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Research Letter

# Utilization of Salvage and Systemic Therapies for Recurrent Prostate Cancer as a Result of $^{18}$F-DCFPyL PET/CT Restaging

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**Abstract**

**Purpose:** Our purpose was to investigate the effect of the addition of prostate-specific membrane antigen (PSMA)-targeted positron emission tomography/computed tomography (PET/CT) in patients with recurrent prostate cancer post-primary radiation therapy.

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**Methods and Materials:** A prospective, multi-institutional clinical trial evaluated 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ($^{18}$F-DCFPyL) PET/CT restaging in 79 men with recurrent prostate cancer post-primary radiation therapy. We report actual patient management and compare this with proposed management both before and after PSMA-targeted PET/CT.

**Results:** Most patients (59%) had a major change in actual management compared with pre-PET/CT proposed management. The rate of major change was underestimated by immediately post-PET/CT surveys (32%). Eighteen patients with PSMA avidity in the prostate gland suspicious for malignancy had a prostate biopsy. Sensitivity, specificity, and positive predictive values of PSMA uptake in the prostate were 86%, 67%, and 92%, respectively. Thirty percent of patients had directed salvage therapy and 41% underwent systemic therapy. Eleven out of 79 patients (14%) had high-dose-rate brachytherapy alone for local recurrence, and 91% were free of recurrence at a median follow-up of 20 months.

**Conclusions:** Most patients had a major change in actual management compared with pre–PSMA-targeted PET/CT planned management, and this was underestimated by post-PET/CT questionnaires.



## Introduction

Prostate-specific membrane antigen (PSMA) positron emission tomography computed tomography (PET/CT) using gallium-68 ($^{68}$Ga) or fluorine-18 ($^{18}$F)-labeled radiotracers shows promise for restaging patients with recurrent prostate cancer.[1,2] Change in proposed management is commonly used as a metric of effectiveness in trials[3-6]; but change in actual management is less consistently reported.[5,6]

## Methods and Materials

Actual management and proposed management changes were compared in a prospective, multicenter study (NCT02793284)[7] of 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ($^{18}$F-DCFPyL) PSMA-targeted PET/CT in men with recurrent prostate cancer after radiation therapy. Eligibility criteria included localized T1-2 prostate cancer at initial staging with zero or 1 high-risk feature (prostate-specific antigen [PSA] >20 or Gleason score 8); treatment with primary radiation therapy, with or without androgen deprivation therapy (ADT); and biochemical failure according to Phoenix criteria.[8] Men enrolled in the study had conventional imaging (CI) including CT chest, abdomen, and pelvis; bone scan; and multiparametric magnetic resonance imaging (mpMRI) of the pelvis before PET/CT. Anatomic site and suspicion score of lesions were assigned based on a standardized template for each imaging modality. Oligometastatic disease was defined as 1 to 4 extraprostatic lesions, inclusive of individual nodal metastases. A pre-PET/CT questionnaire was used to capture the proposed treatment based on CI. All patients then underwent PSMA-targeted PET/CT. A post-PET/CT questionnaire was then used to capture any changes to the proposed management based on the information from the PET/CT. Post-PET/CT interventions actually delivered were captured at a protocol-specified 6-month follow-up visit. The primary endpoint of the study was the proportion of patients with extraprostatic lesions as detected by CI versus PET/CT and has been reported.[7] Secondary endpoints included changes in management. Changes in whether men underwent systemic therapy, directed salvage, or combinations were considered major changes and are the basis of this report.

## Results

Seventy-nine men were enrolled and underwent PSMA-targeted PET/CT. Patient characteristics are described in Table 1. Staging by CI and PET/CT were concordant in 44 out of 79 men (56%), whereas 27 out of 79 men (34%) were upstaged and 8 out of 79 (10%) were downstaged after PET/CT (Table 2). Of note, 7 patients with no disease on CI were found to have extensive metastatic disease on PET/CT. All 7 patients had 5 or more metastases in both pelvic and nonpelvic nodes, and 1 patient had an additional pelvic bony metastasis.

A post–PSMA-targeted PET/CT questionnaire was completed for all 79 men at a median of 10 days after PET/CT (range, 0-160 days). Seventy-six out of 79 men had at least 1 follow-up visit. The 3 patients who were lost to follow-up were assumed to have no further treatment. Actual post–PSMA-targeted PET/CT management included biopsy (28%), systemic therapy (41%, typically ADT), and directed salvage therapy (30%) (Fig 1). The most common directed salvage therapies performed were high-dose-rate (HDR) prostate brachytherapy (17 out of 24) and stereotactic body radiation therapy (4 out of 24).

A major change between pre–PSMA-targeted PET/CT proposed management and actual management occurred in 47 out of 79 patients (59%); Table 3), compared with 25 out of 79 patients (32%) between pre-PET/CT and post-PET/CT proposed plans ($\chi^2$ $P < .01$). Actual management and rates of major change in management by pre–PET/CT PSA and by PET/CT findings are presented

**Table 1** Baseline patient characteristics

| Characteristic | Statistic | Result |
|---|---|---|
| N | | 79 |
| Age | Mean (SD) | 73.2 (7.6) |
| | Median (range) | 75 (51-88) |
| Initial T stage | n (%) | |
| | T1 | 49 (62) |
| | T2 | 2 (3) |
| | T2a | 18 (23) |
| | T2b | 8 (10) |
| | T2c | 2 (3) |
| Initial Gleason score | n (%) | |
| | 3 + 3 | 23 (29) |
| | 3 + 4 | 33 (42) |
| | 4 + 3 | 19 (24) |
| | 4 + 4 | 3 (4) |
| | 5 + 3 | 1 (1) |
| Initial PSA | Mean (SD) | 9.2 (8.5) |
| | Median (range) | 7.4 (1.8-71.0) |
| Initial NCCN risk group | n (%) | |
| | Low risk | 17 (22) |
| | Intermediate risk | 57 (72) |
| | High risk | 5 (6) |
| PSA at enrolment | Mean (SD) | 8.2 (10.6) |
| | Median (range) | 4.8 (2.1-69) |
| PSA doubling time, Memorial Sloan Kettering nomogram (months) | Mean (SD) | 16.2 (10.5) |
| | Median (range) | 14.4 (1.9, 48.6) |
| Previous radiation therapy | n (%) EBRT | 54 (68) |
| | Brachytherapy | 25 (32) |
| Last radiation to registration (months) | Mean (SD) | 79.8 (41.8) |
| | Median (range) | 74.0 (13.0-212.6) |

*Abbreviations:* EBRT = external beam radiation therapy; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; SD = standard deviation.

in Tables 4 and 5. Numerically higher rates of directed salvage with or without systemic therapy were received by patients with PSA of 3 to 3.99 (9 out of 19, 47%) and patients with isolated local recurrence (14 out of 38, 37%) or oligometastatic disease (8 out of 21, 38%) on PET/CT. Any change between post-PET/CT proposed plan and actual management occurred in 34 out of 79 patients (43%). Major change between the post-PET/CT proposed plan and actual management occurred in 24 out of 79 patients (30%; Table 5), owing to patient preference (9 out of 24, 38%), investigator discretion (8 out of 24, 29%), comorbidities (3 out of 24, 13%), or other (4 out of 24, 17%).

Biopsy of any site was performed in 22 men. Prostate biopsy was positive in 14 out of 18 men (78%), negative in 3 out of 18 (17%), and equivocal in 1 out of 18 (6%). Each of the 3 patients with negative biopsy underwent observation. Of the 18 men who underwent prostate biopsy, 11 had prostatic recurrence on PET/CT and mpMRI, 2 on PET/CT alone, 2 on mpMRI alone, and 3 had no detectable prostatic recurrence on PET/CT or mpMRI. Sensitivity, specificity, and positive predictive value (PPV) of PSMA avidity in the prostate were 86% (12 out of 14), 67% (2 out of 3), and 92% (12 out of 13). In comparison, sensitivity, specificity, and PPV of prostatic lesions on mpMRI were 93% (13 out of 14), 100% (3 out of 3), and 100% (13 out of 13). Sensitivity, specificity, and PPV of PET/CT combined with mpMRI were 100% (14 out of 14), 67% (2 out of 3), and 93% (14 out of 15). Histology also confirmed prostate cancer for 3 patients with metastatic sites on PSMA-targeted PET/CT. One patient underwent rectal biopsy for a rectal mass detected on mpMRI but not on PET/CT, and this showed rectal cancer.

Directed salvage therapy alone was performed in 14 out of 79 men. Eleven men underwent HDR brachytherapy alone for local recurrence. Six out of 11 men had a prostate biopsy performed before brachytherapy and all were positive for recurrence. All 11 men had a PSA response. Recurrence-free survival (RFS; none of ADT initiation, new metastases, or biochemical failure by Phoenix criteria) at a median of 20 months post-treatment (range, 3-36) was 91% (10/11). Two men had treatment of nodal disease without ADT (1 stereotactic body radiation therapy, 1 salvage node dissection) and another had HDR brachytherapy alone for local recurrence and a single pelvic bony metastasis.

**Table 2** Conventional imaging and PET/CT findings

| | PET/CT (n = 79) | | | | Total |
|---|---|---|---|---|---|
| | No detected recurrence | Prostate only | Oligometastatic | Extensive metastatic | |
| Conventional imaging (N = 79) | | | | | |
| No detected recurrence | 8 (10%) | 8 (10%) | 3 (4%) | 7 (9%) | 26 (33%) |
| Prostate only | 2 (3%) | 27 (34%) | 9 (11%) | 0 (0%) | 38 (48%) |
| Oligometastatic | 0 (0%) | 2 (3%) | 6 (8%) | 0 (0%) | 8 (10%) |
| Extensive metastatic | 0 (0%) | 1 (1%) | 3 (4%) | 3 (4%) | 7 (9%) |
| Total | 10 (13%) | 38 (48%) | 21 (27%) | 10 (13%) | 79 (100%) |

*Abbreviation:* PET/CT = positron emission tomography/computed tomography.
Shaded cells represent concordance in staging.

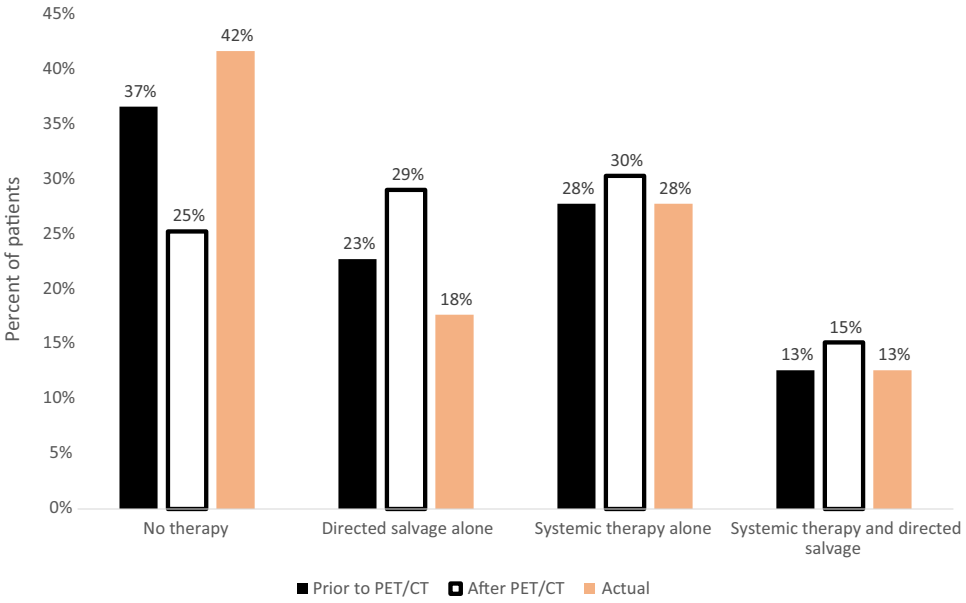


**Figure 1** Proposed and actual management.

## Discussion

In trials of novel imaging techniques, measurement of clinical effect based on questionnaires before and after imaging are commonly used. However, there are scarce data to validate whether such measures are accurate. In our analysis, rates of major change between actual management and pre–PSMA-targeted PET/CT proposed management were significantly higher than suggested by post-PET/CT questionnaires (59% vs 32%, $P < .01$). Proposed post-PET/CT management was different than actual management in 43% of patients, including major change in 30% of patients. Few studies have reported both proposed management after PSMA-targeted PET/CT and actual management, in part due to low rates of questionnaire completion.[9] Rate of change between post–PSMA-targeted PET/CT proposed management and actual management was similar to ours (35%) in 1 study[4] and lower (15%) in another.[10] In our trial, questionnaire completion rate was high, but the timing of the post–PSMA-targeted PET/CT questionnaire completion was variable (median 10 days after PET/CT; range, 0-160 days). Standardizing the completion of post-PET/CT questionnaires to within 7 to 10 days of the patient/physician discussion of PET/CT results may improve the accuracy of post-test questionnaires as a surrogate for management effect.

A recent meta-analysis that evaluated the management effect of PSMA-targeted PET/CT in both recurrence and primary staging showed intermodality change (whether a therapy such as radiation therapy was provided) occurred in 24% of patients.[3] Radiorecurrent patients comprised

**Table 3** Proposed plan before PET/CT and actual management

| | Actual management (N = 79) | | | | Total | Major change |
|---|---|---|---|---|---|---|
| | No therapy | Directed salvage alone | Systemic therapy alone | Directed and systemic therapy | | |
| Pre-PET/CT proposed management (N = 79) | | | | | | |
| No therapy | 14 (18%) | 7 (9%) | 7 (9%) | 1 (1%) | 29 (37%) | 15 (19%) |
| Directed salvage alone | 11 (14%) | 3 (4%) | 1 (1%) | 3 (4%) | 18 (23%) | 15 (19%) |
| Systemic therapy alone | 6 (8%) | 1 (1%) | 12 (15%) | 3 (4%) | 22 (28%) | 10 (13%) |
| Directed and systemic therapy | 2 (3%) | 3 (4%) | 2 (3%) | 3 (4%) | 10 (13%) | 7 (9%) |
| Total | 33 (42%) | 14 (18%) | 22 (28%) | 10 (13%) | 79 (100%) | 47 (59%) |

*Abbreviation:* PET/CT = positron emission tomography/computed tomography.
Shaded cells represent no major change in management.

**Table 4** PET/CT results and actual management by PSA

| PSA | Number of patients | No detected recurrence | Prostate only | Oligometastatic | Extensive metastatic | Biopsy | Directed salvage alone | Systemic therapy alone | Systemic therapy and directed salvage | No therapy | Major change in management compared with pre-PET/CT plan |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2-2.99 | 12 | 2 (17%) | 6 (50%) | 3 (25%) | 1 (8%) | 5 (42%) | 2 (17%) | 2 (17%) | 0 (0%) | 8 (67%) | 5 (42%) |
| 3-3.99 | 19 | 5 (26%) | 10 (53%) | 4 (21%) | 0 (0%) | 9 (47%) | 7 (37%) | 1 (5%) | 2 (11%) | 9 (47%) | 15 (79%) |
| 4-4.99 | 11 | 1 (8%) | 7 (64%) | 3 (27%) | 0 (0%) | 3 (27%) | 2 (18%) | 3 (27%) | 2 (18%) | 4 (36%) | 7 (64%) |
| >4.99 | 37 | 2 (17%) | 15 (41%) | 11 (30%) | 9 (24%) | 5 (14%) | 3 (8%) | 16 (43%) | 6 (16%) | 12 (32%) | 20 (54%) |
| Any | 79 | 10 (83%) | 38 (48%) | 21 (27%) | 10 (13%) | 22 (28%) | 14 (18%) | 22 (28%) | 10 (13%) | 33 (42%) | 47 (59%) |

*Abbreviations:* PET/CT = positron emission tomography/computed tomography; PSA = prostate-specific antigen.

**Table 5** PET/CT results and actual management

| Site of recurrence on PET/CT | Number of patients | Biopsy | Directed salvage alone | Systemic therapy alone | Systemic therapy and directed salvage | No therapy | Major change compared with pre-PET/CT plan | Major change compared with post-PET/CT plan | Reason for major change compared with post-PET/CT plan | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Patient preference | Physician discretion | Comorbidities | Other |
| All patients | 79 (100%) | 22 (28%) | 14 (18%) | 22 (28%) | 10 (13%) | 33 (42%) | 47 (59%) | 24 (30%) | 9 (11%) | 8 (10%) | 3 (4%) | 4 (5%) |
| Any site | 69 (87%) | 18 (26%) | 13 (19%) | 21 (30%) | 10 (14%) | 25 (36%) | 43 (62%) | 22 (32%) | 8 (12%) | 7 (10%) | 3 (4%) | 4 (6%) |
| No detected recurrence | 10 (13%) | 4 (40%) | 1 (10%) | 1 (10%) | 0 (0%) | 8 (80%) | 4 (40%) | 2 (20%) | 1 (10%) | 1 (10%) | 0 (0%) | 0 (0%) |
| Prostate only | 38 (48%) | 12 (32%) | 10 (26%) | 7 (18%) | 4 (11%) | 17 (45%) | 23 (61%) | 15 (39%) | 6 (16%) | 2 (5%) | 3 (8%) | 4 (11%) |
| Oligometastatic | 21 (27%) | 6 (29%) | 2 (10%) | 8 (38%) | 6 (29%) | 5 (24%) | 14 (67%) | 5 (24%) | 0 (0%) | 5 (24%) | 0 (0%) | 0 (0%) |
| Extensive metastatic | 10 (13%) | 0 (0%) | 1 (10%) | 6 (60%) | 0 (0%) | 3 (30%) | 6 (60%) | 2 (20%) | 2 (20%) | 0 (0%) | 0 (0%) | 0 (0%) |

*Abbreviation:* PET/CT = positron emission tomography/computed tomography.

13% to 33% of patients in 6/15 included studies, and management effect in this subgroup was not reported. Notably, rates of intermodality (24%) and intramodality (28%) changes were similar in the meta-analysis. As such, it is likely that the management effect of PSMA-targeted PET/CT, had we tracked intramodality changes (such as boost to or change in volume to include PET-positive nodes[11]), would have been even higher than 59%.

After PSMA-targeted PET/CT, 18 patients had confirmatory prostate biopsy. Sensitivity and PPVs were 86% and 92%, and were similar to previously reported values in patients with recurrence.[12,13] Three additional patients with suspected sites of metastatic disease were all positive for metastatic disease. One second primary cancer (rectal cancer) was detected on mpMRI and this was not seen on PSMA-targeted PET/CT.

Eleven patients had HDR brachytherapy alone for local recurrence. RFS was 91% at a median follow-up of 20 months. This is similar to previous salvage HDR brachytherapy series.[14] The benefit of PSMA-targeted PET/CT restaging for patients who undergo local salvage therapy is currently unclear. A recent study evaluated ultrafocal salvage HDR brachytherapy in 50 locally radiorecurrent patients, including 37 restaged with $^{68}$Ga PSMA PET/CT.[15] Clinical tumor volume (CTV) was gross tumor volume as defined by PSMA PET/CT or choline PET/CT and MRI + 5 mm. CTV D95% was $\geq$19 Gy and CTV D90% was >17 Gy delivered in 1 fraction. RFS (nadir PSA + 2) was 48% after median follow-up of 31 months and was lower compared with other salvage radiotherapy series.[14,16] Differences in RFS may be secondary to differences in patient population, brachytherapy volumes, dosimetry, and fractionation.

Strengths of the current study include the prospective, multicenter design; use of multiple PSMA-targeted PET/CT readers for each scan; high completion rate of standard questionnaires before PET/CT (100%), after PET/CT (100%), and 6 months after PET/CT (96%); and standardized imaging including mpMRI pelvis before PET/CT. Limitations include our strict inclusion criteria, intended to select for local failures (initial T1-T2 disease, Gleason $\leq$7 or T1-T2 disease, Gleason $\leq$8 and PSA $\leq$10). The majority of enrolled patients (72%) had intermediate risk disease. Other limitations include nonstandardized management of recurrence, and no assessment of intramodality management changes.

Changes in management and the presence of nodal or metastatic disease were relatively frequent in men with early biochemical failure (PSA, 2-2.99; Table 4). The Phoenix criteria for biochemical failure was not designed to detect early recurrence such as isolated local failure. In a recent study, $^{68}$Ga PSMA-targeted PET/CT changed management in 73% of patients (16/22) with recurrent prostate cancer after primary radiation therapy who did not meet Phoenix criteria, and 9/22 patients (41%) had nodal or metastatic disease.[9] Characterizing longitudinal PSMA-targeted PET/CT changes after radiation therapy (as previously done using MRI with spectroscopy)[17] could be valuable to determine whether PSMA-targeted PET/CT could be a more sensitive biomarker for early detection of isolated local recurrence.

## Conclusions

Most patients had a major change in actual management compared with planned management pre–PSMA-targeted PET/CT, and this was underestimated by post-PET/CT questionnaires.

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