

¹⁸F-choline and/or ¹¹C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy

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OBJECTIVES

To assess the value of positron emission tomography (PET)/computed tomography (CT) with either ¹⁸F-choline and/or ¹¹C-acetate, of residual or recurrent tumour after radical prostatectomy (RP) in patients with a prostate-specific antigen (PSA) level of <1 ng/mL and referred for adjuvant or salvage radiotherapy.

PATIENTS AND METHODS

In all, 22 PET/CT studies were performed, 11 with ¹⁸F-choline (group A) and 11 with ¹¹C-acetate (group B), in 20 consecutive patients (two undergoing PET/CT scans with both tracers). The median (range) PSA level before PET/CT was 0.33 (0.08–0.76) ng/mL. Endorectal-coil magnetic resonance imaging (MRI) was used in 18 patients. Nineteen

patients were eligible for evaluation of biochemical response after salvage radiotherapy.

RESULTS

There was abnormal local tracer uptake in five and six patients in group A and B, respectively. Except for a single positive obturator lymph node, there was no other site of metastasis. In the two patients evaluated with both tracers there was no pathological uptake. Endorectal MRI was locally positive in 15 of 18 patients; 12 of 19 responded with a marked decrease in PSA level (half or more from baseline) 6 months after salvage radiotherapy.

CONCLUSIONS

Although ¹⁸F-choline and ¹¹C-acetate PET/CT studies succeeded in detecting local residual

or recurrent disease in about half the patients with PSA levels of <1 ng/mL after RP, these studies cannot yet be recommended as a standard diagnostic tool for early relapse or suspicion of subclinical minimally persistent disease after surgery. Endorectal MRI might be more helpful, especially in patients with a low likelihood of distant metastases. Nevertheless, further research with ¹⁸F-choline and/or ¹¹C-acetate PET with optimal spatial resolution might be needed for patients with a high risk of distant relapse after RP even at low PSA values.

KEYWORDS

radical prostatectomy, ¹⁸F-choline, ¹¹C-acetate, PET/CT, salvage radiotherapy

INTRODUCTION

In patients with prostate cancer treated with radical prostatectomy (RP) recurrence is frequent in those diagnosed with positive margins and/or pT3a/b tumours. Many of these patients will develop local relapse and/or distant metastases [1]. The first choice of treatment in patients with suspicious residual or recurrent prostate cancer after surgery is salvage radiotherapy (RT) with or without hormonal therapy. Patients with a PSA level of >2.0 ng/mL before RT are less likely to benefit from this treatment [2,3]. Indeed, the rate of distant metastases increases significantly if

the PSA level is >2 ng/mL before salvage RT [4,5]. In 1999, an American Society for Therapeutic Radiology and Oncology Consensus Panel recommended local salvage RT preferentially for patients with PSA levels of <1.5 ng/mL at relapse [4].

Traditional examination methods, e.g. a DRE, TRUS and CT, are frequently unreliable for the early detection of suspicious residual or recurrent prostate cancer [6]. Contrast enhanced, endorectal-coil MRI has a high sensitivity and specificity for detecting local recurrence after RP [7]. ¹⁸F-fluorodeoxyglucose positron-emission

tomography (PET) is compromised in the staging and re-staging of prostate cancer [8], with a low sensitivity because of a high background activity of the tracer and metabolites in the urinary tract, and a low glucose uptake in prostate cancer [9]. In the absence of reliable imaging able to identify the site of local relapse and/or distant metastases, the prostatic bed (with or without the seminal vesicles) has been most frequently recommended as the clinical target volume for salvage radiotherapy [10,11].

The PET tracers ¹⁸F-choline, ¹¹C-choline and ¹¹C-acetate have shown promising results in

detecting local recurrent and metastatic prostate cancer after surgery [8,12–16]. However, after RP only a few studies have assessed these PET tracers in patients with relatively low PSA values, and most of them were reported to have a low sensitivity for detecting recurrence. In the present study, we aimed to re-investigate the diagnostic potential of ^{11}C -acetate and ^{18}F -choline PET/CT in the early detection of prostate cancer recurrence after surgery at PSA levels of <1 ng/mL.

PATIENTS AND METHODS

PET and PET/CT studies were approved by the ethics committees of both University Hospitals of Geneva and Zurich. Signed informed consent was obtained from all patients. The studies were conducted from January 2004 to July 2005 in 20 consecutive patients with suspected residual or recurrent prostate cancer after RP and with PSA levels of <1 ng/mL. All patients were recruited at the University Hospital of Geneva; the 20 patients had 22 PET/CT studies, 11 with ^{18}F -choline (group A) and 11 with ^{11}C -acetate (group B), and two with both tracers. The median (range) delay between surgery and PET/CT was 32 (4–81) months. In 14 patients the studies were for biochemical progression after RP, while six (two from group A and four from group B) had PET/CT because of suspected residual tumour (PSA level >0.04 ng/mL) immediately after RP. These last patients had their PET/CT evaluation 3–7 months after radical surgery. Nine patients from group A and seven from group B had increasing PSA levels at a median (range) of 46 (14–62) and 42 (10–80) months after RP, respectively. The median PSA doubling time for these patients was 12 (3–36) months (Table 1).

The patients' characteristics are also shown in Table 1. The median (range) PSA level before RP of 9.08 (4.13–23.00) ng/mL decreased after RP to a nadir value of 0.07 (<0.04 –0.51) ng/mL. The pathological T stage was pT2a–c, pT3a, pT3b and pT4 in four, 11, four and one patient, respectively. The Gleason score distribution was ≤ 6 , 7, and ≥ 8 in seven, 10 and three patients, respectively; the surgical margins were positive in 13 patients (65%).

The median PSA was 0.33 ng/mL before PET/CT and a DRE at that time was suspicious for local relapse in eight patients (40%). All

TABLE 1 Patient characteristics at surgery, PET/CT, and the results

Variable	^{18}F -choline	^{11}C -acetate	All
Number of patients	11	11	20
Median (range):			
Age, years at diagnosis	62.0 (54–67)	64.0 (59–73)	63.5 (46–73)
PSA at diagnosis, ng/mL	9.07 (4.13–15.70)	9.22 (4.87–23.00)	9.08 (4.13–23.00)
PSA after RP, ng/mL	0.07 (0.00–0.33)	0.06 (0.00–0.51)	0.07 (0.00–0.51)
Surgical margins positive, n	4	9	13
At PET/CT:			
Number of PET/CT scans	11	11	22
Median (range):			
Time from surgery, months	35 (5–81)	29 (4–63)	32 (4.0–81.0)
PSA doubling time, months in patients with recurrence	7.5 (3–30)	12 (6–36)	12 (3–36)
PSA at PET, ng/mL	0.35 (0.11–0.73)	0.30 (0.08–0.76)	0.33 (0.08–0.76)
DRE positive, n (%)	3	5	8 (40)
Results:			
PET positive, n (%)			
local	5	6	11 (55)
lymph node	–	1	1 (5)
Endorectal MRI locally positive	8/9	9/11	15/18 (85)
PSA level after RT*			
decrease	8	6	12
increase	2	2	4
no change	1	2	3
†	0	1	1

*Change >6 months after RT: a decrease or increase of half or more in PSA 6–10 months after therapy compared with the initial value; changes of less than half denoted as no change; one patient had a highly aggressive tumour (Gleason 5 + 5), and was re-treated with androgen suppression plus RT and was therefore not evaluated for PSA change.

patients were negative for regional or distant disease extension after re-staging with bone scintigraphy and abdominal CT.

All studies with ^{18}F -choline were done at the University Hospital of Zurich. ^{18}F -choline was produced using the method described by Cserenyak *et al.* [17]; ^{18}F -fluorine was prepared by using a 16.8-MeV cyclotron (PET Trace 2000; GE Medical Systems, Uppsala, Sweden). The injected activity of ^{18}F -choline was 214 ± 14 MBq with no adjustment for weight or size, and a purity of $\geq 95\%$.

Patients were scanned with an inline PET/CT scanner (Discovery LS; General Electric Healthcare Technologies, Waukesha, WI, USA) consisting of a full-ring PET scanner with a 14.6-cm transverse field of view and an in-plane resolution of 4.8 mm full width at half maximum at the centre of the field of view, and a multidetector CT scanner. First, an unenhanced CT scan (80 mA, 0.5 s/rotation,

140 kV, 4.25-mm reconstructed section thickness) was obtained from the head to the pelvic floor. Subsequently, the table position was moved axially to the initial position for the PET scanning, so that the first field of view covered the pelvic floor and the bladder. PET scanning was initiated 120 s after an i.v. injection with ^{18}F -choline. Seven cradle positions were scanned, with an acquisition time of 3 min for the emission scan per position. The PET images were reconstructed using a standard iterative (two iterations) ordered-subset expectation maximization reconstruction algorithm, and were reformatted into transverse, coronal and sagittal views.

All ^{11}C -acetate studies were also done at the University Hospital of Geneva. ^{11}C -acetate was prepared at the cyclotron unit of Geneva University Hospital from ^{11}C -carbon dioxide produced on a IBA 18/9 cyclotron, according to a modified [18] and previously published

FIG. 1. Example of a prostate bed-centred PET/CT showing focal hyperactivity in the prostate bed (arrow) that reached a SUV_{max} of 2.0.

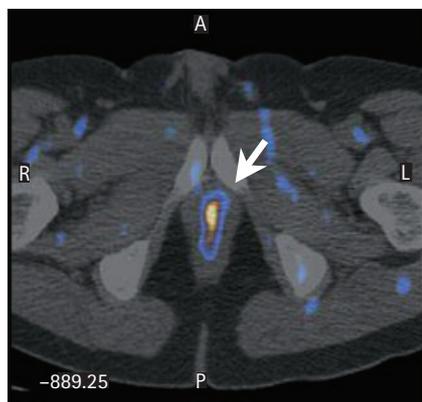
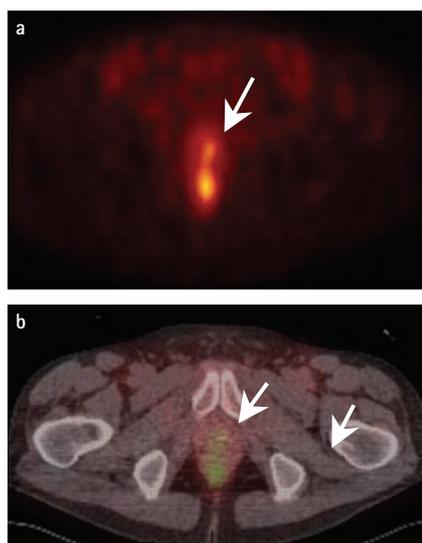


FIG. 2. Example of a ¹¹C-acetate PET scan showing focal hyperactivity in the prostate bed (a) and the fused imaging with the corresponding CT (b). Note the small, focal hyperactivity (arrow) that reached a SUV_{max} of 2.5.



procedure [19]. The radiochemical purity of the injectable solution was $\geq 95\%$. The injected activity was 524 ± 24 MBq with no adjustment for weight or size.

The PET scanner used was an ECAT ART (Siemens/CTI, Knoxville, TN, USA) providing an axial field of view of 16.2 cm. After bladder voiding, patients were placed in the scanning position and a six-run transmission scan (5 min/bed position) using ¹³⁷Cs single-photon point sources was recorded starting at the prostate bed. The laser-defined starting

position was ink-marked on the patient's leg. Patients were then injected under standard precautions with ¹¹C-acetate and the emission scan started 120 s after injection. The initial run of 10 min was centred on the prostate bed, followed by five runs of 7 min each covering the rest of the pelvis, abdomen and thorax. An attenuation correction matrix was calculated by segmenting the attenuation map, followed by forward projection at appropriate angles of the transmission image [20]. The generated attenuation correction map was then used to reconstruct the emission data. The images were scatter-corrected and reconstructed using normalized attenuation-weighted, ordered subset-expectation maximization iterative reconstruction implemented within the ECAT 7.2 software. The default parameters used in clinical routine were used (two iterations and eight subsets) followed by a post-processing Gaussian filter (kernel 6 mm full-width half-maximum height). The voxel size was set to $3.4 \times 3.4 \times 3.4$ mm³. Attenuation-corrected views were obtained for clinical interpretation in transaxial, coronal and sagittal planes. Unenhanced CT imaging from the pelvis to the thorax was done within 2 days of PET using a 16-slice CT scanner. The starting position of the dedicated fusion CT was identical to PET, as verified by the same physician in both examinations. PET to CT images were co-registered using the commercial Hermes multimodal fusion software (Nuclear Diagnostics AB, Stockholm, Sweden).

One patient had a hip prosthesis that led to a CT artefact projecting onto the prostate bed. This PET scan was therefore analysed with and with no attenuation correction. Both evaluations gave the same result (positive for a local recurrence). All other patients had their attenuation corrected PET/CT scan evaluated.

In each centre PET was interpreted by two experienced nuclear medicine physicians who gave their final consensus statement in the clinical report; all clinical and radiological information before PET was made available to them and the PET interpreted visually. PET was considered positive if activity was significantly above the observed background and could not be explained by a normal structure. For ¹¹C-acetate PET the tracer accumulation was considered equivocal if activity was marginally above expected background and if other than tumoral origin could not be excluded. Finally, the results were

compared with the results of an endorectal MRI, whenever available. The maximum standardized uptake value (SUV_{max}), while measured, was not used in the interpretation because partial volume effects were considered to significantly reduce these values, notably for small tumours.

All patients received salvage RT at a median of 36.1 (20–61) days after PET/CT, using a linear accelerator (18 MeV X-rays). The prostatic and seminal vesicle bed was irradiated with four or six coplanar fields in five weekly fractions of 2 Gy/day, to a total of 32 fractions (64 Gy). A boost dose of five fractions (10 Gy) was delivered to the local tumour recurrence if detected on the endorectal MRI and/or on the PET/CT studies. The positive obturator lymph node detected in one patient was included in the treatment volume. One patient with a particularly aggressive tumour (Gleason 5 + 5) was treated with adjuvant androgen deprivation and salvage RT.

All patients had a clinical follow-up with PSA determinations at 1 and 22 days of salvage RT, and 6 weeks and 6–10 months after treatment. The median (range) minimum follow-up after RT was 6 (6–10) months after salvage RT. A decrease by half in the PSA level after salvage RT was considered the endpoint of the response confirming the presence of local disease.

RESULTS

The ¹⁸F-choline and ¹¹C-acetate PET/CT studies were all well tolerated with no clinically evident side-effects. ¹⁸F-choline PET/CT fusion scans detected five positive results for local recurrence. The median (sd) SUV_{max} of locally positive results was 2.0 (0.79). No regional or distant metastasis was detected in this group. An example of a ¹⁸F-choline positive local recurrence on PET/CT is shown in Fig. 1.

The ¹¹C-acetate studies showed four positive and two equivocal results for local recurrence. The median SUV_{max} of locally positive and equivocal results was 2.3 (0.17) and 1.3 (0.12), respectively. In one patient, a small obturator lymph node of <1 cm was interpreted as positive (SUV_{max} 2.6). No further abnormalities were detected in this group. An example of a local and lymph node positive ¹¹C-acetate PET study, and retrospective image registration of sequential PET and CT studies, are shown in Fig. 2. In the two patients having both

^{11}C -acetate and ^{18}F -choline PET/CT studies, there was no abnormal tracer uptake in either examination.

The PET/CT and MRI results were compared in the 15 patients with local disease detected on MRI; eight were positive/equivocal in the PET/CT studies. There was a spatial correlation in the same site between positive/equivocal results in PET/CT and endorectal MRI in both patients from group A and in five of six in group B. The only patient from group A with a negative endorectal MRI was locally positive on the ^{18}F -choline PET/CT. He responded to salvage RT with a decreasing PSA level. In the two patients from group B with a negative endorectal MRI the ^{11}C -acetate PET/CT was also negative. One of them had a stable PSA value 6 months after salvage RT, and the other responded, with a PSA level decreasing by half or more.

All patients completed RT as scheduled; the patient who had a highly aggressive tumour (Gleason 5 + 5) and who received androgen suppression in addition to RT was not eligible for assessing the response. After a minimum follow-up of 6 months after RT the PSA level decreased to a median of 0.07 (<0.04–1.03) ng/mL. There was a significant decrease (>50%) in PSA level after salvage RT in eight patients in group A and in six in group B (Table 1). The PSA level increased by more than half in two patients from each group, and remained stable in one in group A and in two in group B. Thus, in three of five patients from group A and four of five in group B with positive/equivocal PET/CT, the PSA decreased significantly, while 11 of 16 with positive endorectal MRI findings had a significant decrease in PSA level after salvage RT.

DISCUSSION

Recurrent prostate cancer after RP should be suspected at the earliest established increase in PSA level [21–23]. Even very low (above undetectable) PSA values after surgery are likely to be followed by increasing levels, heralding clinical tumour recurrence [1,24]. In the present study, the risk factors for local recurrence or residual tumour were high in all patients. Indeed, eight of 11 in group A and nine of 11 in group B presented with extracapsular disease and/or seminal vesicle involvement, while there were also positive surgical margins in four in group A and nine in group B.

A study by Kotzerke *et al.* [12] comparing ^{11}C -choline and ^{11}C -acetate PET in 10 patients with residual or recurrent prostate cancer showed a similar ability for both tracers to detect local tumour, lymph node and bone metastases, although only at high PSA values. Only a few studies have evaluated ^{11}C -acetate and/or ^{18}F -choline PET in patients with PSA levels of <5 ng/mL after RP. All these studies showed low or moderate sensitivity in detecting local residual/recurrent tumour or distant metastasis [8,14,25]. Indeed, De Jong *et al.* [8] found no positive ^{11}C -choline PET scans in 20 patients with PSA levels of <4 ng/mL after surgery. Oyama *et al.* [14] also reported a very low sensitivity (4%) for patients with PSA level of <3.0 ng/mL assessed with ^{11}C -acetate PET after surgery. Unlike these studies, the results of two others with ^{18}F -choline and ^{11}C -acetate were more in agreement with the present results [13,26]. Heinisch *et al.* [26] recently reported a similar proportion of positive lesions to that in the present study, in patients assessed with ^{18}F -choline PET/CT for recurrent prostate cancer and PSA levels of <5 ng/mL. However, unlike in the present series, there was a higher detection rate of lymph node and bone metastases in their patients, although only two had a PSA level of <1 ng/mL. Kotzerke *et al.* [13] reported on 31 patients with increasing PSA levels after RP and who were evaluated with ^{11}C -acetate PET; eight had a PSA level of <2.0 ng/mL and their PET studies showed recurrent prostate cancer in five, and in four of these patients recurrence was confirmed by biopsy.

Most of the cited studies used no PET/CT co-registration; patients undergoing ^{18}F -choline PET in the present study (group A) were assessed with in-line PET/CT, while those having ^{11}C -acetate PET (group B) were assessed with PET and thoraco-abdominal CT with sequential registration. Either in-line PET/CT or image co-registration studies might be why there was better differentiation of physiological (rectum and bladder) uptake from residual/recurrent prostate cancer, thus explaining the relatively high positivity in half the patients, compared with those reported by most other studies. However, a potential pitfall of ^{11}C -acetate PET with CT registration, as used in the present study, was the low spatial resolution of the technique and the time-related limitation of sequential PET and CT studies. This might have contributed to a suboptimal detection of recurrent tumours.

All the present patients with either suspicious residual or recurrent prostate cancer after RP had a median PSA level of 0.33 ng/mL at the time of PET and none had a PSA level of >0.8 ng/mL. In these patients tumour recurrences or residual tumour were expected to be small. With ^{11}C -acetate and ^{18}F -choline PET/CT the detection of local tumour recurrence was possible in six of 11 and five of 11 patients, respectively.

Histological confirmation of local recurrences was not obtained because a negative result is considered unreliable [27,28]. However, the PSA level 6–10 months after salvage RT decreased significantly (>50%) in eight and seven patients from group A and B, respectively. This result is highly suggestive of predominantly local/regional disease, thus tending to confirm the locally/regionally positive PET/CT findings. The sensitivity of PET/CT scans was 60% with ^{18}F -choline and 66% with ^{11}C -acetate; we did not estimate the specificity of PET/CT because there were too few patients with stable or increasing PSA levels after salvage RT. In two of three patients in group A and three of four in group B with stable or increasing PSA levels after salvage RT, the PET/CT scans were negative. Only one report by Kotzerke *et al.* [13] contained information about the sensitivity and specificity of PET in patients with recurrent prostate cancer at low PSA levels, finding similar values. In nine out of 13 patients with positive endorectal MRI, the PSA evaluation after salvage RT also suggested the presence of mostly local disease.

In two patients the PSA level after treatment increased by more than half, while in three it remained stable. In these patients, regional and/or distant disease cannot be excluded. Only one patient had a positive obturator lymph node; his PSA level decreased significantly 6 months after salvage RT. There were no other regional or distant metastases. These results seem to be in agreement with other reports on ^{11}C -acetate and ^{18}F -choline PET studies, in their ability to detect lymph node and bone metastasis in recurrent prostate cancer almost exclusively at high PSA values [13,14,25]. A low spatial resolution of such PET studies (i.e. <6 mm) might explain this observation. PET/CT with higher spatial resolution might be needed to increase the detectability of potentially existing regional and distant metastasis with ^{11}C -acetate and ^{18}F -choline PET/CT in patients with very low PSA values. In addition, the present study

cannot answer the question of which of the two tracers (¹¹C-acetate or ¹⁸F-choline) is better for detecting residual or recurrent prostate cancer after RP. A prospective study with the two radiotracers assessed in the same patients with the same PET/CT imaging system and acquisition/processing protocols might be a sound recommendation for future clinical research proposals.

In conclusion, although ¹⁸F-choline and ¹¹C-acetate PET/CT studies succeeded in detecting local residual or recurrent disease in about half of the patients with PSA levels of <1 ng/mL after RP, these studies cannot yet be recommended as a standard diagnostic tool for early relapse or suspicion of subclinical minimally persistent disease after surgery. Endorectal MRI might be more helpful, especially if such patients also have a low likelihood of distant metastases. Nevertheless, further research with ¹⁸F-choline and/or ¹¹C-acetate PET/CT studies with PET/CT instrumentation of optimal spatial resolution and scanning conditions might be needed for patients at high risk of distant relapse after RP even at low PSA values.

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CONFLICT OF INTEREST

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Abbreviations: **RP**, radical prostatectomy; **RT**, radiotherapy; **PET**, positron-emission tomography; **SUV_{max}**, maximum standardized uptake value.