Long-term Results of a Comparative PET/CT and PET/MRI Study of ^{11}C-Acetate and ^{18}F-Fluorocholine for Restaging of Early Recurrent Prostate Cancer

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Purpose: The aims of this study were to assess the intraindividual performance of ^{18}F-fluorocholine (FCH) and ^{11}C-acetate (ACE) PET studies for restaging of recurrent prostate cancer (PCa), to correlate PET findings with long-term clinical and imaging follow-up, and to evaluate the impact of PET results on patient management.

Methods: Thirty-three PCa patients relapsing after radical prostatectomy (n = 10, prostate-specific antigen [PSA] ≤3 ng/mL), primary radiotherapy (n = 8, prostate-specific antigen ≤5 ng/mL), or radical prostatectomy + salvage radiotherapy (n = 15) underwent ACE and FCH PET-CT (n = 29) or PET-MRI (n = 4) studies in a randomized sequence 0 to 21 days apart.

Results: The detection rate for ACE was 66% and for FCH was 60%. Results were concordant in 79% of the cases (26/33) and discordant in 21% (retroperitoneal, n = 5; pararectal, n = 1; and external iliac nodes, n = 1). After a median FU of 41 months (n = 32, 1 patient lost to FU), the site of relapse was correctly identified by ACE and FCH in 53% (17/32) and 47% (15/32) of the patients, respectively (2 M1a patients ACE+/FCH−), whereas in 6 of 32 patients the relapse was not localized. Treatment approach was changed in 11 (34.4%) of 32 patients and 9 (28%) of 32 patients restaged with ACE and FCH PET, respectively.

Conclusions: In early recurrent PCa, ACE and FCH showed minor discrepancies, limited to nodal staging and mainly in the retroperitoneal area, with true positivity of PET findings confirmed in half of the cases during FU. Treatment approach turned out to be influenced by ACE or FCH PET studies in one third of the patients.

Key Words: ^{11}C-acetate, ^{18}F-fluorocholine, PET-CT, PET-MRI, prostate cancer

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PET with different tracers showing a tropism for prostate cancer (PCa) cells are largely used for restaging after curative treatment.[1] Among these, ^{11}C-acetate (ACE) and choline-based tracers, either ^{11}C- or ^{18}F-fluorocholine (FCH), share the ability to measure membrane lipid metabolism typically increased in tissues with proliferating tumor cells.[2,3]

We previously reported that ACE and FCH show excellent concordance for recurrent PCa staging, with limited discrepancies for lymph nodes, as assessed in a preliminary report including the first 23 patients of the current study population,[4] describing in detail the lesion-based interobserver and intraobserver variability of the 2 tracers.

The aims of the present study were to report the final results of the intraindividual assessment of performance of FCH versus ACE PET studies for restaging of recurrent PCa in the whole-study patient cohort, to correlate PET findings with long-term clinical and imaging follow-up, and to evaluate the impact of PET results on patient management.

MATERIALS AND METHODS

For this comparative study, we prospectively included 33 PCa patients with early biochemical relapse after primary treatment defined as follows: 10 patients after radical prostatectomy (RP) (prostate-specific antigen [PSA] upper limit ≤3 ng/mL), 8 after definitive radiotherapy (RT) (PSA upper limit ≤5 ng/mL), and 15 after RP and salvage RT (PSA upper limit ≤3 ng/mL) (Table 1). The study was approved by the institutional review board, and all patients provided written informed consent to the study. The study enrollment was prematurely stopped for problems in the ACE synthesis, not reaching the initially planned number of 40 patients. With 33 subjects, the analysis has a power of 86% to compare the detection rates between the 2 tracers at a 5% significance level.

We used the same acquisition and analysis protocol as in the preliminary study.[4] Briefly, a PET scan with ACE (977 ± 124 MBq of injected activity) and 1 with FCH (305 ± 15 MBq) was performed in a randomized sequence 0 to 21 days apart (median interval, 5 days), using PET/CT and PET/MRI modalities in 29 and 4 subjects, respectively. For each patient, the same imaging technique was used with both tracers.

Each patient's scan was assessed independently by 2 experienced nuclear medicine physicians and rated (consensus reading) as positive or negative for local, locoregional, and distant disease, on a per-patient basis. A detailed regional lesion-based analysis was reported in the previous publication.[4]

The criterion standard was based on the results of clinical and imaging follow-up of 32 patients (1 patient lost to follow-up). Standardized follow-up comprised 6-monthly clinical evaluations including PSA and testosterone measurements, associated in case of biochemical recurrence with imaging investigations (bone scan, FCH PET, and pelvic MRI) and biopsies of the suspicious relapses when indicated (n = 6). The median follow-up time was 41 months (range, 17–51 months).

Using a paired *t* test, we compared quantitative parameters derived from FCH and ACE images, namely, the mean background SUV (measured with a planar circular ROI, 6-mm radius, at the

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TABLE 1. Patient and Disease Characteristics (n = 33)

Characteristic	RP	RT ± ADT	RP + Salvage RT
No. of patients	10	8	15
Age, y			
Median	66	67	65
Range	58–78	63–85	50–83
Initial stage, n			
T1	0	1	0
T2	8	3	6
T3	2	4	9
Gleason score			
≤6	3	2	4
7	6	5	7
≥8	1	1	4
PSA, ng/mL			
At diagnosis			
Median	13.3	13.3	13.4
Range	6.3–38.6	8.2–36	5.0–40
At PET			
Median	1.9	2.3	1.9
Range	0.3–3	2.4–5	0.5–3.4*
PSA DT, mo			
Median	7.2	7.2	7.2
Range	2–86	6.6–29	1–24

*PSA < 3 ng/mL at inclusion and 3.4 ng/mL at PET-CT.
DT indicates doubling time.

aortic arc), and tumor-to-background ratio (TBR) for all positive and matched lesions, calculated as the SUV max of the lesion divided by the mean background SUV. The linear association between the TBR obtained on the 2 image series was measured by Pearson *R*.

The patient management was prospectively established during a multidisciplinary urological consensus meeting, based on the combination of all imaging and clinical findings and the institutional treatment policies.[5–7] On the other hands, for the study purposes, the potential impact of each PET tracer on patient management was retrospectively determined at the time of the present analysis by 2 experienced radiation oncologists considering separately the ACE and FCH results on the basis of the treatment strategy previously adopted for each patient.

RESULTS

The detection rate for ACE was 66% (69% for PET/CT and 50% for PET/MRI), and that for FCH was 60% (59% for PET/CT and 75% for PET/MRI). Results were concordant in 79% of the cases (n = 26/33) (Fig. 1) and discordant in 21% (n = 7/33, 6 PET/CT and 1 PET/MRI). All discordant cases involved nodal localizations: retroperitoneal (n = 5), pararectal (n = 1), and external iliac (n = 1). In only 2 of 7 discrepant cases, the additional lesions changed disease stage (Table 2), whereas in the remaining 5 cases, concordant lesions determined the same staging on the 2 examinations, unchanged by the discrepant findings.

The quantitative comparison of the 2 scans showed, for matched lesions, a significant correlation between the TBR calculated on the 2 image series ($R = 0.576$, $P = 0.006$). A paired *t* test showed, however, that FCH uptake was significantly higher than ACE uptake (mean TBR, 6.5 vs 5.2; $P = 0.012$).

The association between PET findings and follow-up is summarized in Table 2, confirming as true positives 2 ACE-positive/FCH-negative M1a patients, and 1 FCH-positive/ACE-negative lymph node, in a patient already classified as M1a on the basis of concordant ACE/FCH findings. Based on follow-up data, the site of relapse was correctly identified by ACE and FCH in 53% (n = 17/32) and 47% (n = 15/32) of the patients, respectively, whereas in 6 of 32 patients, the relapse was not identified at follow-up (all complementary imaging investigations were negative).

In approximately 40% of the patients relapsing after exclusive RT or RP followed by salvage RT, a palliative androgen deprivation therapy (ADT) or watchful-waiting approach was modified for a curative intent including salvage therapies for a local recurrence or oligometastatic progression (Fig. 1). Among the 32 evaluable subjects, 14 patients (44%) were treated with a palliative intent and 18 (56%) with a curative intent. In 2 (22%) of 9 patients relapsing after RP, the treatment field was modified to include pelvic nodes or to boost a macroscopic local relapse in the prostate bed. Both patients were relapse-free at last follow-up. On the other hand, an oligorecurrent disease was found in 7 patients, including 6 (40%) of 15 patients with a biochemical relapse after RP and salvage RT and 1 patient with an isolated nodal relapse following a definitive RT. According to institutional policies, all these patients were treated with a curative salvage RT combined with ADT (Fig 2). At last follow-up, a PSA response after salvage treatment (RT or high-intensity focused ultrasound) was observed in 16 of 18 patients, with 10 patients in complete remission (Fig. 1).

On the retrospective analysis based on the independent performance of the 2 tracers, the treatment approach was changed in 11 (34.4%) of 32 and 9 (28%) of 32 patients restaged with ACE and FCH PET studies, respectively (Table 3). This difference was not significant between the 2 tracers ($P = 0.78$, Fisher exact test). In the 3 patients with discordant PET findings, differences between tracers would potentially impact RT volumes (inclusion of the para-aortic region for 1 FCH-positive/ACE-negative and 1 ACE-positive/FCH-negative patient and additional RT boost to an ACE-positive/FCH-negative suspicious pelvic node).

DISCUSSION

Acetate and FCH are validated tracers for the evaluation of recurrent PCa, with an overall similar biodistribution.[3,4] The main difference is the urinary excretion of FCH, which could impair the detection of lesions in the vicinity of the bladder, although this can be overcome by the acquisition of early pelvic images immediately after injection.

Our data show, despite a higher TBR for FCH, an excellent overall concordance in lesion detection between the 2 tracers, in accordance with our preliminary analyses and with previous reports, as recently reviewed.[3,4,8] The discrepancies were limited to the nodal staging mainly located in the retroperitoneal region, a challenging area for PET/CT staging.[9] These results confirm that urinary excretion of FCH should not be considered a limitation for its use in patients with early recurrence and low PSA.

Clinical impact of assessing disease extension by PET studies in early recurrent PCa patients is large, ranging from optimization of RT plans[7] to the development of curative treatment strategies in patients with a limited number of metastases.[6] Although ACE- or FCH-based PET studies have been shown to detect the relapsing disease better than conventional imaging techniques, patients with low PSA might harbor micrometastatic disease, by definition nonvisible on imaging.[9] For this reason, inclusion of the elective nodal regions in the RT field with a boost to the PET-positive nodes[6] may be a reasonable treatment alternative to focal

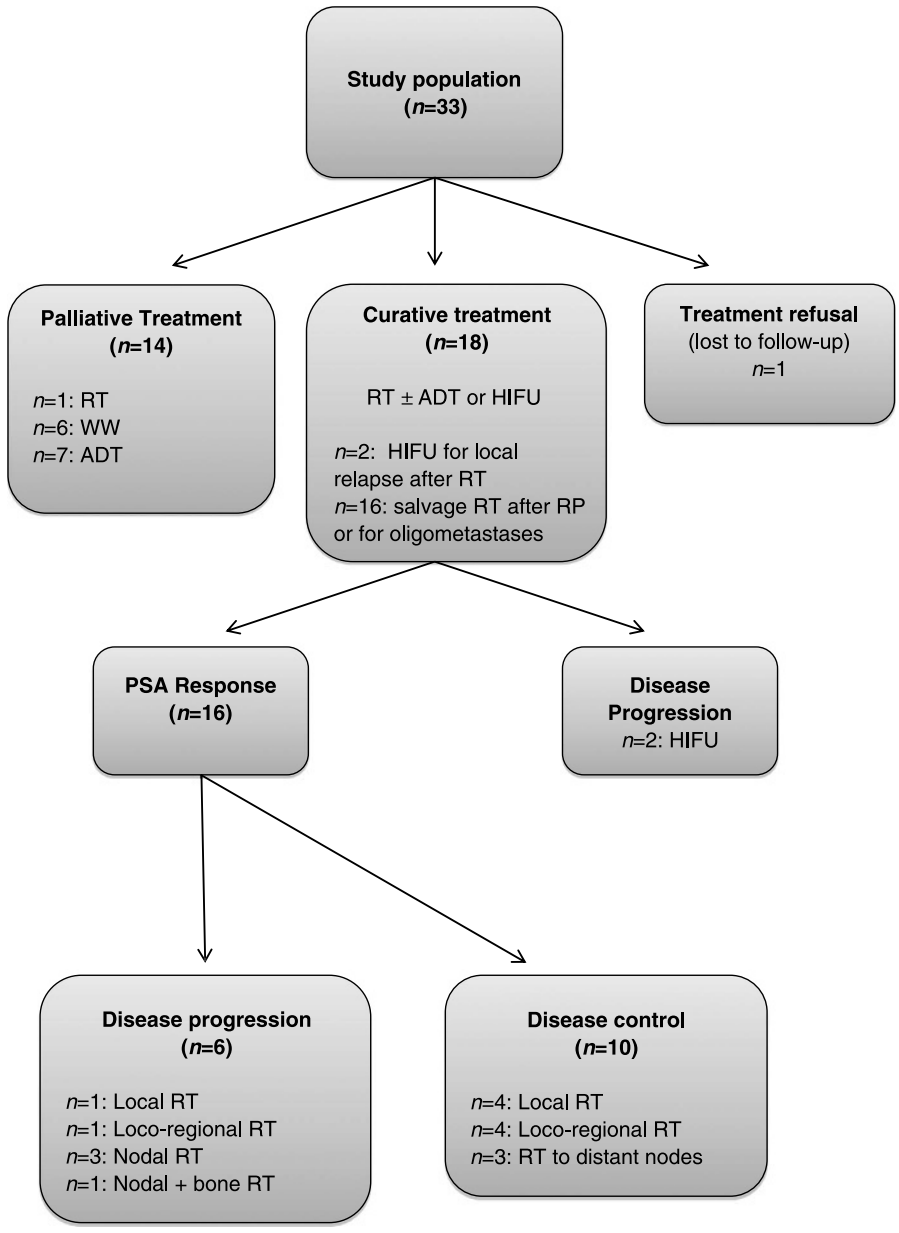

FIGURE 1. Flow diagram of treatment management and outcome of study population.

stereotactic RT treatments to delay disease progression and to postpone androgen ablation treatments.[10]

In our population, both tracers changed the treatment approach in a third of the cases. This proportion is slightly lower than the values previously reported, as expected given the early stage and the relatively low PSA values in our subjects.[11–13]

Ongoing research focuses on the validation of new promising PET tracers, with a superior lesion-to-background contrast and higher detection rates.[1,14] For example, recent experiences with the ^{68}Ga-PSMA, targeting the prostate-specific membrane antigen showed a detection rate of 60% in patients with a PSA less than 1 ng/mL.[15] Comparative studies in the same population have shown that this tracer is superior to FCH, also in patients with PSA values lower than 2 ng/mL.[16]

The main limitations of our study are the relatively small sample size, namely, for patients assessed with the PET/MRI modality and the lack of histological confirmation for all discrepant findings. However, this relatively small cohort of patients evaluated in this study is within the range of the sample size used for this type of comparisons[16] and provides adequate power to detect noninferiority of FCH.

CONCLUSIONS

The field of PET molecular imaging for the detection of disease in patients with biochemical recurrence of PCa is rapidly evolving with the arrival of promising new molecules. Our data show that ACE and FCH provide comparable information in

TABLE 2. Association Between Imaging Findings and Follow-up Results (n = 32)

	Acetate, n (%)			Choline, n (%)		
Disease Localization Based on Follow-up	**Positive**	**Negative**	**Undetermined**	**Positive**	**Negative**	**Undetermined**
			6 (18.8)			6 (18.8)
Local	5 (15.6)	4 (12.5)		5 (15.6)	4 (12.5)	
Regional (N1)	1 (3.1)			1 (3.1)		
Regional + distant (N1 + M1a)	1 (3.1)			1 (3.1)		
Locoregional		2 (6.3)			2 (6.3)	
Locoregional + distant						
N1 + M1b	1 (3.1)			1 (3.1)		
N1+ M1a	1 (3.1)			1 (3.1)		
N1+ M1a + M1b		1 (3.1)			1 (3.1)	
Distant						
Nodal (M1a)	6 (18.8)			4 (12.5)	2 (6.3)	
Bone (M1b)		2 (6.3)			2 (6.3)	
Visceral (M1c)	1 (3.1)			1 (3.1)		
Combined distant (M1a + M1b)	1 (3.1)			1 (3.1)		

N1 indicates regional lymph node metastases; M1a, nonregional lymph-node metastases; M1b, bone metastases; M1c, metastases in other site(s) with or without bone disease.

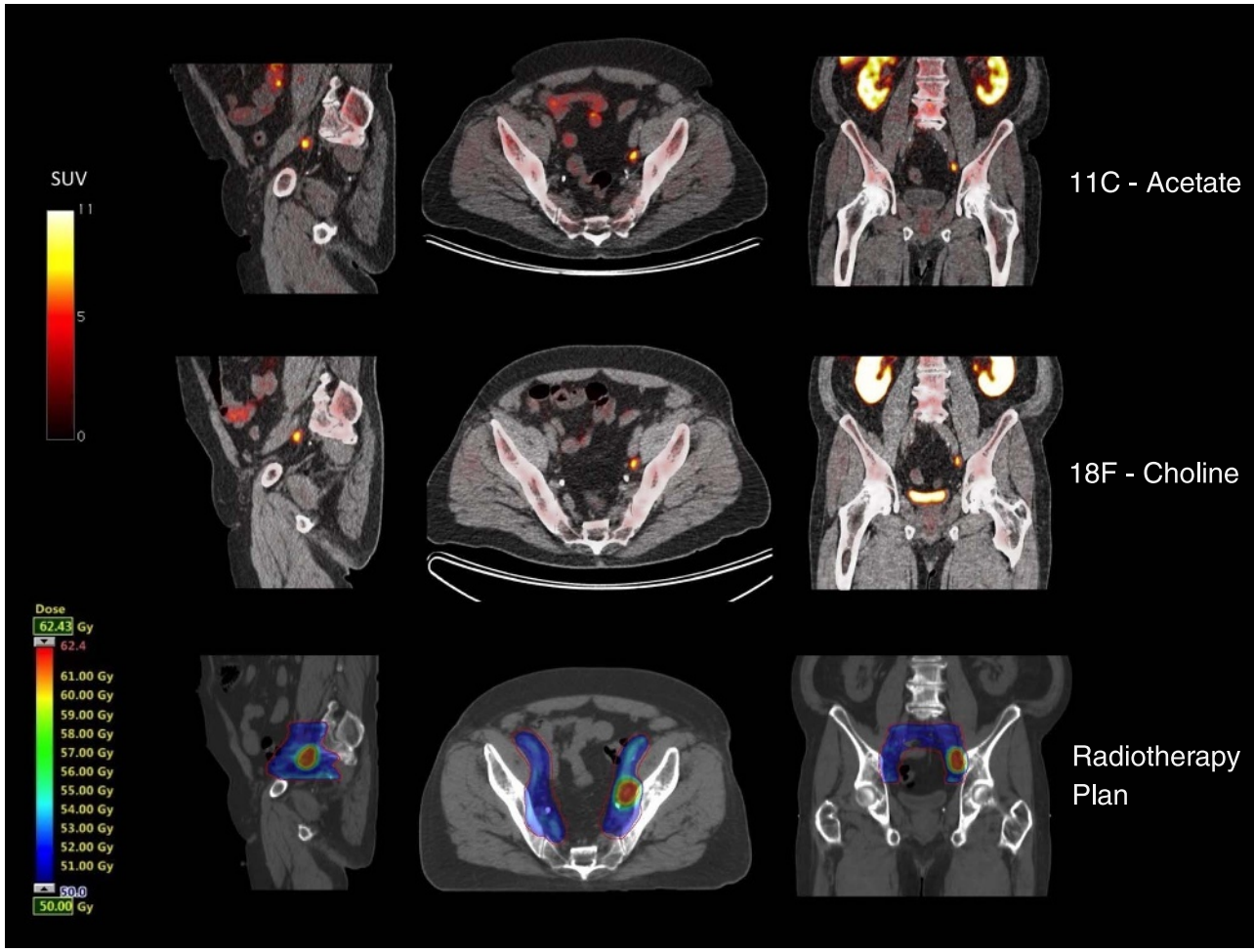

FIGURE 2. PET-CT images representing an ^{11}C-ACE– and ^{18}F-FCH–positive pelvic lymph node in a 63-year-old man with biochemical relapse (PSA 4 ng/mL) after definitive RT and the color-wash dose distribution of the subsequent image-guided salvage RT plan.

TABLE 3. Treatment Management Modifications Based on ^{11}C-ACE and ^{18}F-FCH PET Findings (n = 32)

RP (n = 9)		RP + Salvage RT (n = 15)		RT ± ADT (n = 8)	
Treatment Modification		Treatment Modification		Treatment Modification	
Yes	No	Yes	No	Yes	No
2 (22%) ACE/FCH	7 (78%) ACE/FCH	6 (40%) ACE 4 (27%) FCH	9 (60%) ACE 11 (73%) FCH	3 (37.5%) ACE/FCH	5 (62.5%) ACE/FCH
n = 1: PB RT boost for local relapse and WPRT with boost for N1 disease; n = 1: PB + WPRT with boost for N1 disease)	n = 5: PB RT; n = 2: PB + WPRT for risk factors	n = 6/4: RT + ADT for oligometastases	n = 4/6: palliative ADT; n = 4: WW; n = 1: RT*	n = 2: HIFU local relapse; n = 1: RT + ADT nodal relapse	n = 2: palliative ADT; n = 3: WW

PB indicates prostate bed; WPRT, whole pelvis RT; WW, watchful waiting; HIFU, high-intensity focal ultrasound.
*Locoregional RT despite negative PET findings.

patients with early recurrent PCa, both leading to treatment modification in one third of cases. The results of comparative studies including FCH, which is the most commonly used standard, may thus be considered valid also for ACE.

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