the local recurrence situation. In these patients a conclusive statement on presence or absence of cancer based on a single, static whole body PET would not be possible. This is particularly true when considering that no consensus exists as to which protocol of PET examination should be applied. For single (29) or dual phase PET (5, 19) the PET starting time after injection of ^{18}F-fluorocholine may be particularly critical. However, in the recently reported dual phase PET, "early" PET acquisition was varied in between 5 and 15 minutes after injection of ^{18}F-fluorocholine (5). The added dynamic acquisition in 3 phase PET does not extend the scanning time significantly allowing for adequate whole body scan to be performed immediately after with no significant increase in the whole scan duration.

In the post-surgical situation, PET/CT was performed in a majority of patients with

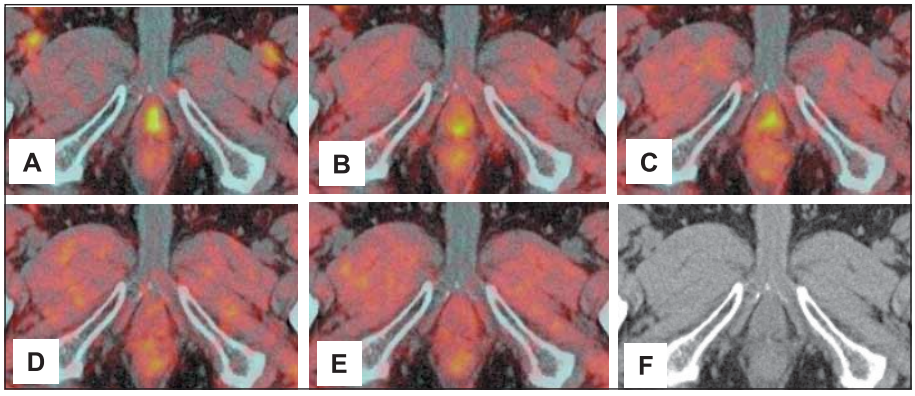

Fig. 4 Three-phase PET/CT (frames are identical as in Figure 1) showing the late disappearance of vascular activity at bulbar level. Dynamic scanning (A-C) shows that vascular bulbar activity persists until frame C (6–9 min p. i.) and disappears on frames D and E.

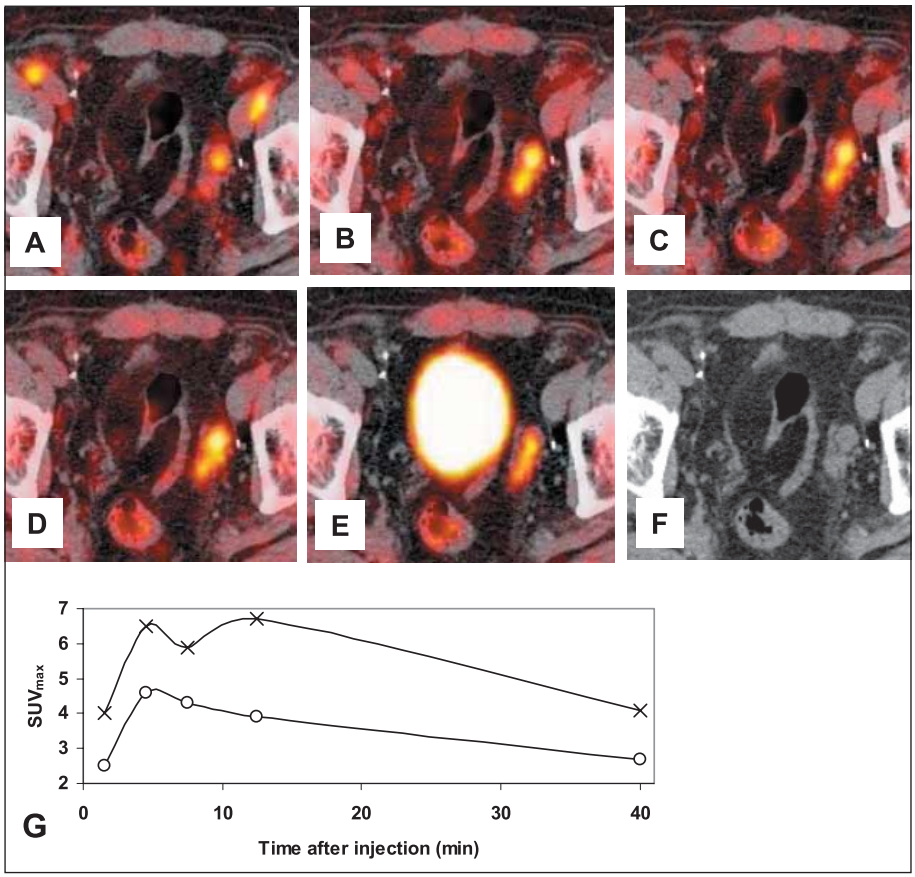

Fig. 5 Three-phase PET/CT display (frames are identical as in Figure 1) illustrating the evolution of uptake over time of three suspicious left internal iliac lymph nodes. CT (F) shows a moderately enlarged adenopathy (1.4 x 1.1 cm) and 2 small lymph nodes (few millimeters in size). SUV_{max} in the 3 lymph nodes showed a similar evolution with notably an initial increase (G, x = anterior lesion, o = posterior lesion) similar to results shown in Figure 3A, qualifying them as suspicious for recurrent cancer.

PSA < 2 ng/ml. PET/CT detected suspicious tracer uptake in 4/13 patients (31%) with PSA below 2 ng/ml, though this percentage is only indicative in view of the small number of patients. The result appears in accordance with previous observations with ^{18}F-fluorocholine, ^{11}C-choline or ^{11}C-acetate (1, 12, 13, 17, 18, 25, 27, 34). We have calculated the mean positive detection rate of ^{11}C-choline from 4 recent studies where the number of patients and PET/CT positivity at PSA < 2 ng/ml were accessible (12, 18, 25, 27). This retrospective analysis indicated a summed PET/CT positivity for 45 patients out of 136 patients (33%) with PSA<2 ng/ml. Interestingly, this positivity rate correlates quite well with a 5th study (13). Though patient numbers are not given for subgroups in this latter report including a large number of 357 patients at recurrence after initial radical prostatectomy, a PET positivity of 17 and 51% (mean 34%) for patients with PSA < 1 ng/ml and PSA between 1.5 and 2 ng/ml, respectively, was found. The latter result indicates that further differences exist for subgroups of patients at PSA < 2 ng/ml which would also mean that comparisons for PET/CT using different tracers should also be comparable at these different PSA levels.

For individual patients, the early detection of recurrence, though not always possible, can be of particular value since it may modify therapy by allowing a salvage intervention at a precise localization of recurrence. Thus, a boost radiation dose by IMRT (intensity modulated radiation therapy) could be given.

In a recent report on early relapses of prostate cancer, uptake of ^{11}C-choline was shown in only 23 of 33 biopsy-proven local recurrences (25). Negative PET was observed in the 10 of 33 patients with low PSA values < 2 ng/ml. According the authors, these negative findings could indicate a different biological behavior of recurrent prostate cancer (25). The higher detection rate of ^{18}F-fluorocholine in patients with higher PSA levels would, however, argue against a biological difference of recurrent cancer. A negative PET result in patients with low PSA levels could, however, be due to the physical limitation of PET in the detection of very small lesions.

At PSA values > 2ng/ml, ^{18}F-fluorocholine PET/CT was positive in all patients, though negative biopsy results in 3 patients would suggest a possible false positive interpretation of PET either bilaterally or unilaterally. While a false positive PET result is likely in one patient with subsequent spontaneous decrease of PSA level, in the other two patients, a negative biopsy should not necessarily be considered as a proof of absence of cancer. Interestingly, in 4 relapsing patients a mean of 12 biopsies were analyzed, and only a single biopsy was positive for 3 of these patients. In the fourth patient all biopsies were negative and only the surgical specimen showed cancer recurrence. This demonstrates that recurrences were frequently small in these patients and difficult to find by biopsy. A negative biopsy result is therefore not always a proof of absence of cancer.

Conclusion

In this study, 3-phase PET of the pelvis combined with whole body PET improved the diagnostic accuracy of recurrence in prostate cancer patients with biochemical suspicion of relapse. The results showed that tracer uptake in histologically confirmed cancer lesions increased up to 14 minutes post injection. Conversely, benign inguinal lymph nodes with mild uptake of ^{18}F-fluorocholine, showed an early decreasing SUV_{max}. A good scanning time for optimal discrimination of benign lymph nodes and cancer is therefore between 10 to 15 minutes, however, high urinary activity compromises interpretation of a single PET at that time. Three-phase PET was shown to provide essential additional diagnostic information in a subgroup of patients with prostate cancer recurrence, there changing management. Our result suggest that the 3-phase ^{18}F-fluorocholine PET protocol as presented here, dynamic imaging being performed prior to standard static whole-body PET and a delayed acquisition covering the prostate bed and draining lymph nodes, allows more accurate evaluation of recurrent prostate cancer than whole body PET alone or dual time PET.

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