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ORIGINAL ARTICLE

Impact of sodium ^{18}F-fluoride PET/CT, ^{18}F-fluorocholine PET/CT and whole-body diffusion-weighted MRI on the management of patients with prostate cancer suspicious for metastasis: a prospective multicentre study

Mathieu Gauthé[1,2] · Cyrielle Aveline[1] · Frédéric Lecouvet[3] · Laure Michaud[1] · Caroline Rousseau[4,5] · Marc Tassart[6] · Olivier Cussenot[7,8] · Jean-Noël Talbot[1] · Isabelle Durand-Zaleski[2,9]

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Abstract

Purpose To compare the impact of 18F-sodium-fluoride (NaF) PET/CT, 18F-fluorocholine (FCH) PET/CT and diffusion-weighted whole-body MRI (DW-MRI) on the management of patients with prostate cancer (PCa) suspicious for distant metastasis.

Methods Prostate cancer patients were prospectively included between December 2011 and August 2014 and benefited from these three whole-body imaging (WBI) modalities within 1 month in addition to the standard PCa workup. Management was prospectively decided by clinicians during two multidisciplinary meetings, before and after the whole-body imaging workup. Rates of induced changes of whole-body imaging modalities were compared by Cochran's Q test.

Results One-hundred-one patients (27 at staging, 59 at first biochemical recurrence (BCR) and 15 at first episode of rising serum level of prostate-specific antigen during androgen-deprivation therapy) were included. The overall rate of management changes was 52%: 29% as a consequence of WBI, higher for FCH-PET/CT than for NaF-PET/CT or DW-MRI ($p < 0.0001$) and highest (41%) for FCH-PET/CT at BCR. Actual management was adequate in all patients but two.

Conclusions Whole-body imaging induced a change in management in approximately a third of PCa patients suspicious for metastasis. The impact rate was determined to be greatest at first BCR using FCH-PET/CT. NaF-PET/CT and DW-MRI seemed less useful in this context.

Keywords Prostate cancer imaging · PET/CT · DW-MRI · Impact on management · Progression-free survival

✉ Mathieu Gauthé
mathieugauthe@yahoo.fr

[1] Department of Nuclear Medicine, Hôpital Tenon, Assistance Publique Hôpitaux de Paris (AP-HP), Sorbonne Université, 4 rue de la Chine, 75020 Paris, France

[2] AP-HP Health Economics Research Unit, INSERM UMR 1123, Paris, France

[3] Department of Radiology, Centre du Cancer, Institut de Recherche Expérimentale Et Clinique, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

[4] Nuclear Medicine Unit, ICO Gauducheau Cancer Centre, Saint-Herblain, France

[5] Nantes-Angers Cancer Research Centre, INSERM U892, CNRS UMR 6299, Université de Nantes, Nantes, France

[6] Department of Radiology, Hôpital Tenon, AP-HP, Sorbonne Université, Paris, France

[7] Department of Urology, Hôpital Tenon, AP-HP, Sorbonne Université, Paris, France

[8] GRC No 5, ONCOTYPE-URO, Institut Universitaire de Cancérologie, Sorbonne Université, Paris, France

[9] Service de Santé Publique, Hôpital Henri Mondor, AP-HP, Université Paris 12, Créteil, France

Introduction

In patients with prostate cancer (PCa) suspicious for distant metastasis, imaging of the whole-body (at least head, neck, torso and the proximal part of the limbs) is used to guide the therapeutic strategy. Sodium ^{18}F-fluoride (NaF) positron emission tomography/computed tomography (PET/CT), ^{18}F-fluorocholine (FCH) PET/CT and diffusion-weighted whole-body magnetic resonance imaging (DW-MRI) are recent whole-body imaging modalities (WBI) proposed in this aim. NaF-PET/CT is currently recommended for staging high-risk PCa by the National Comprehensive Cancer Network (NCCN) [1] as the skeleton is the preferential site of metastasis and is the single one in approximately 62% of PCa [2]. However, bone-dedicated NaF-PET/CT almost always fails in detecting extra-osseous metastases. PET/CT with ^{11}C-choline, another choline-based radiotracer similar to FCH in diagnostic performance [3], is recommended for localisation of recurrent PCa by the NCCN and the European Association of Urology (EAU) [1, 4]. DW-MRI has not been evaluated by medical agencies since no contrast medium is involved, and it is not yet recommended by clinical guidelines, although its effectiveness has been assessed [5].

The diagnostic performance of WBIs is an important characteristic [5–12], but their impact on patient management in the real world better reflects their operational value, as recommended by the European Medicine Agency (EMA) [13]. As a direct comparison was lacking, we compared the rate of change in PCa management induced by those three WBIs performed in the same patients, based on a prospective survey of the decisions taken during multidisciplinary meetings and on follow-up data. In accordance with the EMA guidelines [13], we also checked the adequacy of the patients' management, and the consequence of the changes on progression-free survival (PFS) reflecting patients' outcomes.

Materials and methods

Population

Patients with histologically proven PCa and without a known history of metastases were eligible for the French multicentre study "FLUPROSTIC" (NCT01501630) aiming to compare the utility of NaF-PET/CT, FCH-PET/CT and DW-MRI for detecting unknown PCa metastasis. Inclusion was offered to any PCa patient suspicious for distant metastasis referred by their clinician in any of the following settings: initial staging, biochemical recurrence (BCR) without ongoing androgen-deprivation therapy (ADT), biochemical recurrence during ADT, corresponding to castration-resistant prostate cancer (CRPC). Patients were considered at risk of developing metastases if they were presenting any of the following situations: Gleason score 8–10, time to BCR less than 3 years, stage T3b or higher, or a PSA doubling time less than 3 months (for BCR and CRPC) [14–16]. Patients presenting suspicious bone pain were also considered.

BCR was diagnosed after surgery, radiotherapy or alternative local treatment options with curative intent according to current recommendation for BCR and CRPC patients, respectively [17]. In addition to the standard PCa workup, patients underwent those three WBIs within less than a month without any therapeutic intervention during this period of time. Exclusion criteria were other progressive neoplasias, therapy change during the imaging workup, WBI workup not completed within 1 month, and contra-indications to any of the imaging modalities.

Five centres recruited patients. WBI was performed in two centres that specialised in cancer imaging (Hôpital Tenon, Paris and ICO René Gauducheau, St-Herblain).

Imaging protocols

PET/CT

Two PET/CT devices were used: GEMINI TF16 (Philips Medical Systems, Cleveland, Ohio, USA) in Hôpital Tenon and Biograph mCT (Siemens, Erlangen, Germany) in St-Herblain. For FCH-PET, dynamic images were acquired on the pelvis immediately after FCH injection of 2–3 MBq/kg of body mass (8 one-minute images); 15 min after injection, this step was followed by a "whole-body" acquisition from vertex to mid-thigh. For NaF-PET, a whole-body acquisition from vertex to toes was performed 60 min after NaF injection of 3–4 MBq/kg of body mass.

Low-dose CT without contrast-enhancement was performed prior to PET acquisition (120 kVp, 80 mA.s, slice thickness 2.5 mm, pitch 0.813, rotation time 0.5 s, FOV 600 mm) for attenuation correction and anatomic land-marking. Duration of the PET images acquisition was 2 min per bed position.

MRI

Two MRI devices were used: 1.5 T Sonata MR (Siemens, Erlangen, Germany) in Hôpital Tenon and 1.5 T Ingenia (Philips, Best, The Netherlands) in St-Herblain. The "whole-body" examination field covered the vertex to mid-thigh. T1-weighted and STIR sequences were performed in the axial and sagittal planes, without contrast-enhancement. The

diffusion sequences were performed in the axial plane using values of *b* of 0–600.

Imaging interpretation

Reading was performed on-site by unblinded imaging specialists who recorded abnormal findings in the prostatic lodge, lymph nodes, skeleton and viscera.

Changes in patients' management, PFS, and adequacy of management

The management plan was decided for each patient by clinicians during multidisciplinary meetings; the meetings before and after WBI were considered for the purpose of this study.

The multidisciplinary meeting panels were constituted by the same specialists at each of the two cancer centres (a urologist, a radiation oncologist, a pathologist and a PCa imaging specialist), who decided the management both pre- and post-WBI.

All data were made available to the panel, including clinical assessment, biochemistry and imaging results. For each patient, the panel prospectively filled in a dedicated form recording initially scheduled management, any change in management, if a change was triggered by WBI and, in this case, which of the three modalities contributed to this change, with the possibility of including several.

All follow-up data were collected over at least 6 months after the final management decision. These data were used by an independent assessor to determine the PFS and the adequacy of the actual patients' management.

Statistical analysis

Data were analysed using SPSS statistical software (IBM-Corporation). In a given patient, the three WBI modalities were performed in an order corresponding to one of the six possible sequences. The Chi-square test was performed to check for uneven patient distribution between the six sequences. Rates of management changes were compared between imaging modalities using Cochran's Q test. A p value less than 0.05 was considered to be statistically significant.

Results

Patients' characteristics

One-hundred-one patients were prospectively included between December 2011 and August 2014 and benefited from the three WBIs within less than one month (Table 1). Twenty-seven patients were referred for staging, 59 at their first BCR without ongoing androgen ADT, with the median time to BCR being 54.5 months [95% CI 43–82.5], and 15 were referred for a first episode of rising serum PSA during ADT, with the median time from PCa diagnosis to CRPC being 129 months [95 CI 64–167]. There was no significant difference in the frequency of the six possible sequences for performing the three WBIs ($p = 0.1$).

Changes in management plan and impact of WBI

The management initially scheduled was changed in 52% [95% CI 42–61] of the patients (Table 2). The proportion of patients for whom WBI had a decisive impact was 29% [95% CI 20–39] by triggering a major change in 28 patients and a minor change in ADT regimen in one patient.

The WBI that was considered to be decisive for changing the management was FCH-PET/CT alone in 19/29 patients, NaF-PET/CT alone in 1/29 patient, both FCH-PET/CT and DW-MRI in 4/29 patients and the three WBI together in 5/29 patients.

The overall impact rate of FCH-PET/CT on patients' management (28%) was statistically greater than those of NaF-PET/CT or DW-MRI ($p < 0.0001$). The superiority of the FCH PET/CT impact rate was significant at BCR (39%) ($p < 0.0001$) but not at staging or for CRPC.

The main impact of WBI was on deciding ADT, either indicating ADT in 10/101 patients who were initially planned for a targeted treatment (surgery, radiation therapy (RT), high-intensity focussed ultrasound (HIFU), and/or brachytherapy) or preferring a targeted treatment or an active surveillance in 7/101 non-metastatic patients initially planned for ADT.

At BCR, the impact rate of WBI on deciding ADT was 24% [95% CI 14–36]. Nine patients initially planned for a targeted treatment, for active surveillance or in whom the management was undecided, were finally treated by ADT but five non-metastatic patients initially planned for ADT were finally managed by targeted treatment ($n = 4$) or active surveillance ($n = 1$).

In 23% of patients, the planned management was changed at the post-WBI multidisciplinary meeting independently from the results of WBI. In 11 patients (nine referred for staging, one for BCR and one for CRPC), it consisted of a change within the four modalities of targeted treatment (three patients refused surgery that was planned and were treated by RT; two patients planned for RT were treated by HIFU as they presented an intra-prostatic disease; two patients planned for RT were treated by surgery, as they presented an intermediate-risk non-metastatic disease; one patient planned for surgery was treated by RT, as surgery was contra-indicated because of cardiovascular comorbidity; one patient planned for HIFU was treated

Table 1 Patients' characteristics

Characteristic	Total	Staging	Biochemical recurrence	Castration-resistant prostate cancer
N	101 (100%)	27 (27%)	59 (58%)	15 (15%)
Median age [range] in years				
At PCa diagnosis	65 [46–87]	67 [53–87]	65 [46–78]	66 [52–80]
At inclusion	71 [50–87]	67 [53–87]	71 [50–87]	77 [59–84]
Initial group risk according to d'Amico				
Low	11 (11%)	2 (7%)	8 (14%)	1 (7%)
Intermediate	32 (32%)	4 (15%)	24 (41%)	4 (27%)
High	48 (47%)	21 (78%)	19 (32%)	8 (53%)
Unknown	10 (10%)	0 (0%)	8 (13%)	2 (13%)
Initial Gleason score				
≤ 6	21 (21%)	5 (19%)	14 (24%)	2 (13%)
7	47 (46%)	7 (26%)	32 (54%)	8 (53%)
≥ 8	28 (28%)	15 (55%)	8 (14%)	5 (34%)
Unknown	5 (5%)	0 (0%)	5 (8%)	0 (0%)
First-line treatment				
Radical prostatectomy	–	–	32 (54%)	5 (33%)
Definitive radiation therapy	–	–	20 (34%)	7 (47%)
High-intensity focalised ultrasound	–	–	7 (12%)	0 (0%)
Androgen-deprivation therapy	–	–	0 (0%)	3 (20%)
PSA serum level at inclusion				
< 10 ng/ml	68 (67%)	10 (37%)	46 (78%)	12 (80%)
10 ng/ml ≤ ≤ 20 ng/ml	19 (19%)	11 (41%)	7 (12%)	1 (7%)
> 20 ng/ml	14 (14%)	6 (22%)	6 (10%)	2 (13%)
Sequence of performing the three imaging modalities				
FCH-PET/CT → NaF-PET/CT → DWI-MRI	22 (22%)	6 (22.2%)	13 (22%)	3 (20%)
FCH-PET/CT → DWI-MRI → NaF-PET/CT	24 (24%)	8 (29.6%)	13 (22%)	3 (20%)
NaF-PET/CT → FCH-PET/CT → DWI-MRI	25 (25%)	4 (14.8%)	19 (32.2%)	2 (13.3%)
NaF-PET/CT → DWI-MRI → FCH-PET/CT	9 (9%)	2 (7.4%)	3 (5.2%)	4 (26.7%)
DWI-MRI → FCH-PET/CT → NaF-PET/CT	21 (21%)	7 (26%)	11 (18.6%)	3 (20%)
DWI-MRI → NaF-PET/CT → FCH-PET/CT	0 (0%)	0 (0%)	0 (0%)	0 (0%)

by surgery, as he was suspicious for pelvic lymph node extension on the MRI of the pelvis; one patient planned for surgery was treated by RT, as he presented a low-risk PCa; and one patient was treated by salvage RT as salvage surgery was not feasible); in three patients, a previous doubt was lifted, and a targeted treatment was decided (one targeted pelvic lymph node dissection in a patient with history of RT of the pelvis; one prostatectomy in a non-metastatic patient with a PSA serum level of 27 ng/ml and one RT of the prostatic lodge and pelvic lymph nodes in a patient who had a suspicious bone lesion on bone scan which was finally considered to be benign); in five patients, ADT was initiated due to a rapid rise in PSA serum level; in the last three patients, active surveillance was finally chosen in view of the stability of PSA serum levels and the absence of evidence of metastatic disease.

Patient follow-up and adequacy of management

The median duration of follow-up was 28 months (range 6–70). Five patients were lost to follow-up and excluded from this analysis; WBI performed at staging ($n=1$), BCR ($n=3$) or CRPC ($n=1$) had an impact on the management in 2 of them. Eighty of the 101 patients were evaluable for bone metastases (21 staging, 48 BCR and 11 CRPC) according to a composite standard of truth based on the evolution of the lesion on imaging during follow-up, evolution of PSA in response to targeted prostate cancer therapy, excluding ADT and histological findings, if available. At least one bone metastasis was found in 14/80 patients at the time of WBI: 5/21 staging patients; 7/48 BCR patients and 2/11 CRPC patients.

At the time of database lock, 26/26 patients referred for staging were PCa recurrence–free; 46/56 BRC patients

Table 2 Management plans advised by the multidisciplinary panel before and after imaging workup, and impact of the results of whole-body imaging

	Number of patients	Number of patients with a change in management prompted by whole-body imaging	Type of whole-body imaging which was decisive for the change in management			Number of patients with a change in management decided on other arguments
			FCH-PET/CT	NaF-PET/CT	DWI-MRI	
All patients ($n=101$)						
Active surveillance → active surveillance	5	0	0	0	0	0
Active surveillance→ local treatment	5	5	5	1	1	0
Active surveillance → ADT	5	4	4	0	3	1
Local treatment → local treatment	34	3[a]	3	1	1	11
Local treatment → active surveillance	1	0	0	0	0	1
Local treatment → ADT	4	3	2	3	2	1
ADT → ADT	26	2[b]	2	0	0	0
ADT → active surveillance	1	1	1	0	0	0
ADT → local treatment	6	6	6	0	1	0
Undecided → active surveillance	3	0	0	0	0	3
Undecided → local treatment	5	2	2	1	1	3
Undecided → ADT	6	3	3	0	0	3
Total	101	29 (29%)	28 (28%)	6 (6%)	9 (9%)	23 (23%)
Staging ($n=27$)						
Local treatment → local treatment	19	1[a]	1	1	1	9
Local treatment → active surveillance	1	0	0	0	0	1
Local treatment → ADT	1	1	1	1	1	0
ADT → ADT	4	0	0	0	0	0
Undecided → local treatment	2	0	0	0	0	2
Total	27	2	2	2	2	12
Biochemical recurrence ($n=59$)						
Active surveillance → active surveillance	5	0	0	0	0	0
Active surveillance → local treatment	5	5	5	1	1	0
Active surveillance → ADT	4	4	4	0	3	0
Local treatment → local treatment	14	2[a]	2	0	0	1
Local treatment → ADT	3	2	1	2	1	1
ADT → ADT	12	1[b]	1	0	0	0
ADT → active surveillance	1	1	1	0	0	0
ADT → local treatment	4	4	4	0	0	0
Undecided → active surveillance	3	0	0	0	0	3
Undecided → local treatment	3	2	2	1	1	1

Table 2 (continued)

	Number of patients	Number of patients with a change in management prompted by whole-body imaging	Type of whole-body imaging which was decisive for the change in management			Number of patients with a change in management decided on other arguments
			FCH-PET/CT	NaF-PET/CT	DWI-MRI	
Undecided → ADT	5	3	3	0	0	2
Total	59	24 (41%)	23 (39%)	4 (7%)	6 (10%)	8 (14%)
Castration-resistant prostate cancer ($n=15$)						
Active surveillance → ADT	1	0	0	0	0	1
Local treatment → local treatment	1	0	0	0	0	1
ADT → ADT	10	1[b]	1	0	0	0
ADT → Local treatment	2	2	2	0	1	0
Undecided → ADT	1	0	0	0	0	1
Total	15	3	3	0	1	3

Local treatment surgery, radiation therapy, brachytherapy or high-intensity focalised ultrasounds (HFIU), *ADT* androgen-deprivation therapy

[a]2 patients planned for prostatectomy and finally treated by HFIU; 1 patient planned for prostatectomy and finally treated by radiation therapy associated with long-term ADT

[b]1 patient in whom a lymphoma was detected; 1 patient in whom a change in the type of ADT was decided

had no scalable disease whereas 10/56 presented with continuous PCa evolution; 9/14 CRPC patients had no scalable disease, whereas 5/14 had progressive disease.

The global adequacy rate of management decisions was 98% (95% CI 95–100%). Of the 27 assessable patients in whom WBI had a clinical impact, the changes were considered as adequate in 26/27 = 96% (95% CI 89–100%) of patients but inadequate in one single case: in a high-risk (according to d'Amico) patient initially treated by prostatectomy, who was planned for ADT due to his first BCR event (serum PSA 0.9 ng/mL), suspicious pelvic lymph nodes were detected on FCH-PET/CT and dissected. Pathology results were negative and serum PSA level continued to rise to 4.57 ng/mL 6 months after surgery. ADT was finally introduced which led to a decrease in PSA serum level (0.51 ng/mL 3 years after FLUPROSTIC workup).

The management of the 68 assessable patients in whom WBI had no impact was considered adequate in all patients but one: in a high-risk patient initially treated by HIFU presenting with his first BCR event (serum PSA 16.5 ng/mL), resuming HIFU was planned and performed because an isolated prostate lesion was detected on imaging. HIFU was complicated by infection and prostate necrosis which required hospitalisation and was followed by a rapid increase in serum PSA level to 92 ng/mL. 8 months after the WBI workup, a bone metastasis was detected on MRI of the pelvis.

Discussion

To the best of our knowledge, this report describes the first direct comparison of the impact of NaF-PET/CT, FCH-PET/CT and DW-MRI findings on the management of PCa patients referred for suspected metastasis at three different phases of evolution. WBI with those three modalities prompted management changes in 29% of patients, which were considered as adequate in all patients but two. If only one single WBI examination would have been performed in our 101 patients, the impact rate would have been 28% with FCH-PET/CT, 6% with NaF-PET/CT and 9% with DW-MRI.

This result confirms, on a rational basis, the observation that introducing FCH-PET/CT for routine PCa WBI results in a decrease in demand for nuclear imaging of the skeleton (NaF-PET/CT and bone scintigraphy) [18].

According to the evolution status of PCa, the impact at staging was of 2/27 patients for each of the three WBI, which showed bone metastases in the same two patients. Hillner et al. retrospectively evaluated the impact rate of NaF-PET (without CT fusion) to be 12.2% at staging in 1024 PCa patients [6]. In the study of Kjölhede et al. on 90 patients, the impact rate of combined NaF and FCH PET/CTs on first-line treatment plan was 20% [19]. The impact of FCH and DWI-MRI performed for staging PCa was never evaluated. However, in our study, changes in

management at staging were most frequently decided independent of WBI (Table 2).

Our main finding was that WBI had its highest impact rate in BCR, 41% overall and 39% for FCH-PET/CT, significantly superior to NaF-PET/CT or DW-MRI ($p < 0.0001$). This impact rate of 39% is within the confidence limits of those reported by Soyka et al. (48% on 156 patients) [20] and Gillebert et al. (56% on 179 patients) [21]. Using ^{11}C-choline-PET/CT, Ceci et al. reported an impact rate of 46.7% on 150 patients [22].

In 15 CRPC patients, we found no statistically significant difference between the impact of the three WBI, only a trend for a greater rate of FCH-PET/CT (3/15 patients vs. 1/15 for DW-MRI and 0/15 for NaF-PET/CT). To the best of our knowledge, the impact of WBI in CRPC has never been reported.

An interesting finding was that the planned management was changed at the post-WBI multidisciplinary meeting independent of the results of WBI in 23% of patients. We assumed that these changes were motivated by rethinking the risk of metastatic evolution of PCa during that time interval. In 8/23 of these cases the decision was based on serum PSA changes.

Limitations

A limitation, common to studies comparing impact on management is that the decisions are made on the basis of on-site reading. Therefore, carry-over of information between the reports of the WBI may exist: the latter examination can have an advantage. However, we found no significant difference in the order of performing the three WBI. Furthermore, FCH-PET/CT, which had the highest impact overall and in the BCR group, was performed first in a large proportion of patients (Table 1), which rules out systematic carry-over information from the two other WBI.

Another limitation is the relatively small number of patients and the heterogeneity of their PCa status (staging, BCR, CPRC). However, we did not aim to compare the results between the three groups of patients as they did not present the same risk for metastatic disease, but to cover different settings of PCa, reflecting the prescription of the clinicians. Furthermore, the impact that rate we found for NaF or FCH-PET/CT was similar to those previously reported at staging or for BCR in larger non-comparative series.

There is a difference between WBIs in the actual field of view: a real whole-body for FNa-PET/CT (similarly to bone scintigraphy) vs. from vertex to mid-thigh for FCH-PET/CT and DW-MRI. However, no abnormality suggestive of "peripheral" bone metastasis in the limbs was discovered on NaF-PET/CT, confirming that bone metastases of PCa are predominant in the axial skeleton [23] and validating WBI from vertex to mid-thigh.

According to "local habits", imagers and clinicians more familiar with one WBI modality might have been more prone to "believe it" and implement changes guided by this modality. Indeed, in both imaging centres, clinical trials evaluating FCH-PET/CT were performed for several years [12, 18, 21], whereas NaF and DW-MRI were introduced on the year before the start of FLUPROSTIC, possibly contributing to their lower impact compared to FCH-PET/CT.

Modern WBI is evolving rapidly. For DW-MRI, a *b* value of 600 was used, which is below the currently recommended values of at least 800, probably limiting its impact.

In this study, MRI was performed without contrast-enhancement, which does not contribute to improved performances of DW-MRI, which was the MRI sequence that we aimed to evaluate. Thus, we chose to not perform contrast-enhancement to avoid a potential adverse reaction of gadolinium contrast media.

Prostate-specific membrane antigen (PSMA) radioligands [24] were not available when FLUPROSTIC was started. PET/CT appears to yield better diagnostic performance with PSMA radiotracers than with FCH [25], with a significant impact on patients' management [26–28]. However, PSMA ligands are not currently approved and are not as widely available as FCH in the EU.

Conclusions

Within the limits of a relatively small series of PCa patients suspicious for distant metastasis where imaging was performed early in the disease transition, we found that WBI led to management changes in approximately 1/3 of cases. For BCR, FCH-PET/CT had the greatest impact rate and may therefore be recommended as first-line WBI. For staging PCa, FCH should be considered instead of NaF-PET/CT, as is currently recommended in clinical guidelines, since it provides additional information on extra-osseous extension of PCa, but this is also true for WB-MRI, which has the advantage of avoiding radiation exposure at this early stage of evolution. Prescribing WBI at a multidisciplinary meeting led to management changes at the post-WBI meeting independent of WBI results in approximately 1/4 of the patients as a consequence of rethinking and of the evolution of PCa during that time interval. These results warrant further investigation. In particular, exploring management changes induced by WBI according to PSA serum levels, which are correlated with imaging performances, will be of interest.

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Compliance with ethical standards

Conflict of interest The "FLUPROSTIC" study (IDRCB 2011-A01041-40) was selected and granted by the French Ministry of Health (STIC 2009 P090105), and sponsored by the Assistance Publique-Hôpitaux de Paris (AP-HP). The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This protocol was approved by institutional and local human investigations committees, and informed written consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

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