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ORIGINAL PAPER

Recurrent prostate cancer after radical prostatectomy: restaging performance of 18F-choline hybrid PET/MRI

Verane Achard[1] · Giorgio Lamanna[1] · Antoine Denis[2] · Thomas De Perrot[3] · Ismini Charis Mainta[2] · Osman Ratib[2] · Christophe Iselin[4] · Raymond Miralbell[1] · Valentina Garibotto[2] · Thomas Zilli[1]

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Abstract

To evaluate the diagnostic performance of a whole-body 18F-choline (FCH) hybrid PET/MRI for prostate cancer patients at biochemical relapse after radical prostatectomy (RP) compared to pelvic multiparametric MRI (mpMRI), one of the standard imaging modality for this patient population. From 2010 to 2016, 58 whole-body FCH PET/MRI studies with mpMRI acquisitions were performed in 53 prostate cancer patients relapsing after curative RP. Median PSA and PSA doubling time (PSA DT) at PET study were 1.5 ng/ml and 6.5 months, respectively. The overall positivity rate of FCH PET/MRI was 58.6% ($n=34$), dropping to 44% in patients with a PSA ≤ 2 ng/ml ($n=36$). Median PSA values in positive and negative PET/MRI studies were 2.2 ng/ml and 0.8 ng/ml, respectively, with no differences in PSA DT (6.5 vs. 6.6 months). A PSA value ≥ 1.5 ng/ml was a significant predictor of positivity on PET/MRI studies. Compared to PET, mpMRI identified more local relapses (17 vs. 14, $p=0.453$) while PET outperformed whole-body Dixon MRI for regional (16 vs. 9, $p=0.016$) and distant (12 vs. 6, $p=0.031$) metastases. Compared to pelvic mpMRI, the treatment approach turned out to be influenced more frequently using whole-body FCH hybrid PET/MRI studies (58.6% vs. 38%). In prostate cancer patients with biochemical recurrence after RP, whole-body FCH PET/MRI achieved a higher detection rate of nodal/distant metastases compared to pelvic mpMRI alone, increasing the change of treatment strategy by more than 20%.

Keywords Prostate cancer · Biochemical recurrence · Radical prostatectomy · Whole-body FCH hybrid PET/MRI · Pelvic mpMRI

Introduction

Radical prostatectomy (RP) with or without pelvic lymphadenectomy is one of the main treatment options for localized prostate cancer. Biochemical recurrence, defined as detectable or rising prostate-specific antigen (PSA) value after surgery, can occur in more than 30% of the patients undergoing RP and it is associated with an overall higher risk of death from prostate cancer [1, 2].

✉ Thomas Zilli
Thomas.Zilli@hcuge.ch

[1] Radiation Oncology Division, Geneva University Hospital, 1211 Geneva 14, Switzerland

[2] Nuclear Medicine, Geneva University Hospital, Geneva, Switzerland

[3] Radiology, Geneva University Hospital, Geneva, Switzerland

[4] Urology, Geneva University Hospital, Geneva, Switzerland

Radiotherapy (RT) to the prostatic bed is the most employed salvage treatment for recurrent non-metastatic patients [3, 4], with low-PSA values at salvage and is clearly associated with a better outcome [5]. An early identification of the site of relapse through imaging is a challenging issue that may translate in changing the treatment approach by adapting the treatment intent, the radiation field and dose, or by intensifying treatment with androgen deprivation.

Despite the clinical relevance of this issue, there is no consensus on the need of restaging for patients with biochemical recurrence after RP or on an optimal imaging modality to be recommended [6]. The choice between surveillance, waiting for a further increase of the PSA value, and imaging positivity, versus early salvage RT to the prostatic bed is an argument for debate.

Multiparametric MRI (mpMRI) is considered one of the standard modalities for restaging the local disease after postsurgical relapse [7, 8]. An anatomical evaluation of the prostatic bed by T2-weighted sequences combined to

diffusion-weighted, and dynamic contrast-enhanced imaging, have gained acceptance to assess recurrent disease, with a sensitivity rate superior to 90% at PSA levels of approximately 1 ng/ml [9].

Choline-based PET/CT imaging has been the most widely investigated modality to image recurrent prostate cancer with a sensitivity of 85% to 100% and specificity of 76% to 96% at PSA values of 1.7 ng/ml or greater [10–12] though below this PSA level, the overall detection rate decreases significantly. Nonetheless, short PSA doubling times (PSA DT, ≤6 months) or high Gleason scores are predictive factors of PET positivity [13–15].

Hybrid PET/MRI is a recent technological development that integrates in a single examination metabolic, functional, and morphological information [11]. The acquisition of all images in a single session and in the same reference system can improve the accuracy of prostate cancer lesions' detection through improved co-registration and a combined analysis of the PET and MRI series.

In this prospective study, we aimed, first, to evaluate the diagnostic performance of a whole-body 18F-choline (FCH) hybrid PET/MRI in a single center cohort of prostate cancer patients with a biochemical relapse after RP, comparing detection rates of MRI and PET for local disease and for regional and distant lesions. Second, we aimed to assess the impact on treatment of whole pelvis mpMRI versus whole-body FCH PET/MRI in prostate cancer patients' candidates for salvage RT.

Materials and methods

Patient characteristics

From July 2010 to November 2016, 58 whole-body FCH hybrid PET/MRI studies were performed in a single institution in 53 consecutive prostate cancer patients with a first biochemical recurrence after curative RP. Five patients underwent two PET/MRI examinations due to the negative findings at the first exam. Biochemical recurrence after RP was defined as two consecutive rises with final PSA value > 0.1 ng/ml, or three consecutive rises. To assess the performance of PET versus mpMRI in detecting prostate bed local relapses, patients who received adjuvant or salvage prostate bed RT treatments before whole-body FCH hybrid PET/MRI were excluded from the analysis. All included patients were hormone-naïve. Use of PET/MRI as restaging modality over PET/CT was at the discretion of the referring physician.

The median interval time between RP and PET/MRI examinations was 35 months (range 1.4–220), with a median PSA value at restaging of 1.5 ng/ml (range 0.1–31.8). Table 1 summarizes the patient and tumor characteristics.

Table 1 Patient and tumor characteristics ($n = 53$)

Characteristics	
Age (years)	67 (47–83)
PSA at diagnosis (ng/ml)	8.9 (2.5–172)
PSA at PET-MRI (ng/ml)	1.5 (0.1–31.8)
PSADT at PET-MRI (months)	6.5 (1.1–42)
Interval time between RP and PET-MRI (months)	35 (1.4–220)
Stage	
pT2	25 (47%)
pT2a	3 (6%)
pT2b	1 (2%)
pT2c	21 (39%)
pT3	28 (53%)
pT3a	18 (34%)
pT3b	10 (19%)
cN0	21 (40%)
pN0	22 (41%)
pN1	9 (17%)
Risk category	
Localized (T2 N0)	24 (45%)
Locally advanced, high (T3a N0)	17 (32%)
Locally advanced, very high (T3b/4 N0)	3 (6%)
Nodal disease (N1)	9 (17%)
Gleason score	
6	7 (13%)
7	33 (62%)
≥8	12 (23%)
N/A	1 (2%)
Surgical margins	
R0	24 (45%)
R1	28 (53%)
N/A	1 (2%)

Data presented as median values (range) or patient numbers (percent)
PSA prostate-specific antigen; *DT* doubling time

The study protocol aiming to evaluate the role of hybrid PET/MRI was approved by the Institutional Review Board of the Geneva University Hospitals (IRB 09-302). All patients provided written informed consent before imaging.

Whole-body PET/MRI protocol

All exams were performed on a whole-body hybrid PET/MRI system (Philips Ingenuity, Philips Healthcare, Cleveland OH) in which the PET and the MRI acquisitions are performed sequentially, following a previously described protocol [16, 17]. Specifically, PET images were acquired over 7 or 8 positions, depending on patient size, of 4 min each, and were reconstructed on a 256 × 256 matrix with 4-mm slice thickness, using a fully three-dimensional time-of-flight maximum-likelihood ordered-subsets expectation

maximum algorithm with 2 iterations and 28 subsets. We adapted a dynamic three-phase protocol previously described and used for PET/CT acquisitions [18]. Briefly, the first phase was a list-mode acquisition of 10 min centered on the prostatic bed, starting with the administration of 300 MBq of FCH intravenously, a standardized dose used in our department for all patients; the second phase, a standard whole-body PET from the mid-thigh to the skull, and the third phase, a late (approximately 60 min after injection) acquisition of two beds of the lower abdomen and the pelvis.

The mpMRI protocol included morphological T2-weighted sequences, covering the pelvis in 3D and the prostatic bed with an endorectal coil, followed by a diffusion and dynamic contrast-enhanced (DCE) sequences (after the administration of 0.1 mmol/kg of gadoterate dimeglumine). The whole-body acquisition included an axial fast field echo sequence used for attenuation correction and a 3D T1-W gradient echo (GRE) Dixon sequence, allowing the correlation with PET images. The Dixon sequence was acquired in transverse orientation, with a TR of 3.4 ms, TE 1.2/2.1 ms, flip angle 7°, 47 slices, slice thickness of 6 mm, field of view of 500×390 mm^2 and an acquisition voxel size of $1.6 \times 1.7 \times 6$ mm^3, reconstructed as $0.78 \times 0.78 \times 3$ mm^3. The acquisition time was 19 s per stack over 8 stacks. Median length of PET/MRI acquisition was 2.5 h as previously reported [17]. Images in the thoraco-abdominal area were acquired during patient breath-hold. Local recurrence in the prostate bed was defined as a soft tissue nodule on T2-weighted sequences with an early contrast medium enhancement on DCE. Diffusion-weighted MRI was analyzed qualitatively with tumor recurrence visualized as a high signal intensity focal lesion on the high b-value image corresponding to a low signal intensity lesion on the corresponding Apparent Diffusion Coefficient (ADC) map (impeded diffusion due to high cellularity).

Statistical analysis

Data were analyzed with SPSS software (version 25.0; IBM SPSS statistics), using descriptive statistics to describe patient data as median, range, or number (percent). For the purposes of the study, we analyzed the overall detection rate of whole-body hybrid PET/MRI, as well as performance of whole-body PET and whole-body MRI Dixon imaging including multiparametric sequences of the pelvis separately using different PSA cutoffs. Three different regions of detection were used for the analyses: local (prostate bed), regional (pelvic nodes) and distant (distant lymph nodes, bone lesions and visceral lesions). Differences in the proportion of positive patients at each region between PET and MRI were assessed using a Mc Nemar test. For the purposes of this study, a new reading of whole-body PET imaging was performed by one experienced nuclear medicine specialists with 11 years of experience (VG), while mpMRI and whole-body MRI Dixon were re-analyzed and interpreted separately by a dedicated uro-radiologist (TDP) with 15 years of experience.

The effect of different clinical related variables on the overall detection rate of PET/MRI was also analyzed. The following categorical variables were considered in the analysis: PSA at PET/MRI (<1.5 vs. ≥ 1.5 ng/ml), PSA DT (<6.5 vs. ≥ 6.5 months), Gleason score (≤ 7 vs. ≥ 8), pT stage (pT2 vs. pT3) and surgical margins (R1 vs. R0), with proportions compared using a Chi square test. To evaluate the potential clinical impact of different imaging modalities in treatment changes, we used the results of the independent re-analysis of the different imaging modalities to assess how the indication of salvage RT to the prostatic bed might be modified based on findings of mpMRI of the pelvis versus whole-body hybrid FCH PET/MRI. Specifically, we established two theoretical treatment plans, one based on the results of the mpMRI alone and another on the results of the whole-body FCH PET/MRI studies with mpMRI. The detection of a local relapse recommended the delivery of an additional boost to the macroscopic recurrence in the prostatic bed [19]; the detection of nodal pelvic disease recommended to enlarge the treatment fields in order to include the involved pelvic lymph nodes [20]; and distant metastases induced to change the treatment strategy towards a palliative approach with androgen deprivation. To illustrate the differences in management using mpMRI and FCH PET/MRI information a Sankey diagram was generated.

Results

The overall positivity rate of the FCH hybrid PET/MRI was 58.6% (34/58 cases), with a 44% rate in patients with a PSA ≤ 2 ng/ml ($n=36$). Median PSA values in PET/MRI-positive and -negative patients were 2.2 ng/ml vs. 0.8 ng/ml ($p=0.0001$), respectively. No differences were observed in PSA DT (6.5 vs. 6.6 months) between the two PET/MRI-positive and -negative groups. A PSA value ≥ 1.5 ng/ml correlated significantly with PET/MRI-positive results ($p=0.001$). FCH hybrid PET/MRI identified 19 local relapses, 16 nodal, and 12 distant metastases. Six out of sixteen (37.5%) patients with nodal relapse presented with a synchronous local recurrence; while 2/12 (17%) patients with distant metastases presented with local disease, too. PET/MRI positivity decreased in patients with low-PSA values. Detection rate of hybrid FCH PET/MRI was 12.5% in patients with a PSA level ≤ 0.5 ng/ml ($n=8$), 42.9% in patients with PSA levels comprised between 0.5 and 1.0 ng/ml ($n=14$), 60% for PSA between 1.0 and 2.0 ng/ml ($n=15$), and 85.7% in men with PSA >2 ng/ml ($n=21$). Overall, PET and MRI studies showed concordant findings in 44% of the cases (15/34 cases).

Compared to PET, mpMRI identified more local relapses (17 vs. 14) even though this difference was not significant ($p = 0.453$) (Fig. 1). Local recurrence was identified by mpMRI in 17 of the 58 studies (29%) and was most frequently located in the anastomotic region ($n = 8$), while in seven and two patients the relapse were located at the bladder neck and the seminal vesicles, respectively. The median size of the local relapse was 11 mm (range, 5 to 22). Compared to mpMRI, PET identified local recurrences in 14 cases (21%), with two cases identified by PET only in the anastomotic region (Fig. 2). The median PET SUV uptake was 4.1 (range 2.3–8.5) for all patients.

On the other hand, as shown in Fig. 3, PET outperformed pelvic mpMRI in identifying regional disease, namely in 16 patients (27%) vs. 9 (15%) ($p = 0.016$), respectively. The percentage of PET positive distant recurrences was also higher when compared to the whole-body MRI Dixon ($p = 0.031$): 12 (21%) vs. 6 (10%) patients. There was no nodal or distant recurrence identified by MRI (pelvic or whole-body) that was not identified by PET, too. The median PET SUV for nodal disease ranged between 1.5 and 6.4 (median 3.4). Among the 12 patients with PET positive distant disease, metastases were detected in bones ($n = 9$) and viscera ($n = 3$; 2 lungs and 1 rectal wall). Whole-body MRI Dixon acquisitions missed distant metastases in 6/12 patients (4 bone and 2 lung metastases). The four bone metastases that were missed at whole-body MRI reading were located in the vertebral bodies of D10 and L2 and in the vertebral lamina of C3 and D11.

At the end, whole-body PET/MRI studies were potentially more able to induce changes to the initial treatment strategy than pelvic mpMRI (i.e., 58.6% vs. 38% of changes). Combined hybrid FCH PET/MRI disclosed 14 relapses that mpMRI was unable to reveal. With a FCH PET/MRI restaging, more patients were eligible for whole pelvis RT and in four patients the attitude was changed for a palliative approach due to extrapelvic metastatic disease. Potential changes in treatment management using pelvic mpMRI or FCH PET/MRI are illustrated on Fig. 4.

Discussion

This study aimed to investigate the performance of whole-body FCH hybrid PET/MRI, for prostate cancer patients with biochemical relapse after RP. With a median PSA value of 1.5 ng/ml at restaging the overall detection rate was 58.6%.

An ideal imaging technique for prostate cancer recurrence after RP should be able to detect as much local relapses as nodal or distant metastases. Combining mpMRI of the pelvis and choline PET imaging to map the sites of recurrence in 202 prostate cancer patients with biochemical relapse post RP, Sobol et al. observed that up to 53% of the relapsing patients may harbor a mix of local and/or regional

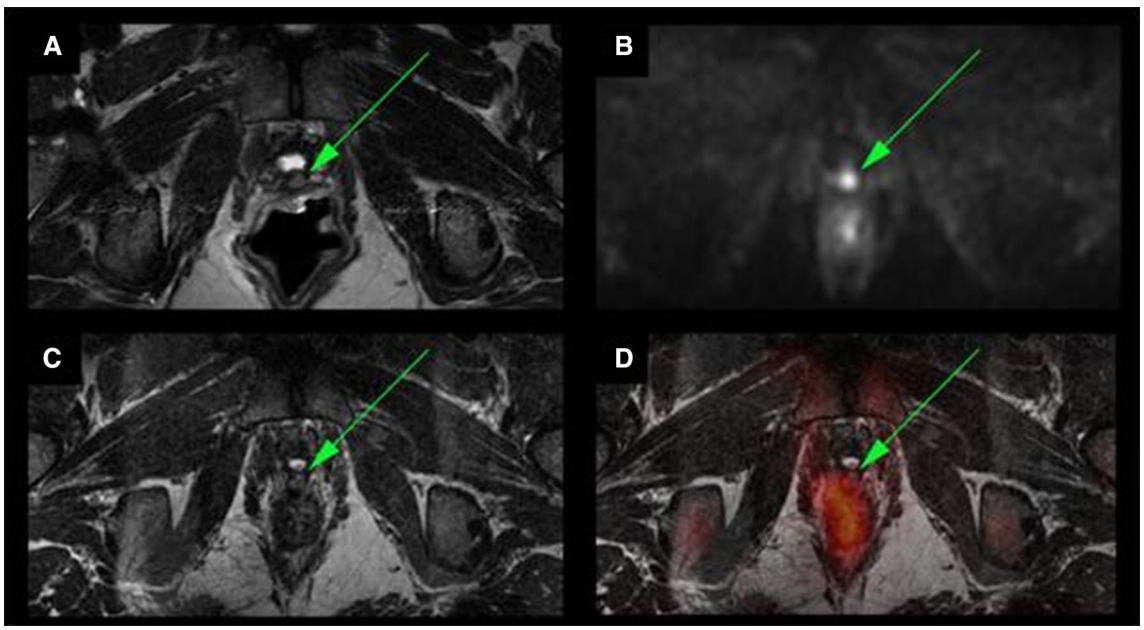

Fig. 1 mpMRI images showing a local recurrence with negative FCH findings in a 55-year-old man with a pT3 pN0 R1 Gleason 3 + 4 disease in biochemical recurrence (PSA 0.56 ng/ml) after radical prostatectomy. **a** T2-weighted images, **b** diffusion-weighted images, **c** VISTA sequences, **d** absence of FCH uptake on fused PET/MRI images. The patient is in complete remission 74 months after salvage prostate bed radiotherapy

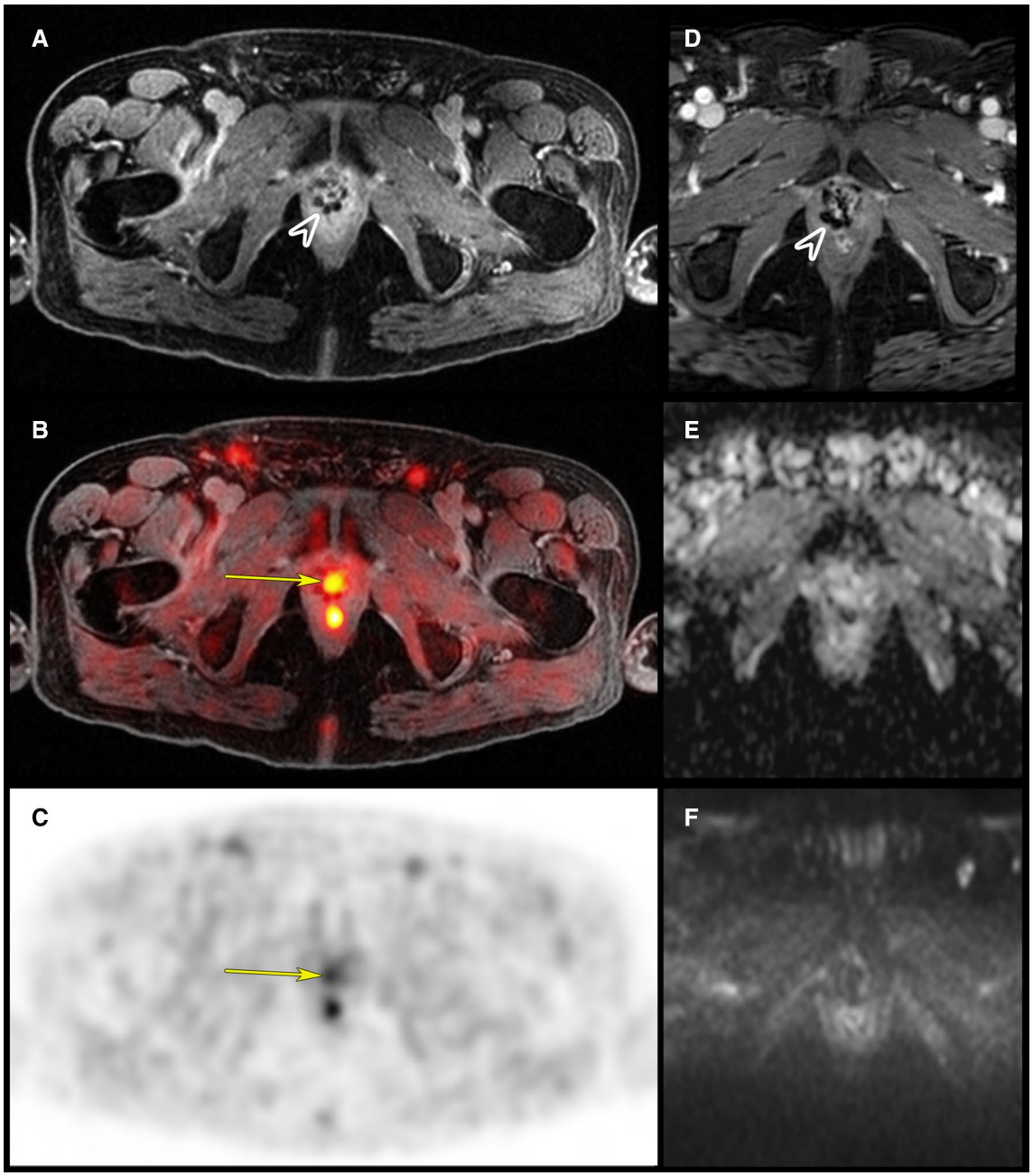

Fig. 2 FCH PET/MRI images showing a local recurrence with positive FCH (yellow arrows) and negative mpMRI findings in a 66-year-old man with a pT2a pN1 R0 Gleason 4 + 5 disease in biochemical recurrence (PSA 1.1 ng/ml) after radical prostatectomy. **a** Dixon water sequence, **b** FCH uptake on fused PET/MR image, **c** native PET image, **d** Dynamic contrast-enhanced (DCE), **e** apparent diffusion coefficient (ADC) map, **f** diffusion-weighted sequences. Hypointensities surrounding the anastomotic region (blank arrow heads) correspond to surgical clips

recurrences confined to the pelvis, while 45% of men exhibit metastatic only relapse with no evidence of local recurrence [21]. These findings are similar to ours with a large number of patients presenting nodal or distant metastases not showing signs of local recurrence (Table 2).

In our study, we have been able to observe a higher detection rate for local relapse in the prostate bed for mpMRI compared to PET, though the difference was not significant. Indeed, in five patients mpMRI was able to detect local disease, whereas PET did not. Of note, in these patients, the PSA value at restaging was < 2 ng/ml suggesting a better detection rate of mpMRI over PET especially at low-PSA levels [22]. Similar findings have been confirmed by other authors. Freitag et al, demonstrated that mpMRI of the pelvis

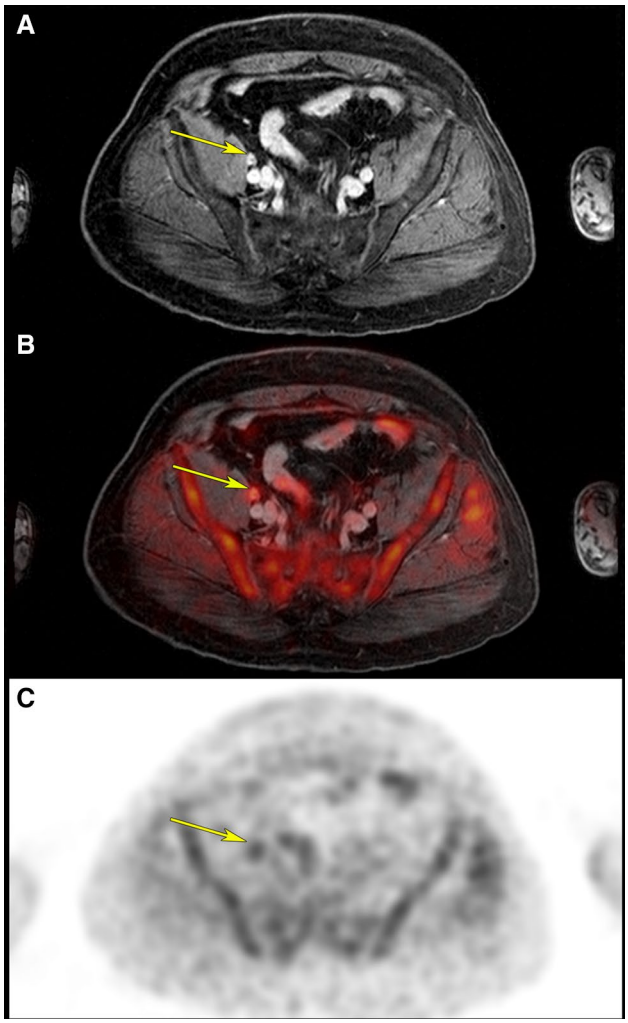

Fig. 3 FCH PET/MRI images showing a FCH positive and mpMRI negative pelvic lymph node recurrence in a 71-year-old man with a pT3a pN0 R0 Gleason 3+4 disease in a biochemical recurrence (PSA 0.6 ng/ml) after radical prostatectomy. **a** Right external iliac nodal recurrence with non-specific findings on axial VISTA sequences, **b** with positive FCH uptake on fused PET/MRI, **c** and native PET images. The patient is in complete biochemical remission 31 months after salvage whole pelvis radiotherapy

outperformed ^{68}Ga-PSMA-11 PET (PET/CT or PET/MRI) to detect local recurrence [23]. Kitajima et al. compared mpMRI to 11C-Choline PET/CT to detect recurrence after RP and mpMRI proved to be more efficient than 11C-Choline PET/CT to detect local relapses [9].

To the best of our knowledge, there is only one previous study investigating PET/MRI and mpMRI in recurrent prostate cancer. Eiber et al., using hybrid ^{11}C-Choline PET/MRI with mpMRI of the pelvis outperformed ^{11}C-Choline PET/CT to detect local relapse, in agreement with our results [24].

The detection power of mpMRI is strongly related to the PSA value at relapse. Although, the detection rate of a local relapse with mpMRI for PSA values ranging between 0.21 and 0.3 ng/ml is of, approximately, 11 to 25% [25–27], at PSA levels ranging between 0.2 and 0.5 ng/ml this rate increases up to 50% [28]. Compared to mpMRI, the performance of ^{11}C-Choline PET/CT in detecting local relapse is relatively low at these low-PSA values [29]. Indeed, as shown in a recent meta-analysis pooling the results of eleven studies the overall detection rate of ^{11}C-Choline PET/CT for local relapse is 27% only (95% CI 16–38%) [30].

As far as the detection of nodal or distant metastases is concerned, PET imaging in our study outperformed whole-body MRI Dixon or pelvic mpMRI. Indeed, there were no nodal or distant metastases found on MRI that were not also detected by PET imaging. Kranzbuhler et al. using a hybrid ^{68}Ga-PSMA PET/MRI technology observed similar results with PET increasing the detection rate of nodal and bone metastases compared to whole-body MRI [31]. Therefore, by integrating in a single-study mpMRI for local relapse and whole-body PET for nodal and distant metastases, hybrid PET/MRI can be considered a diagnostic tool of choice for mapping prostate cancer recurrence in the post-prostatectomy salvage setting. However, as far as bone lesions detection is concerned, we acknowledge that our whole-body MRI protocol using only basic Dixon imaging was inferior to the currently recommended standards for whole-body staging and might have affected the diagnostic performances measured here [32].

In this study, we used as PET tracer FCH. However, the landscape of alternative tracers for imaging prostate cancer is evolving rapidly. Among them, PSMA has demonstrated better performance rates compared to FCH. In patients with biochemical relapse with PSA levels < 2 ng/ml, the detection rate of PSMA PET/CT is almost twice better than choline PET/CT (93% vs. 43%) [33]. By analyzing PET/MRI series, using a ^{68}Ga-labelled PSMA ligand, Afshar-Oromieh et al, observed in a small cohort of 20 patients with a median PSA of 2.62 ng/ml at relapse an overall detection rate of 80% [34]. Even at median PSA values of 0.99 ng/ml, Kranzbuhler et al. reported an overall positivity rate of 78.6% [31]. Finally, Freitag et al. published two studies, one validating ^{68}Ga-PSMA PET/MRI as equivalent to ^{68}Ga- PSMA PET/CT for the detection of lymph nodes and bone metastases and a second, demonstrating the benefit of adding pelvic mpMRI to ^{68}Ga-PSMA PET/MRI in order to increase the detection rate of local recurrences, which is also consistent with our data [23, 35]. ^{68}Ga-PSMA PET/MRI with dedicated mpMRI pelvic sequences may, therefore, represent the most efficient imaging technique currently available to detect as well local relapses than nodal and distant ones in patients with biochemical failure after RP. However, and independently of PET tracers, published studies investigating in this setting the role of whole-body FCH PET/MRI studies with mpMRI acquisitions are scarce in the literature, and all

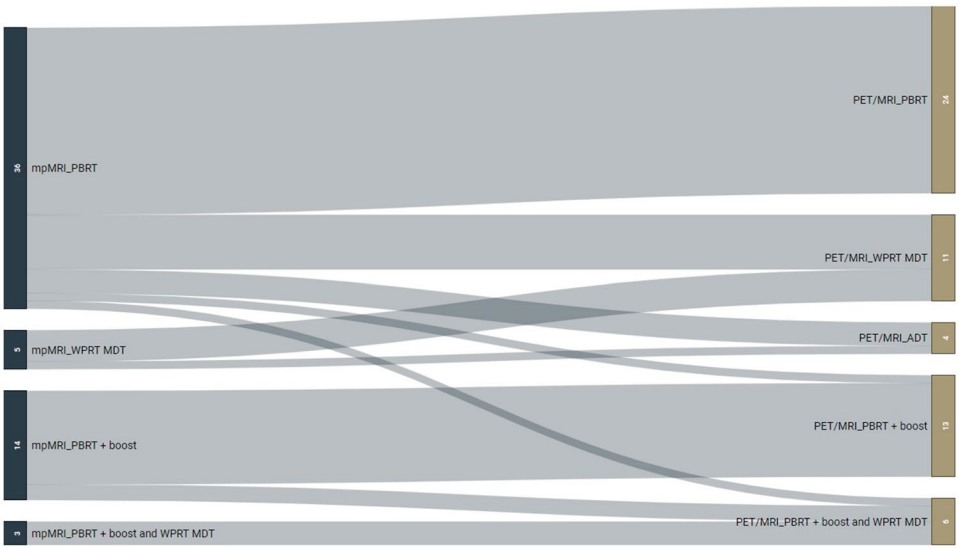

Fig. 4 Sankey diagram illustrating for the 58 exams the change from theoretical treatment options according to mpMRI (therapy options with mpMRI) to the implemented treatment after integration of FCH PET/MRI information (therapy options with FCH PET/MRI). *PBRT* prostate bed radiotherapy; *PBRT* + *boost* prostate bed radiotherapy with boost to the local recurrence; *MDT* metastasis directed therapies; *WPRT* whole pelvis radiotherapy; *ADT* androgen deprivation therapy

Table 2 FCH PET/MRI-based overlaps of the three different types of relapse (local, regional and distant) ($n = 58$)

	LN+ (16/58)	LN– (42/58)	DM+ (12/58)	DM– (46/58)
LR+ (19/58)	6	13	2	15
LR– (39/58)	10	29	10	31

LR local relapse, *LN* lymph node relapse, *DM* distant metastases

results available should be carefully reported to determine the best performing imaging technique for restaging.

Several drawbacks of our study have to be mentioned. First, there was no histopathological confirmation of the relapses detected on the hybrid PET/MRI; second, we analyzed a relatively small patients cohort leading to potential inherent bias and we used a suboptimal protocol for our whole-body MRI acquisitions; and third, to compare the two restaging modalities, the clinical impact of the change in management induced by the procedure, as compared with standard mpMRI, was hypothetical and based on an independent reinterpretation of the two imaging strategies. For this reason, the actual impact on the real clinical outcome of the patients could not be assessed. Lastly, it should be noted that the PET/MRI system used in our institution is based on a sequential technology implying a longer acquisition time and limiting direct comparison with more modern PET/MRI simultaneous systems.

Conclusions

Compared to standard restaging using mpMRI alone, whole-body FCH PET/MRI achieved a higher detection rate of nodal/distant metastases in prostate cancer recurrent patients after RP. Restaging with whole-body FCH hybrid PET/MRI may increase the change of treatment strategy by more than 20% compared to pelvic mpMRI alone, although the impact on clinical outcomes of this modality remains still to be prospectively established in patients with recurrent prostate cancer.

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Author contributions All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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