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

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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 time-frames 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 $\geq 2$ 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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3-Phasen-PET/CT mit $^{18}$F-Fluorcholin zur Evaluation des Prostatakrebsrezidivs

E valuation 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 $\geq 2$ 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-
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 and $^{18}$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 to 18 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 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 $2 \times 5$, $5 \times 2$ and $3 \times 3$ 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-

### Table 1 Characteristics of 47 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$^{18}$F-fluorocholine, PET/CT scanning</th>
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<tbody>
<tr>
<td>$^{18}$F-fluorocholine (fluorocholinefluoromethyl-dimethyl-2-hydroxyethylammonium)</td>
<td>18F-fluorocholine PET/CT scanning</td>
</tr>
<tr>
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<tr>
<td>Following Fourier rebinning and model-based scatter correction, PET images were reconstructed using two-dimensional iter-</td>
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</table>
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. 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\textsubscript{max}) was calculated within regions of interest (ROIs) drawn over focal hyperactivity using standard formula (3). SUV\textsubscript{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\textsubscript{max} time-activity in different tissues (cancer and inguinal lymph nodes) SUV\textsubscript{max} values were normalized to the first dynamic frame recorded between 0 and 3 minutes after tracer injection by setting this SUV\textsubscript{max} to 1.0 (100%). This normalization limits potential bias from partial volume effects particularly in small inguinal lymph nodes (28).

<table>
<thead>
<tr>
<th>PSA</th>
<th>prostate or prostate bed</th>
<th>locoregional lymph nodes positive</th>
<th>distant sites positive</th>
<th>patients positive</th>
<th>total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 30</td>
<td>&lt; 2</td>
<td>1**</td>
<td></td>
<td>1 (100%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>≥ 2</td>
<td>26 3**</td>
<td>5</td>
<td>29 (100%)</td>
<td>29</td>
</tr>
<tr>
<td>surgery</td>
<td>&lt; 2</td>
<td>3</td>
<td>1</td>
<td>5 (100%)</td>
<td>5</td>
</tr>
<tr>
<td>n = 17</td>
<td>≥ 2</td>
<td>2</td>
<td>3</td>
<td>5 (100%)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>all</td>
<td>30 3**</td>
<td>8</td>
<td>8</td>
<td>38 (81%) 47</td>
</tr>
</tbody>
</table>

* 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.
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 $SUV_{\text{max}}$ 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 means that as time passes, $SUV_{\text{max}}$ 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 $SUV_{\text{max}}$ 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 <2 ng/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.

<table>
<thead>
<tr>
<th>patient</th>
<th>PET</th>
<th>biopsy</th>
<th>bone scintigraphy</th>
<th>PSA at PET (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>r</td>
<td>r</td>
<td>not done</td>
<td>negative</td>
</tr>
<tr>
<td>16</td>
<td>l</td>
<td>l</td>
<td>l</td>
<td>5.1</td>
</tr>
<tr>
<td>19</td>
<td>r+l</td>
<td>r+l</td>
<td>not done</td>
<td>6.0</td>
</tr>
<tr>
<td>26</td>
<td>l</td>
<td>l</td>
<td>l</td>
<td>4.1</td>
</tr>
<tr>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td>5.1</td>
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<td>4.1</td>
</tr>
<tr>
<td>31</td>
<td>r+l</td>
<td>r+l</td>
<td>r+l</td>
<td>2.5</td>
</tr>
<tr>
<td>40*</td>
<td></td>
<td></td>
<td></td>
<td>3.4</td>
</tr>
<tr>
<td>42</td>
<td>l</td>
<td></td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td>6.3</td>
</tr>
<tr>
<td>54</td>
<td></td>
<td></td>
<td></td>
<td>2.2</td>
</tr>
<tr>
<td>56</td>
<td></td>
<td></td>
<td>not done</td>
<td>3.0</td>
</tr>
<tr>
<td>57</td>
<td></td>
<td></td>
<td>negative</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* after a positive PET examination, PSA decreased from 3.4 ng/ml at PET to 1 ng/ml without any treatment, strongly suggesting of a false positive PET, possibly due to an inflammatory process; l (r): left (right side)
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 ($\kappa < 0.001$) and a correlation value $\kappa$ 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$_{\text{max}}$ 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$_{\text{max}}$ 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$_{\text{max}}$ 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$_{\text{max}}$ values in the dynamic scanning was also observed after normalizing the data to the first timeframe (Fig. 3C).

The different behavior of normalized SUV$_{\text{max}}$ 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$_{\text{max}}$ 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 bulb 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$_{\text{max}}$ evolution in this lesion was typical for recurrent cancer and matched a second lesion in the right prostate (Fig. 2G).
Discussion

We report our experience with a new 3-phase 18F-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\textsubscript{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\textsubscript{max} up to 14 minutes post injection. This pattern of 18F-fluorocholine uptake is similar to the findings previously reported for 11C-choline (32). Delayed PET performed in 9 of 11 patients with biopsy-proven prostate cancer confirmed the persistence of elevated SUV\textsubscript{max} with a minor tendency of late decrease. The latter result is only in partial agreement with previous observations of “dual phase” 18F-fluorocholine PET, where delayed PET images showed an increasing SUV\textsubscript{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\textsubscript{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, 18F-fluorocholine uptake in tumor has not yet reached its peak.

Inguinal lymph nodes showing mild uptake of 18F-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\textsubscript{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\textsubscript{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 18F-Fluorocholine would lie between 10 to 15 minutes post injection, however, high urinary activity at that time can compromise PET interpretation. Clearly, when using 11C-choline PET, urinary activity would not be an issue in these patients. Dynamic initial scanning after injection of 18F-fluorocholine, however, can allow avoiding this difficulty.

Optimal timing of early imaging after 18F-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 proven prostate cancer confirmed the persistence of elevated SUV\textsubscript{max}, with a minor tendency of late decrease. The latter result is only in partial agreement with previous observations of “dual phase” 18F-fluorocholine PET, where delayed PET images showed an increasing SUV\textsubscript{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\textsubscript{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, 18F-fluorocholine uptake in tumor has not yet reached its peak.
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 $^{18F}$-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 $^{18F}$-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 $^{18F}$-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 $\text{SUV}_{\text{max}}$ 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 $^{18F}$-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 $^{18F}$-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
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 18F-fluorocholine, 11C-choline or 11C-acetate (1, 12, 13, 17, 18, 25, 27, 34). We have calculated the mean positive detection rate of 11C-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 11C-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 18F-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 > 2 ng/ml, 18F-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 18F-fluorocholine, showed an early decreasing SUVmax. 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 18F-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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