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ORIGINAL ARTICLE

^{18}F-FACBC (anti1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid) versus ^{11}C-choline PET/CT in prostate cancer relapse: results of a prospective trial

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Abstract
Purpose To compare the accuracy of ^{18}F-FACBC and ^{11}C-choline PET/CT in patients radically treated for prostate cancer presenting with biochemical relapse.
Methods This prospective study enrolled 100 consecutive patients radically treated for prostate cancer and presenting with rising PSA. Of these 100 patients, 89 were included in the analysis. All had biochemical relapse after radical prostatectomy (at least 3 months previously), had ^{11}C-choline and ^{18}F-FACBC PET/CT performed within 1 week and were off hormonal therapy at the time of the scans. The two tracers were compared directly in terms of overall positivity/negativity on both a per-patient basis and a per-site basis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated for both the tracers; follow-up at 1 year (including correlative imaging, PSA trend and pathology when available) was considered as the standard of reference.
Results In 51 patients the results were negative and in 25 patients positive with both the tracers, in eight patients the results were positive with ^{18}F-FACBC but negative with ^{11}C-choline, and in five patients the results were positive with ^{11}C-choline but negative with ^{18}F-FACBC. Overall in 49 patients the results were false-negative (FN), in two true-negative, in 24 true-positive (TP) and in none false-positive (FP) with both tracers. In terms of discordances between the tracers: (1) in one patient, the result was FN with ^{11}C-choline but FP with ^{18}F-FACBC (lymph node), (2) in seven, FN with ^{11}C-choline but TP with ^{18}F-FACBC (lymph node in five, bone in one, local relapse in one), (3) in one, FP with ^{11}C-choline (lymph node) but TP with ^{18}F-FACBC (local relapse), (4) in two, FP with ^{11}C-choline (lymph nodes in one, local relapse in one) but FN with ^{18}F-FACBC, and (5) in three, TP with ^{11}C-choline (lymph nodes in two, bone in one) but FN with ^{18}F-FACBC. With ^{11}C-choline and ^{18}F-FACBC, sensitivities were 32 % and 37 %, specificities 40 % and 67 %, accuracies 32 % and 38 %, PPVs 90 % and 97 %, and NPVs 3 % and 4 %, respectively. Categorizing patients by PSA level (<1 ng/ml 28 patients, 1 – <2 ng/ml 28 patients, 2 – <3 ng/ml 11 patients, ≥3 ng/ml 22 patients), the number (percent) of patients with TP findings were generally higher with ^{18}F-FACBC than with ^{11}C-choline: six patients (21 %) and four patients (14 %), eight patients (29 %) and eight patients (29 %), five patients (45 %) and four patients (36 %), and 13 patients (59 %) and 11 patients (50 %), respectively.
Conclusion ^{18}F-FACBC can be considered an alternative tracer superior to ^{11}C-choline in the setting of patients with biochemical relapse after radical prostatectomy.

Keywords Anti-3-^{18}F-FACBC · Fluciclovine · ^{11}C-Choline · PET/CT · Prostate cancer · PSA

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Introduction

Not infrequently patients radically treated for prostate cancer (PCa) and showing biochemical relapse do not show any

recurrence either clinically or by conventional imaging. This may be a relevant issue in choosing an appropriate treatment since generally patients with oligometastatic disease may be selected for local treatment (surgery or radiotherapy) to delay as long as possible systemic treatment (androgen deprivation therapy or chemotherapy), which is more appropriate for patients with multimetastatic disease [1, 2]. For this purpose, ^{11}C-choline and ^{18}F-choline are two tracers that have been used in the last few years for PET/CT imaging of PCa. Although choline PET/CT is a whole-body noninvasive single-step procedure and has a higher sensitivity than other imaging procedures, its diagnostic accuracy is still suboptimal. Reported data show a variable detection rate according to serum prostate serum antigen (PSA) level, ranging from 36 % if PSA at relapse is lower than 1 ng/ml to 73 % if PSA at relapse is higher than 3 ng/ml [3].

An investigational amino acidic PET tracer (anti1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid, ^{18}F-FACBC) has recently been synthesized and has been initially tested in patients to calculate its dosimetry and its potential preliminary sensitivity for the detection of PCa relapse. ^{18}F-FACBC uptake was shown to correlate with the expression level of the ASC (alanine, serine, cysteine) amino acid system on PCa cells, along with LAT1 expression (another amino acid transporter system) [4]. All the preliminary PCa imaging results have been very promising [5, 6] and its sensitivity has been shown to be higher than that of traditional nuclear medicine methods [7].

More recently, three preliminary studies in different patient populations have been reported by our group comparing ^{11}C-choline and ^{18}F-FACBC in groups of patients with suspected PCa relapse [8–10]. Initial results suggested that the detection rate seems to be higher with ^{18}F-FACBC than with ^{11}C-choline in both patient-based and lesion-based analysis. The aim of this study was, therefore, to compare the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of ^{18}F-FACBC PET/CT and ^{11}C-choline PET/CT in a population of patients with PCa radically treated and with biochemical relapse. This approach is more reliable than detection rate, usually employed in PCa imaging, because detection rate includes only positive findings without taking into consideration true-negative (TN) and false-negative (FN) findings.

Materials and methods

Study design

All patients referred by the Urology Unit of S. Orsola-Malpighi Hospital and consecutively enrolled as outpatients underwent ^{18}F-FACBC PET/CT within 1 week after ^{11}C-choline PET/CT. Inclusion criteria were: (1) PCa treated with radical prostatectomy at least 3 months before enrolment, (2) recurrent PCa suspected on the basis of an absolute PSA level of 0.2 mg/mL or greater after prostatectomy, (3) conventional imaging performed, (4) age ≥18 years, and (5) ^{11}C-choline PET/CT performed within 1 week of ^{18}F-FACBC PET/CT.

Patients were followed up for an average of 1 year (range 6 – 24 months) after the ^{18}F-FACBC PET/CT scan, during which their PSA serum level was monitored and further imaging procedures, including bone scan, transrectal ultrasonography (TRUS), MR and CT, or biopsies were performed according to the clinical situation including the ^{18}F-FACBC/^{11}C-choline results. The standard of reference was therefore a re-evaluation of the clinical and imaging history after the ^{18}F-FACBC PET/CT scan. These data were used to categorize the PET/CT results into true-positive (TP), TN, false-positive (FP), or FN. All negative PET/CT scans were considered FN (because of PSA rise) except in two patients who had a completely negative 24-month follow-up.

Radiotracer synthesis

^{18}F-FACBC ^{18}F-Fluoride (necessary for tracer labelling) was produced in the cyclotron unit of S.Orsola-Malpighi Hospital. ^{18}F-FACBC, more specifically fluciclovine (^{18}F) injection, was prepared in the Radiopharmacy of S.Orsola-Malpighi Hospital using a commercial synthesis module (FastLab™; GE Healthcare, Waukesha, WI) as preloaded single-use cassettes for research purposes (GE Healthcare), and processed based on a previously reported method [11].

^{11}C-Choline ^{11}C-Choline was synthesized using a solid-phase method as described by Pascali et al. [12], using a commercial synthesis module (TracerLab™ FXC Pro; GE Healthcare, Waukesha, WI).

Imaging procedure

^{18}F-FACBC and ^{11}C-choline PET/CT acquisitions were performed similarly. Briefly, approximately 370 MBq of ^{18}F-FACBC or 3.4 MBq/kg of ^{11}C-choline was injected. No fasting was needed for ^{11}C-choline but fasting for 4 h was required prior to injection of ^{18}F-FACBC. The uptake time from the end of the injection to the start of the scan was 3 – 4 min for both tracers [5–7] (3.6 ± 0.7 min, range 3 – 5 min, for ^{18}F-FACBC; 3.5 ± 0.7 min, range 3 – 5 min, for ^{11}C-choline). Images were acquired on a 3D tomograph (Discovery STE; GE Healthcare, Waukesha, WI) for 2 min per bed position. The field of view included the skull to the mid-femurs. A low-dose CT scan (120 kV, 80 mA) without contrast medium was performed both for attenuation correction and anatomical mapping. Iterative reconstruction (3D ordered-subsets expectation maximization, with two iterations

and 20 subsets, followed by smoothing with a 6-mm 3D gaussian kernel) and CT-based iterative correction of the emission data for attenuation, scatter, random coincidence events, and system dead-time were performed to optimize the PET images [13].

Table 1 Patients characteristics

Characteristic	Value
No. of patients	
Enrolled	100
Included	89
Age (years)	
Mean	69
Range	55 – 83
Trigger PSA level (ng/ml)	
Mean	6.99
Median	3.35
Standard deviation	17.5
Range	0.20 – 20.72
Gleason score, *n*	
≤6	12
7	33
8 – 10	32
Not specified/not available	12
T stage, *n*	
1c	1
2	17
3	59
Not specified/not available	12
N stage, *n*	
0	27
1	39
x	11
Not specified/not available	12
Postsurgical treatment, *n* (%)	
Radiotherapy + hormonal therapy	28 (31)
Radiotherapy only	12 (13)
Hormonal therapy only	23 (26)
None	26 (29)
Interval between radical prostatectomy and PET (months)	
Mean	79
Median	75
Standard deviation	57
Range	3 – 228
Interval between radical prostatectomy and PET, *n* (%)	
<6 months	6 (7)
6 – ≤24 months	15 (17)
Interval between PET and last follow-up (months)	
Mean	16
Median	14
Standard deviation	7
Range	6 – 29

Image interpretation

PET/CT scans were independently evaluated by two nuclear medicine physicians with extensive experience in oncology (C.N. and L.Z.). The readers were aware of each patient's clinical history (including standard imaging results) but were blinded to the ^{11}C-choline result. In the event of disagreement, final consensus was reached. Criteria to define PET/CT positivity included the following: presence of focal areas of detectable increased tracer uptake (more intense than background) excluding articular processes and areas of physiological uptake, with or without any underlying lesion identified on CT [14, 15]. The semiquantitative criterion standardized uptake value (SUV) ratio (SUVmax in the lesion/SUVmean in surrounding background) was used to aid visual analysis. If mild focal uptake was found, a ratio ≥1.5 was considered significant.

The workstation used for image reading and semiquantitation was provided by General Electric (Xeleris; GE Medical Systems, Waukesha, WI). Maximum intensity projection, PET, CT and PET/CT fused images in various slices (axial, sagittal and coronal) were visualized simultaneously to correctly interpret the scans.

Statistical analysis

Sensitivity, specificity, PPV, NPV, accuracy and detection rate were calculated. MedCalc was used for statistical analysis. The chi-squared exact test was used to compare the ^{11}C-choline and ^{18}F-FACBC results. Kaplan-Meier curves were used to analyse the time to PSA progression in imaging-positive and imaging-negative patients. Agreement between the two tracers was evaluated in terms of the interrater kappa coefficient of agreement (κ).

Table 2 Correspondence between ^{11}C-choline and ^{18}F-FACBC PET/CT results: patient-based analysis

^{18}F-FACBC	^{11}C-Choline		
	Negative	Positive	Total
Negative	51	5 (2 lymph node, 1 bone, 1 local relapse)	56
Positive	8 (5 lymph node, 1 bone, 1 local relapse)	25[a]	33
Total	59	30	89

Weighted kappa = 0.681

[a] The concordant results can be estrapolated from paragraphs "local relapse", "lymph nodes", "bones"

Table 3 Correspondence between ^{11}C-choline and ^{18}F-FACBC PET/CT results: patient-based analysis in relation to trigger PSA level

Imaging result		PSA level (ng/ml)	
^{18}F-FACBC	^{11}C-Choline	Median	Range
Negative	Negative	1.24	0.2 – 14.6
Positive	Positive	2.1	0.55 – 16
Negative	Positive	7	1.42 – 20.72
Positive	Negative	1.71	0.24 – 0.48

Table 5 Performance of ^{11}C-choline and ^{18}F-FACBC PET/CT in relation to trigger PSA level

Trigger PSA (ng/ml)	Sensitivity (%)		Detection rate (%)	
	^{11}C-Choline	^{18}F-FACBC	^{11}C-Choline	^{18}F-FACBC
<1	14	21	14	21
1 – <2	29	29	29	45
2 – <3	36	45	45	45
≥3	50	59	59	59

Results

Of 100 patients enrolled, 11 dropped out for screening or follow-up failure. Thus the patient population consisted of 89 patients (mean age 69 years, range 55 – 83 years). Patient characteristics are summarized in Table 1. None of the patients had adverse reactions to ^{11}C-choline or ^{18}F-FACBC.

Patient-based analysis

In 51 patients (57 %) neither tracer contributed to the detection of the disease relapse site. In 25 patients (28 %) both ^{11}C-choline and ^{18}F-FACBC PET/CT were positive. In eight patients (9 %) ^{18}F-FACBC PET/CT was positive and ^{11}C-choline PET/CT was negative. In five patients (6 %) ^{18}F-FACBC PET/CT was negative and ^{11}C-choline PET/CT was positive (Tables 2 and 3). The κ value for inter-rater agreement between the two tracers was 0.68.

According to the follow-up data, ^{18}F-FACBC PET/CT was TP in 32 patients, TN in two, FN in 54 and FP in one, leading to an overall sensitivity, specificity, PPV, NPV and accuracy of 37 %, 67 %, 97 %, 4 % and 38 %, respectively. ^{11}C-Choline PET/CT was TP in 27 patients, TN in two, FN in 57 and FP in three, leading to an overall sensitivity, specificity, PPV, NPV and accuracy of 32 %, 40 %, 90 %, 3 %, 32 %, respectively (Table 4).There was a statistically significant difference in terms of TP, TN, FP and FN patients between the two tracers in favour of ^{18}F-FACBC (chi-squared test, $p < 0.0001$). Categorizing the patients according to serum PSA level, the sensitivity with ^{11}C-choline was slightly lower than that with ^{18}F-FACBC ($p = 0.0001$ for patients with PSA <1 ng/ml), but the difference in detection rates of the two tracers was less significant due to a higher number of FP and a lower number of TP findings with ^{11}C-choline (Table 5; Fig. 1).

Local relapse

Overall, 13 patients were positive in the prostate bed with at least one tracer. Of these 13 patients, ten were positive with both tracers, one was positive with ^{11}C-choline but negative with ^{18}F-FACBC, and two were negative with ^{11}C-choline but positive with ^{18}F-FACBC. The other 76 patients were negative in the prostate bed with both tracers. At follow-up, all ten concordantly positive patients were TP: four were validated by biopsy, three by imaging (MRI in one, TRUS in one, and TRUS and MRI in one), and three by clinical evaluation (PSA trend after therapy). Of the remaining three patients with discordant results: one was FP with ^{11}C-choline but TN with ^{18}F-FACBC and two were TP with ^{18}F-FACBC but FN with ^{11}C-choline. The standards of reference were the clinical findings (PSA trend after salvage radiotherapy in one) and clinical and imaging findings (MRI in one, persistent PSA level after surgery in one). Among the 76 patients who were concordantly negative in the prostatic bed with both tracers, at the time of this report four were FN. Two were validated by biopsy and two by clinical evaluation and imaging (MRI in one, TRUS in one).

TN was confirmed (at the time of this report) in 19 patients. The standards of reference were biopsy in six patients (TRUS in three, bladder endoscopy showing inflammation in three), imaging in 11 patients (negative for local relapse but positive for systemic disease in lymph-nodes, in bone or at other sites, e.g. lung), and clinical evaluation in two patients (the two patients were still negative after 24 months and therefore

Table 4 Overall performance of ^{11}C-choline and ^{18}F-FACBC PET/CT in the 89 included patients

	True-positive (*n*)	True-negative (*n*)	False-positive (*n*)	False-negative (*n*)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
^{11}C-Choline	27	2	3	57	32	40	90	3	32
^{18}F-FACBC	32	2	1	54	37	67	97	4	38

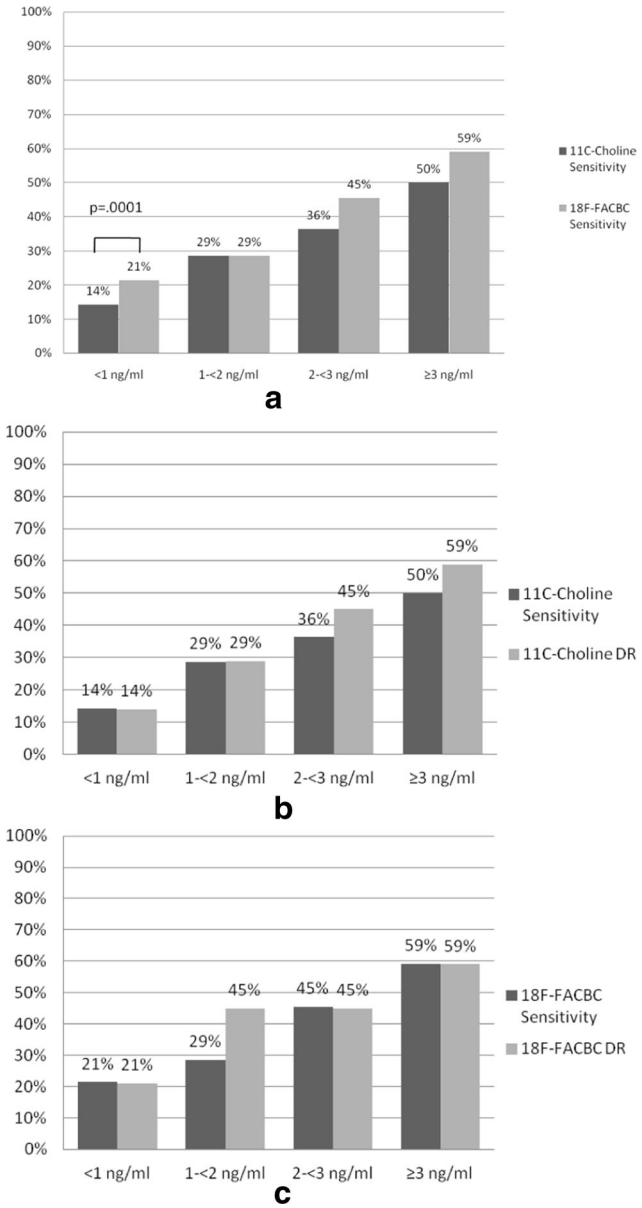

Fig. 1 Comparison between ^{11}C-choline and ^{18}F-FACBC PET/CT sensitivity and detection rate (*DR*) in relation to trigger PSA level

considered TN). In the remaining 53 of the 76 patients concordantly negative in the prostate bed, TN or FN could not be determined because of insufficient evidence during follow-up (Table 6).

Lymph nodes

Overall, 26 patients were positive for nodal involvement with at least one tracer. Of these 26 patients, 13 were positive with both ^{11}C-choline and ^{18}F-FACBC (12 TP, one FP), nine were negative with ^{11}C-choline (eight FN, one TN) but positive with ^{18}F-FACBC (eight TP, one FP), and four were positive with ^{11}C-choline (two TP, two FP) but negative with ^{18}F-FACBC (two FN, two TN; Table 7). The standards of reference for these positive findings are specified in Table 8.

Table 6 Local relapse among the 89 included patients

^{11}C-Choline	^{18}F-FACBC		
	Positive	Negative	Total
Positive	10 (10 disease confirmed)	1 (1 disease free)	11
Negative	2 (2 disease confirmed)	76 (4 disease confirmed, 19 disease free, 53 insufficient evidence)	78
Total	12	77	89

Among the 63 patients who were concordantly negative for nodal involvement, at the time of this report five were FN. In these five patients the standards of reference were lymphadenectomy in one and clinical evaluation and imaging in four. TN was confirmed (at the time of this report) in 19 patients. The standards of reference were clinical evaluation and imaging (negative for nodal metastases but positive for disease at the level of the prostate bed, in bone or at other sites) in most patients, and clinical evaluation in two patients. The remaining 39 of the 63 patients concordantly negative for nodal involvement remained indeterminate TN or FN because of insufficient evidence during follow-up.

Bone

Overall, seven patients were positive for bone lesions with at least one tracer. Four patients were positive with both tracers, two were positive with ^{11}C-choline (one FP, one TP) but negative with ^{18}F-FACBC (one TN, one FN), and one was negative with ^{11}C-choline (FN) but positive with ^{18}F-FACBC (TP; Table 9). The standards of reference for these positive findings are specified in Table 10.

Among the 82 patients who were concordantly negative for bone involvement with both tracers, four were FN. The standard of reference was clinical evaluation and imaging in all patients (two CT, one follow-up ^{11}C-choline PET/CT, one bone scan + MRI both depicting a lesion in the tibia outside

Table 7 Lymph node involvement among the 89 included patients

^{11}C-Choline	^{18}F-FACBC		
	Positive	Negative	Total
Positive	13 (12 disease confirmed, 1 disease free)	4 (2 disease confirmed, 2 disease free)	17
Negative	9 (8 disease confirmed, 1 disease free)	63 (5 disease confirmed, 19 disease free, 39 insufficient evidence)	72
Total	22	67	89

Table 8 Lymph node lesion-based analysis in 26 patients positive for nodal involvement

Imaging performance		No. of patients	No. of positive nodes		Standard of reference		Treatment after PET
^{11}C-Choline	^{18}F-FACBC		^{11}C-Choline ($n=23$)	^{18}F-FACBC ($n=31$)	Result	Procedure	
True-positive	True-positive	7	1	1	Positive (same site)	1 lymphadenectomy, 6 clinical evaluation	1 not available, 1 target RT, 3 target RT + HT, 1 HT, 1 lymphadenectomy
		2	1	2	Positive (different sites)	2 clinical evaluation	1 HT + target RT + HT, 1 RT prostate bed + lymph nodes
		1	2	2	Positive (same site)	1 clinical evaluation + imaging	HT + chemotherapy + bisphosphonate
		1	3	1	Single positive	1 clinical evaluation + imaging	HT + bowel surgery
		1	2	3	Positive (same site)	1 clinical evaluation	Target RT + HT
False-positive	False-positive	1	1	1	Negative (positive nodal metastasis other site)	1 lymphadenectomy	Lymphadenectomy (pelvic and retroperitoneal, multiple left iliac nodal metastases) + HT
True-positive	False-negative	2	1	0	Positive (most likely not single)	1 clinical evaluation	1 retroperitoneal stereotactic RT + HT, 1 aortocaval lymphadenectomy + HT
False-positive	True-negative	1	3	0	Negative (positive for single bone metastasis outside PET field of view)	1 clinical evaluation + imaging (MRI)	HT
		1	1	0	Negative (positive for local relapse)	1 clinical evaluation + imaging	HT
False-negative	True-positive	5	0	1	Positive (1 locoregional, 4 distant)	1 clinical evaluation + imaging, 4 clinical evaluation	3 RT + HT, 2 HT
		2	0	2	Positive	2 clinical evaluation + imaging	1 chemotherapy + HT, 1 HT + salvage RT (prostate bed + lymph nodes)
		1	0	3	Positive	1 lymphadenectomy	Lymphadenectomy + HT
True-negative	False-positive	1	0	1	Negative (reactive node)	1 lymphadenectomy	Lymphadenectomy (bilateral iliac-obturator) + HT

RT radiotherapy, *HT* hormonal therapy

Table 9 Bone involvement among the 89 included patients

^{11}C-Choline	^{18}F-FACBC		
	Positive	Negative	Total
Positive	4 (4 disease confirmed)	2 (1 disease confirmed, 1 disease free)	6
Negative	1 (1 disease confirmed)	82 (4 disease confirmed, 32 disease free, 46 insufficient evidence)	83
Total	5	84	89

the PET field of view). At the time of this report 32 patients were free of bone involvement (TN). The standards of reference were PSA decrease after target treatment to the prostate bed or lymph nodes (radiotherapy to the prostate bed and/or lymph nodes, lymphadenectomy) or imaging (negative for bone metastases but positive for local relapse or nodal involvement or dissemination to other sites) in most patients, and clinical evaluation in two patients. The remaining 46 patients were indeterminate TN or FN because of insufficient evidence during follow-up. The numbers of TP and TN per site of relapse for the two tracers are shown in Fig. 2.

In general, the PPV of ^{18}F-FACBC PET/CT for the prediction of local, lymph node and bone relapse was higher than that of ^{11}C-choline PET/CT (Table 11).

Time to PSA progression

No specific treatment was performed in 17 patients after ^{11}C-choline and ^{18}F-FACBC PET/CT. Kaplan-Meier curves were therefore calculated for time to PSA progression in imaging-positive and imaging-negative patients. There was no significant difference between ^{11}C-choline-positive and ^{11}C-choline-negative patients or between ^{18}F-FACBC-positive and ^{18}F-FACBC-negative patients.

Lesion size

Table 12 shows the sizes of positive lesions in relation to the PET imaging performance of the two tracers.

Discussion

The introduction into clinical practice of new and very effective drugs for PCa (such as enzalutamide and abiraterone) and the opportunity to exploit targeted treatments in patients with oligometastatic disease (such as radiotherapy and salvage surgery) increase the need for more accurate imaging tests aimed to identify the site of disease relapse. In this prospective study, we analysed a homogeneous population of patients on the basis of biochemical relapse after radical treatment (surgery and/or

Table 10 Bone lesion-based analysis in seven patients positive for bone involvement

Imaging performance		No. of patients	No. of positive bone findings		CT appearance	Standard of reference		TREATMENT PERFORMED AFTER PET
^{11}C-Choline	^{18}F-FACBC		^{11}C-Choline	^{18}F-FACBC		Result	Procedure	
True-positive	True-positive	1	1	1	Negative	Single bone metastasis	Clinical evaluation	Target RT + HT
		1	3`	3	Negative	Oligometastatic	Imaging (bone scan, MRI, ^{11}C-choline)	HT + RT + bisphosphonate
		1	2	3	Schmorl's nodules/ degenerative	Oligometastatic	Imaging (follow-up ^{11}C-choline: progressive disease)	HT + chemotherapy + bisphosphonate
		1	>5	>5	Multiple osteosclerotic	Multimetastatic	Patient dead from progressive disease	Not available
True-positive	False-negative	1	>5	0	Multiple small osteosclerotic	Multimetastatic	Imaging (bone scan)	HT
False-negative	True-positive	1	0	1	Degenerative	Single bone metastasis	Imaging (follow-up ^{11}C-choline)	Not available
False-positive	True-negative	1	1	0	Osteosclerotic	Bone island	Imaging (MRI)	HT

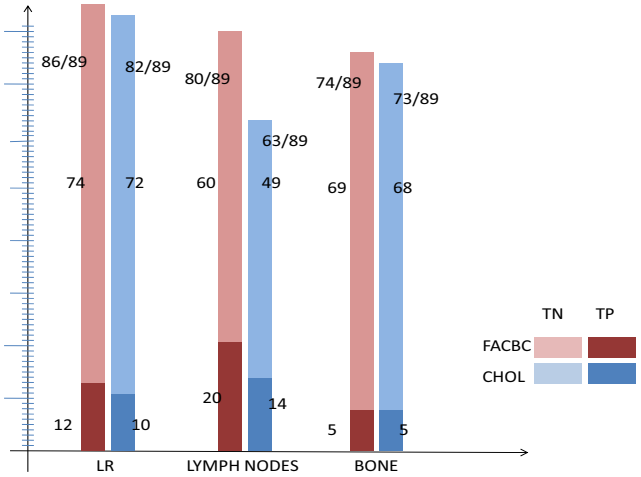

Fig. 2 Analysis per patient and site of relapse (absolute number of patients). *LR* local relapse, *FACBC* ^{18}F-FACBC, *CHOL* ^{11}C-choline, *TN* true-negative, *TP* true-positive

radiotherapy and/or adjuvant androgen deprivation therapy). We compared the results of PET/CT with ^{11}C-choline (a tracer widely used in Europe) and a relatively new radiotracer, ^{18}F-FACBC, that was expected to provide better performance on the basis of published preliminary papers.

The detection rates with ^{18}F-FACBC were higher than those with ^{11}C-choline overall and for local, lymph nodal and bone relapse. ^{18}F-FACBC also showed higher sensitivity and specificity (37 % and 67 % vs. 32 % and 40 %). This difference was particularly significant in patients with low PSA levels (<1 ng/ml). Besides a mild improvement in overall performance (also demonstrated by relatively good concordance between the two tracers), there are some practical advantages making ^{18}F-FACBC a very interesting compound. One is the long half-life of ^{18}F that enables ^{18}F-labelled tracers to be distributed to PET centres without a cyclotron and to be easily handled in clinical routine. Other advantages are its proven stability over time in vitro, easy production based on preloaded cassettes, delayed renal excretion associated with more favourable distribution in the abdomen and pelvis, lower background, higher tumour-to-background ratio for positive lesions and proven safety for the patient.

One interesting aspect of these results is the analysis of sensitivity and specificity. In the field of functional imaging of PCa, most publications do not report data on sensitivity but

Table 11 Positive predictive value of the two tracers for different relapse sites

Site	Positive predictive value (%)	
	^{11}C-Choline	^{18}F-FACBC
Local	91	100
Lymph nodes	82	91
Bone	83	100

Table 12 Sizes of positive lesions in relation to the PET imaging performance of the two tracers.

Imaging performance		Lesion size (mm)		
^{11}C-choline	^{18}F-FACBC	Lymph nodes	Bone	Local relapse
True-positive	True-positive	7 – 21	5 – 10	8 – 21
False-positive	False-positive	6	–	–
True-positive	False-negative	9 – 11	5	–
False-positive	True-negative	10 – 13	8	6
False-negative	True-positive	5 – 7	6	9 – 18
True-negative	False-positive	5	–	–

rather report positivity/detection rates of different tracers, assuming that a positive and focal finding at a site where disease relapse is common can considered a true relapse. There are several logical and practical reasons for this. One is that many compounds for prostate imaging are considered relatively specific. Furthermore, PCa is a slow-growing disease: evolution of one lesion can take a long time, and so salvage therapy is set up before any possible further confirmation can be obtained. Another reason is that PCa metastasizes to areas difficult to biopsy such as bone (where they are usually very sclerotic and relatively small) and pelvic lymph nodes. Finally, since all the tracers used in PCa imaging are specifically used for PCa only in patients with biochemical failure, there is a lack of control cases.

In this study we tried to overcome the problems related to detection rate. We analysed the imaging results with ^{11}C-choline and ^{18}F-FACBC patient-by-patient (independently of one another) in the light of biopsy data and/or clinical follow-up. We found a difference of approximately 10 % between the detection rate and sensitivity of ^{11}C-choline, indicating that the detection rate may significantly overestimate sensitivity. The difference was lower for ^{18}F-FACBC (as a consequence of a lower number of FP and a higher number of TN findings).

The sensitivity of the two tracers was between 30 % and 40 %, with ^{18}F-FACBC providing the higher values. Although these results seem suboptimal, they are comparable to or even better than those in the literature. We have to emphasize that, in this patient population, all the negative scans were categorized as FN because of PSA failure. Only two patients showing a mild increase in PSA that was stable over time and without any equivocal finding on follow-up were considered TN. This approach is certainly the worst hypothesis against which each tracer can be tested, and reinforces their possible clinical utility.

The still relatively low sensitivity and NPV are mainly a result of the low intrinsic spatial resolution of PET (<5 mm), that is not suitable for the detection of micrometastases (with both the tracers). In our study, most patients had a PSA level

<2 ng/ml (<1 ng/ml in half the patients) that contributed to the relatively low positive detection rate. This is of great importance when PET is performed to guide local and targeted therapy, that must be chosen so as not to achieve a radical result but to simply postpone as long as possible the onset of a systemic approach. Interestingly, the PPV for local relapse was significantly higher than that found by Schuster et al. (100 % vs. 66 %) [7]. This was because of the image interpretation criteria, that certainly enhanced specificity and reduced sensitivity in our patient population. This variable approach draws the attention to the importance of standardization not only of the imaging flow chart and technical procedure, but also of image reading through reproducible criteria.

In this study two issues remain unresolved and as well as in many other similar studies. One relates to the clinical management of patients once the diagnosis of relapse is reached, before all the lesions observed on functional imaging are proven (i.e. systemic therapy started in patients with confirmed bone lesions and concomitant suspected but not confirmed lymph nodal metastasis). Thus we performed an accurate patient-by-patient analysis but a partial lesion-by-lesion analysis. This is the main reason why both the concordance between ^{11}C-choline and ^{18}F-FACBC and the validation results are reported, but no clear conclusion regarding site-by-site sensitivity and specificity could be drawn. The other issue relates to the Kaplan-Meier curves for time to PSA progression. For the clinical reasons discussed above, in our sample only 17 patients were not treated after imaging and could therefore be included in this analysis. This preliminary evaluation showed a nonsignificant difference in time to PSA progression between ^{11}C-choline-positive and ^{11}C-choline-negative patients and between ^{18}F-FACBC-positive and ^{18}F-FACBC-negative patients. Despite this, the two curves suggested a different trend. A larger sample of nontreated patients is needed to evaluate this critical issue.

Overall, in our preliminary experience ^{18}F-FACBC was slightly superior to ^{11}C-choline and was easier to handle and interpret, suggesting that it could fully replace ^{11}C-choline in clinical practice in the near future. However, in some patients minimal differences were found, mainly but not only in favour of ^{18}F-FACBC. Further and deeper studies on clinical impact and prognosis may be able to definitively confirm this approach.

Conclusion

From our preliminary experience, we conclude that ^{18}F-FACBC can be considered an alternative tracer superior to ^{11}C-choline both for clinical and technical reasons in the setting of patients with biochemical relapse after radical prostatectomy. Further subgroup, semiquantitative and statistical analyses, however, are needed to exactly identify the possible clinical impact of this new tracer.

Compliance with ethical standards

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Conflicts of interest None.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This Italian monocentric prospective protocol was approved by the Ethical Committee of S.Orsola-Malpighi Hospital.

Informed consent All the enrolled patients signed specific informed consent.

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