

---

---

# Prospective Comparison of $^{18}\text{F}$ -Fluoromethylcholine Versus $^{68}\text{Ga}$ -PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy

Joshua J. Morigi<sup>1,2</sup>, Phillip D. Stricker<sup>3,4</sup>, Pim J. van Leeuwen<sup>3,4</sup>, Reuben Tang<sup>1,5</sup>, Bao Ho<sup>1</sup>, Quoc Nguyen<sup>3,4</sup>, George Hruby<sup>6</sup>, Gerald Fogarty<sup>3</sup>, Raj Jagavkar<sup>3</sup>, Andrew Kneebone<sup>6</sup>, Adam Hickey<sup>1</sup>, Stefano Fanti<sup>2</sup>, Lisa Tarlinton<sup>1</sup>, and Louise Emmett<sup>1,5</sup>

<sup>1</sup>Department of Diagnostic Imaging, St. Vincent's Public Hospital, Sydney, Australia; <sup>2</sup>Nuclear Medicine Operative Unit, Policlinico S. Orsola-Malpighi Hospital, Bologna, Italy; <sup>3</sup>St. Vincent's Prostate Cancer Centre, St. Vincent's Clinic, Sydney, Australia;

<sup>4</sup>Australian Prostate Cancer Research Centre, Garvan Institute of Medical Research/Kinghorn Cancer Centre, Sydney, New South Wales, Australia; <sup>5</sup>University of New South Wales, Sydney, New South Wales, Australia; and <sup>6</sup>University of Sydney, Sydney, New South Wales, Australia

---

In prostate cancer with biochemical failure after therapy, current imaging techniques have a low detection rate at the prostate-specific antigen (PSA) levels at which targeted salvage therapy is effective.  $^{11}\text{C}$ -choline and  $^{18}\text{F}$ -fluoromethylcholine, though widely used, have poor sensitivity at low PSA levels.  $^{68}\text{Ga}$ -PSMA (Glu-NH-CO-NH-Lys-(Ahx)-[ $^{68}\text{Ga}$ -N,N'-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N'-diacetic acid]) has shown promising results in retrospective trials. Our aim was to prospectively compare the detection rates of  $^{68}\text{Ga}$ -PSMA versus  $^{18}\text{F}$ -fluoromethylcholine PET/CT in men who were initially managed with radical prostatectomy, radiation treatment, or both and were being considered for targeted therapy. **Methods:** A sample of men with a rising PSA level after treatment, eligible for targeted treatment, was prospectively included. Patients on systemic treatment were excluded.  $^{68}\text{Ga}$ -PSMA,  $^{18}\text{F}$ -fluoromethylcholine PET/CT, and diagnostic CT were performed sequentially on all patients between January and April 2015, and the images were assessed by masked, experienced interpreters. The findings and their impact on management were documented, together with the results of histologic follow-up when feasible. **Results:** In total, 38 patients were enrolled. Of these, 34 (89%) had undergone radical prostatectomy and 4 (11%) had undergone radiation treatment. Twelve (32%) had undergone salvage radiation treatment after primary radical prostatectomy. The mean PSA level was  $1.74 \pm 2.54$  ng/mL. The scan results were positive in 26 patients (68%) and negative with both tracers in 12 patients (32%). Of the 26 positive scans, 14 (54%) were positive with  $^{68}\text{Ga}$ -PSMA alone, 11 (42%) with both  $^{18}\text{F}$ -fluoromethylcholine and  $^{68}\text{Ga}$ -PSMA, and only 1 (4%) with  $^{18}\text{F}$ -fluoromethylcholine alone. When PSA was below 0.5 ng/mL, the detection rate was 50% for  $^{68}\text{Ga}$ -PSMA versus 12.5% for  $^{18}\text{F}$ -fluoromethylcholine. When PSA was 0.5–2.0 ng/mL, the detection rate was 69% for  $^{68}\text{Ga}$ -PSMA versus 31% for  $^{18}\text{F}$ -fluoromethylcholine, and when PSA was above 2.0, the detection rate was 86% for  $^{68}\text{Ga}$ -PSMA versus 57% for  $^{18}\text{F}$ -fluoromethylcholine. On lesion-based analysis,  $^{68}\text{Ga}$ -PSMA detected more lesions than  $^{18}\text{F}$ -fluoromethylcholine (59 vs. 29,  $P < 0.001$ ). The tumor-to-background ratio in positive

scans was higher for  $^{68}\text{Ga}$ -PSMA than for  $^{18}\text{F}$ -fluoromethylcholine (28.6 for  $^{68}\text{Ga}$ -PSMA vs. 9.4 for  $^{18}\text{F}$ -fluoromethylcholine,  $P < 0.001$ ). There was a 63% (24/38 patients) management impact, with 54% (13/24 patients) being due to  $^{68}\text{Ga}$ -PSMA imaging alone. Histologic follow-up was available for 9 of 38 patients (24%), and 9 of 9  $^{68}\text{Ga}$ -PSMA-positive lesions were consistent with prostate cancer ( $^{68}\text{Ga}$ -PSMA was true-positive). The lesion positive on  $^{18}\text{F}$ -fluoromethylcholine imaging and negative on  $^{68}\text{Ga}$ -PSMA imaging was shown at biopsy to be a false-positive  $^{18}\text{F}$ -fluoromethylcholine finding ( $^{68}\text{Ga}$ -PSMA was true-negative). **Conclusion:** In patients with biochemical failure and a low PSA level,  $^{68}\text{Ga}$ -PSMA demonstrated a significantly higher detection rate than  $^{18}\text{F}$ -fluoromethylcholine and a high overall impact on management.

**Key Words:**  $^{18}\text{F}$ -fluoromethylcholine;  $^{68}\text{Ga}$ -PSMA; molecular imaging; PET/CT; prostate cancer; prostate-specific membrane antigen

**J Nucl Med 2015; 56:1185–1190**  
DOI: 10.2967/jnumed.115.160382

---

**D**espite advances in surgical technique and radiotherapeutic delivery, initial curative therapy will fail in a significant proportion of men with prostate cancer (1). In those men with biochemical failure after initial therapy, the currently available imaging techniques (2,3) have a low detection rate at the levels of prostate-specific antigen (PSA) at which targeted salvage therapy has optimal effect. With regard to PET/CT, whereas  $^{18}\text{F}$ -fluoromethylcholine (4) and  $^{11}\text{C}$ -choline (5) remain the best validated tracers for detection of recurrent prostate cancer (6,7), they have significant limitations that preclude their effectiveness in patients with a low PSA level (8). Recent retrospective data on the novel PET tracer  $^{68}\text{Ga}$ -PSMA (Glu-NH-CO-NH-Lys-(Ahx)-[ $^{68}\text{Ga}$ -N,N'-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N,N'-diacetic acid]) have demonstrated promising sensitivity and specificity for the detection of prostate cancer in the setting of biochemical recurrence (9) and suggest that this agent is likely to be more sensitive than  $^{18}\text{F}$ -fluoromethylcholine or  $^{11}\text{C}$ -choline for the assessment of systemic spread (10,11). This promising tracer relies on overexpression of prostate-specific

---

Received May 4, 2015; revision accepted Jun. 17, 2015.  
For correspondence or reprints contact: Joshua J. Morigi.  
E-mail: joshuajames.morigi@studio.unibo.it  
Published online Jun. 25, 2015.  
COPYRIGHT © 2015 by the Society of Nuclear Medicine and Molecular Imaging, Inc.

membrane antigen (a transmembrane folate hydrolase) on the surface of prostate cancer cells. This overexpression has been demonstrated both locally and in metastatic lesions within bone, lymph nodes, and soft tissue (12,13).

The aim of this study was to prospectively compare the detection rates and management impact of  $^{68}\text{Ga}$ -PSMA PET/CT and  $^{18}\text{F}$ -fluoromethylcholine PET/CT in patients with prostate cancer and a low but detectable PSA relapse after curative therapy.

## MATERIALS AND METHODS

### Study Design and Data Collection

Thirty-eight prostate cancer patients with a rising PSA level after radical prostatectomy, radiotherapy (external beam or other), or both, who were not yet on systemic therapy and were actively being considered for further targeted therapy, were enrolled in the trial. No target had been identified for treatment through clinical examination or imaging. Patients on hormonal or systemic treatment were excluded. Data on age, previous therapy, time since therapy, initial pathologic findings (including T stage and Gleason score), PSA doubling time, PSA at the time of scanning, and prior imaging results were collected at enrollment. The trial was approved by the Institutional Human Research and Ethics Committee, and informed consent was obtained from all participants.

### Scan Acquisition

Both the  $^{18}\text{F}$ -fluoromethylcholine and the  $^{68}\text{Ga}$ -PSMA were produced onsite with good-laboratory-practice-compliant procedures using an automated radiopharmacy cassette (Trasis S.A.). Radiopharmacy quality control was undertaken using a high-pressure liquid chromatography method.

$^{18}\text{F}$ -fluoromethylcholine PET/CT and then  $^{68}\text{Ga}$ -PSMA PET/CT plus diagnostic contrast-enhanced abdominopelvic CT were performed within 30 d. The diagnostic CT scan was embedded within the attenuation-correction CT scan for the clinically indicated  $^{18}\text{F}$ -fluoromethylcholine scan but was separately reconstructed by standard CT methods and separately interpreted for the purposes of the study.

The routine clinical protocol was followed (for  $^{18}\text{F}$ -fluoromethylcholine, a 3.5 MBq/kg dose and a 10-min dynamic pelvic acquisition plus a 20-min static whole-body acquisition; for  $^{68}\text{Ga}$ -PSMA, a 2.0 MBq/kg dose and whole-body scanning 45 min after injection). Whole-body images were acquired from the vertex to the knees.

PET/CT was performed using an Ingenuity time-of-flight PET/64-slice CT scanner (Philips). For  $^{68}\text{Ga}$ -PSMA, unenhanced CT was performed 45 min after tracer injection using the following CT parameters: 2-mm slice thickness, 2-mm increment, soft-tissue reconstruction kernel, 120 keV and 50 mAs, 0.828 pitch, 600-mm field of view, and 512 matrix. Immediately after CT scanning, a whole-body PET scan was acquired for 2 min per bed position. For  $^{18}\text{F}$ -fluoromethylcholine PET/CT scans, low-dose and modulated diagnostic CT with intravenous contrast material was performed. The initial low-dose CT scan was acquired immediately before injection of  $^{18}\text{F}$ -fluoromethylcholine using the following parameters: 2-mm slice thickness, 2-mm increment, soft-tissue reconstruction kernel, 120 keV and 50 mAs, 0.828 pitch, 600-mm field of view, and 512 matrix.  $^{18}\text{F}$ -fluoromethylcholine was injected simultaneously with the PET acquisition of 1 bed position for 10 min, acquired in list mode to obtain dynamic reconstruction. Immediately afterward, modulated diagnostic whole-body CT with intravenous contrast material (vertex to mid thigh) was performed with the following parameters: 2-mm slice thickness, 2-mm increment, soft-tissue reconstruction kernel, 120 keV and 50–350 mAs, 0.828 pitch, 600-mm field of view, and 512 matrix. The whole-body PET scan was then acquired for 2 min per bed position. For both  $^{68}\text{Ga}$ -PSMA and  $^{18}\text{F}$ -fluoromethylcholine

scans, the emission data were corrected for randoms, scatter, and decay using the body-dynamic.xml and body.xml reconstruction protocols (Philips). All images were viewed and reported using Fusion Viewer (Philips).

### Image Interpretation

The PET images were interpreted by 2 experienced nuclear medicine physicians who did not know the clinical or imaging results. Data for both the  $^{18}\text{F}$ -fluoromethylcholine and the  $^{68}\text{Ga}$ -PSMA scans were analyzed visually and semiquantitatively. Visual analysis included a 4-point certainty scoring scale, as well as site and size of lesions. Semiquantitative analysis was performed using an automated maximum standardized uptake value for both  $^{18}\text{F}$ -fluoromethylcholine and  $^{68}\text{Ga}$ -PSMA. No direct comparison was attempted. Instead, tumor-to-background ratios (TBRs) were determined for each lesion on both the  $^{68}\text{Ga}$ -PSMA and the  $^{18}\text{F}$ -fluoromethylcholine images. TBR was established by placing a 2-dimensional region of interest in the pelvis and measuring the maximum standardized uptake value of background fat within the area. This value was then used as the denominator for the maximum standardized uptake value of the lesion, resulting in TBR. The diagnostic CT results were interpreted separately by an experienced radiologist who did not know the PET results or clinical information.

### Follow-up and Patient Management

Treating physicians were asked to report on the management plan prior to and subsequent to each PET scan. Changes in management after the  $^{18}\text{F}$ -fluoromethylcholine and  $^{68}\text{Ga}$ -PSMA results became known were classified as none, minor (change in delivery or site of selected treatment), or major (change in selected treatment). Detailed questions were posed on the type of management undertaken on the basis of the imaging results and whether  $^{68}\text{Ga}$ -PSMA had an added impact over  $^{18}\text{F}$ -fluoromethylcholine on management. All clinical data, along with any added value of imaging, were considered by treating physicians in defining further treatment. Histopathologic follow-up results were gathered when available.

### Statistical Analysis

McNemar testing was used to analyze scan positivity at different PSA levels (0–0.5, 0.5–2.0, and 2.0–12.0 ng/mL). Pearson correlation and stepwise regression analysis were used to identify the determinants of scan positivity. PSA at the time of scanning, PSA doubling time, Gleason score, age, initial treatment, and years from treatment were included in the analysis. Wilcoxon signed-rank testing was used for lesion-based analysis and management-impact analysis. Two-tailed, paired *t* testing assuming unequal variance was used to analyze and compare TBR ratios between scans. PSA doubling time was calculated only for patients with a PSA level above 0.2 according to standard formulas, based on at least 2 PSA values separated by at least 3 mo within 1 y after recurrence and no adjuvant radiation or hormonal therapy before recurrence. Statistical analysis was performed with SPSS, version 21 (IBM).

## RESULTS

The characteristics of the 38 patients are presented in Table 1. The primary treatment was radical prostatectomy in 34 patients (89%) and radiotherapy in 4 patients (11%). Twelve patients (32%) had undergone salvage radiotherapy after radical prostatectomy. The mean PSA level was 1.72 ng/mL (range, 0.04–12 ng/mL), and 30 patients (79%) had a PSA level of 2.0 ng/mL or less at the time of imaging. The mean PSA doubling time was 15.6 mo (range, 2.6–111.2 mo) and was calculated in 31 patients (insufficient data or low absolute PSA levels in the other 7 patients).

Overall, 26 patients (68%) had positive scan results. Of these 26, 14 (54%) were positive with  $^{68}\text{Ga}$ -PSMA alone, 11 (42%) with

**TABLE 1**  
Patient Characteristics and Preimaging Data

Characteristic	Data
Age (y)	
Mean	68
Range	54–81
PSA at time of scan (ng/dL)	
Mean ± SD	1.72 ± 2.54
Range	0.04–12.0
PSA doubling time (mo)	
Mean ± SD	15.6 ± 22.1
Range	2.6–111.2
Initial treatment (n)	
Radical prostatectomy	34/38 (89%)
Radiotherapy*	4/38 (11%)
Surgery + salvage radiotherapy	12/38 (32%)
PSA at diagnosis (ng/dL)	
Mean ± SD	9.7 ± 4.9
Range	2.8–20.2
Years since diagnosis	
Mean	7
Range	1–18
Gleason score (n)	
6–7	23/38 (61%)
8–9	15/38 (39%)
Risk group† (n)	
Intermediate	11/38 (24%)
High	27/38 (76%)

\*External-beam radiation therapy or brachytherapy.  
†According to European Association of Urology guidelines.

both <sup>18</sup>F-fluoromethylcholine and <sup>68</sup>Ga-PSMA, and only 1 (4%) with <sup>18</sup>F-fluoromethylcholine alone (subsequently confirmed as false-positive on biopsy). Overall, 12 of the 38 scans (32%) were negative with both tracers.

The most significant predictor of a positive PET result for both <sup>18</sup>F-fluoromethylcholine and <sup>68</sup>Ga-PSMA was PSA at the time of imaging ( $P < 0.001$ ). In men with a PSA level below 0.5 ng/mL, 50% of scans were positive with <sup>68</sup>Ga-PSMA versus 12.5% with <sup>18</sup>F-fluoromethylcholine ( $P = 0.03$ ). When PSA was 0.5–2.0 ng/mL, 71% were <sup>68</sup>Ga-PSMA-positive and 36% were <sup>18</sup>F-fluoromethylcholine-positive ( $P = 0.02$ ). When PSA was above 2.0 ng/mL, 88% were <sup>68</sup>Ga-PSMA-positive and 63% were <sup>18</sup>F-fluoromethylcholine-positive

(Table 2). Additionally, <sup>68</sup>Ga-PSMA identified a higher number of lesions in every PSA cohort than did <sup>18</sup>F-fluoromethylcholine (Fig. 1). Overall, <sup>68</sup>Ga-PSMA detected more lesions than <sup>18</sup>F-fluoromethylcholine (59 vs. 29,  $P < 0.001$ ). More lesions (Fig. 2) were identified locoregionally, in lymph nodes and bone, with <sup>68</sup>Ga-PSMA. Local lesions occurred both in radiotherapy patients (Fig. 3) and in radical prostatectomy patients. Uptake in residual radiotreated prostate tissue was detected on a single <sup>18</sup>F-fluoromethylcholine scan and on three <sup>68</sup>Ga-PSMA scans. For radical prostatectomy patients, seminal vesicle uptake was detected in 3 scans on solely <sup>68</sup>Ga-PSMA (<sup>18</sup>F-fluoromethylcholine-negative, <sup>68</sup>Ga-PSMA-positive). Finally, in a radical prostatectomy patient, the prostate bed was positive with <sup>68</sup>Ga-PSMA but negative with <sup>18</sup>F-fluoromethylcholine. Qualitative evaluation of the PET scan and the 2-mm-thick enhanced-CT slices was used to differentiate between activity within the urine and activity within the pelvis. With lesion-based analysis, only PSA at the time of scanning correlated significantly with total number of lesions on <sup>68</sup>Ga-PSMA ( $P < 0.001$ ) or <sup>18</sup>F-fluoromethylcholine ( $P = 0.002$ ). There was no significant correlation between PSA doubling time or Gleason score and the detection rate of either <sup>18</sup>F-fluoromethylcholine or <sup>68</sup>Ga-PSMA. On diagnostic enhanced CT, no lesions were considered definitely positive.

After imaging, there was a major or moderate impact on management in 24 cases (63%) (Fig. 4), 54% (13/24) of which were attributable to the findings on <sup>68</sup>Ga-PSMA imaging alone (Fig. 5). In the 11 of 24 patients (46%) for whom both <sup>18</sup>F-fluoromethylcholine and <sup>68</sup>Ga-PSMA had an impact, the <sup>68</sup>Ga-PSMA results caused an additional change in management for 4 (36%). In no case was management changed on the basis of the results of <sup>18</sup>F-fluoromethylcholine alone. In summary, <sup>68</sup>Ga-PSMA imaging accounted (either alone or in concordance with <sup>18</sup>F-fluoromethylcholine) for the entire impact on management in our patient cohort (24/38 for <sup>68</sup>Ga-PSMA vs. 11/38 for <sup>18</sup>F-fluoromethylcholine,  $P < 0.001$ ). <sup>68</sup>Ga-PSMA TBR was higher than <sup>18</sup>F-fluoromethylcholine TBR in scans with positive findings (Fig. 6). The mean TBR was 9.4 for <sup>18</sup>F-fluoromethylcholine but 28.6 for <sup>68</sup>Ga-PSMA ( $P < 0.001$ ). Mean uptake in fat was similar between the two types of scan (maximum standardized uptake values of 0.3 for <sup>18</sup>F-fluoromethylcholine and 0.26 for <sup>68</sup>Ga-PSMA).

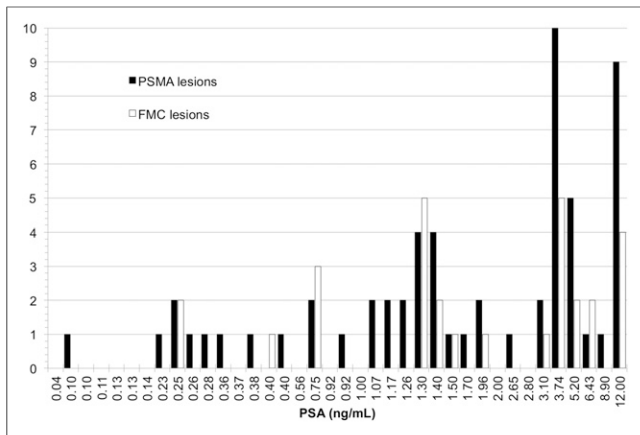
Histopathologic confirmation was possible for 9 (24%) of the 38 patients with positive findings on <sup>68</sup>Ga-PSMA or <sup>18</sup>F-fluoromethylcholine imaging. All 9 of the <sup>68</sup>Ga-PSMA-positive lesions that underwent biopsy were confirmed to be true-positive. Of the 2 lesions that were <sup>18</sup>F-fluoromethylcholine-positive, one was true-positive. The other was false-positive with <sup>18</sup>F-fluoromethylcholine (and on MR imaging) and true-negative with <sup>68</sup>Ga-PSMA.

## DISCUSSION

Our key finding was that in patients with rising PSA after curative treatment, <sup>68</sup>Ga-PSMA has a higher detection rate than

**TABLE 2**  
Detection Rates of <sup>18</sup>F-Fluoromethylcholine and <sup>68</sup>Ga-PSMA

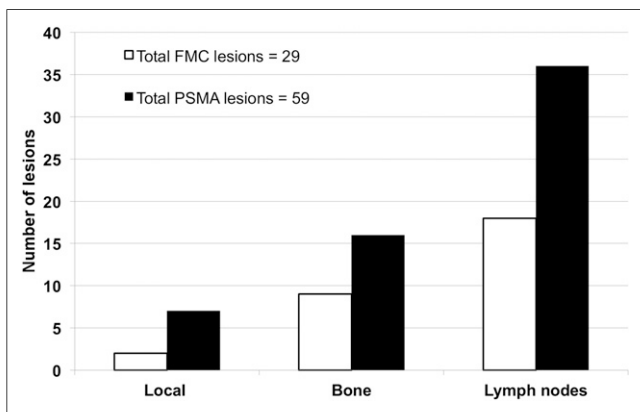
PSA level (ng/mL)	<sup>18</sup> F-fluoromethylcholine	<sup>68</sup> Ga-PSMA	<i>P</i>
<0.5	12.5% (2/16)	50% (8/16)	0.03
0.5–2.0	36% (5/14)	71% (10/14)	0.02
>2.0	63% (5/8)	88% (7/8)	0.18
Total	32% (12/38)	66% (25/38)	<0.001



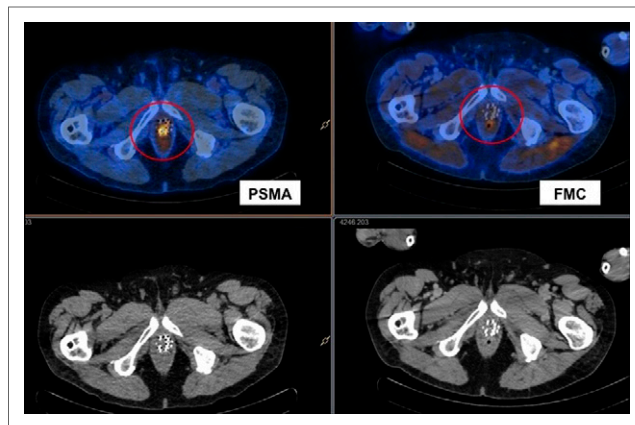
**FIGURE 1.** Total number of lesions detected for each patient with  $^{18}\text{F}$ -fluoromethylcholine (FMC) and  $^{68}\text{Ga}$ -PSMA, ranked by ascending PSA value.

$^{18}\text{F}$ -fluoromethylcholine regardless of PSA level. This finding was most evident in patients with low PSA levels ( $<0.5$  ng/mL), with 50% of such patients having positive  $^{68}\text{Ga}$ -PSMA results. The high sensitivity at low PSA levels has important implications for the management of patients in whom PSA is rising after therapy with curative intent (radical prostatectomy or radiation) (14). There is a paucity of published literature on  $^{68}\text{Ga}$ -PSMA in humans. Although 3 retrospective studies (9,11,15) demonstrated promising results, to our knowledge no prospective studies have been published. The diagnostic value of  $^{11}\text{C}$ -choline and  $^{18}\text{F}$ -fluoromethylcholine is well documented (6,16), and the use of these agents in the setting of biochemical relapse is increasing (17). However, both tracers lack sensitivity at low PSA levels (8), and neither is yet standardized (18). Our results reinforce the limited sensitivity of  $^{18}\text{F}$ -fluoromethylcholine at low PSA levels and suggest that  $^{68}\text{Ga}$ -PSMA may more effectively detect recurrent disease at low PSA levels. The value of treating recurrent prostate cancer at low PSA levels has recently been outlined in European guidelines (14) and is associated with a reduced incidence of biochemical failure (19).

Currently, men with low PSA levels who experience biochemical relapse after radical prostatectomy often undergo salvage radiotherapy to the prostatic bed even when there are no



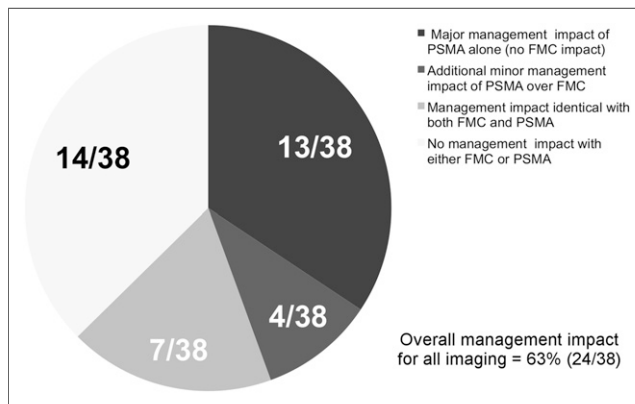
**FIGURE 2.** Total number of  $^{18}\text{F}$ -fluoromethylcholine (FMC) and  $^{68}\text{Ga}$ -PSMA-positive lesions per anatomic site, including prostate bed or seminal vesicles (local), bone, or lymph nodes.



**FIGURE 3.** A 70-year-old man with Gleason 7 prostate cancer treated with radiation therapy who presented with rising PSA level (8.9) and PSA doubling time of 9.5 mo.  $^{18}\text{F}$ -fluoromethylcholine (FMC) scan was negative, whereas  $^{68}\text{Ga}$ -PSMA scan demonstrated intense uptake in prostate (maximum standardized uptake value, 4.5). Subsequent biopsy confirmed local recurrence.

significant imaging findings. Hence, it is no surprise that, per the nomogram of Stephenson et al. (20), only about half these men are currently cured. Furthermore, in a few men salvage radiation treatment may be harmful. Therefore, the high detection rate of  $^{68}\text{Ga}$ -PSMA at low PSA levels—demonstrated in this trial—may benefit management in patients with an early rise in PSA level after initial treatment. On the basis of our findings, disease outside the prostate bed is identified on  $^{68}\text{Ga}$ -PSMA alone in up to 75% (6/8) of  $^{68}\text{Ga}$ -PSMA-positive patients who would be eligible for salvage radiotherapy of the prostate bed (those patients with a PSA level of  $<1.0$  ng/mL). The current clinical paradigm of either  $^{18}\text{F}$ -fluoromethylcholine-guided or unguided salvage radiotherapy of the prostate bed would have failed in these patients.

The superior sensitivity of  $^{68}\text{Ga}$ -PSMA compared with  $^{18}\text{F}$ -fluoromethylcholine was previously demonstrated in a single retrospective study (11), but there were important differences between that study population and ours. Most patients in our study had a PSA level below 2.0 ng/mL, whereas the previous study had a mean PSA level of 11.1 ng/mL and therefore was less able to demonstrate an added benefit for  $^{68}\text{Ga}$ -PSMA over  $^{18}\text{F}$ -fluoromethylcholine at low PSA levels. However, despite the difference in patient cohorts, both studies demonstrated a statistically higher total number of lesions



**FIGURE 4.** Impact on management. FMC =  $^{18}\text{F}$ -fluoromethylcholine.

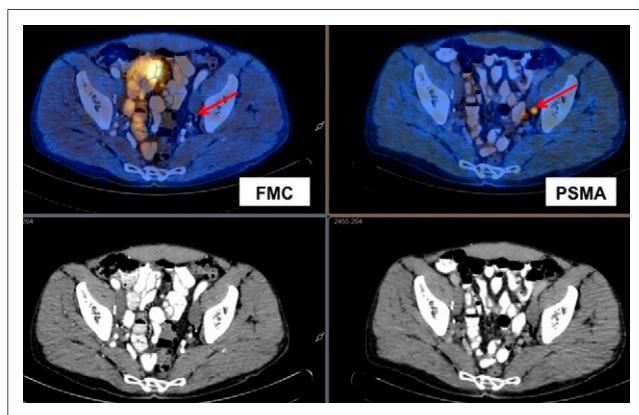
detected with  $^{68}\text{Ga}$ -PSMA than with  $^{18}\text{F}$ -fluoromethylcholine in all positive patients.

Our study found that when  $^{68}\text{Ga}$ -PSMA was performed at low absolute PSA levels, the impact on management was exceptionally high. There are several reasons for this. First, when tumor recurred in the prostate bed, potentially curative and directed salvage radiation was delivered. Second, when oligometastatic disease was present, targeted treatments such as stereotactic body radiotherapy or lymph node dissection were used. Finally, when metastatic disease was found with  $^{68}\text{Ga}$ -PSMA (or less likely, with  $^{18}\text{F}$ -fluoromethylcholine), systemic treatment was begun and the patient was spared from undergoing salvage radiation to the prostatic fossa.

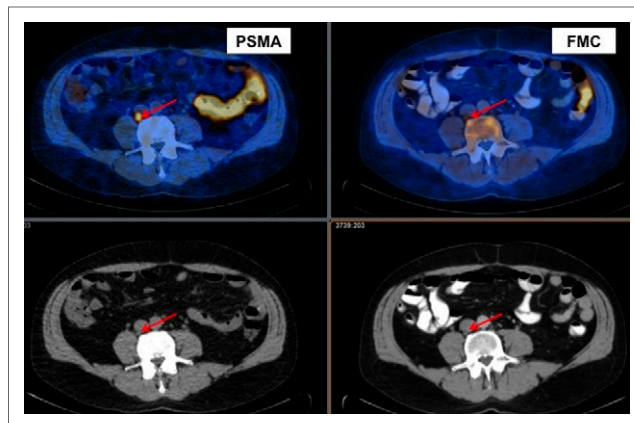
This study demonstrated a significantly higher TBR with  $^{68}\text{Ga}$ -PSMA than with  $^{18}\text{F}$ -fluoromethylcholine. Lesions detected with  $^{68}\text{Ga}$ -PSMA were more than twice the intensity of those detected with  $^{18}\text{F}$ -fluoromethylcholine, compared with background tissue. The significantly higher TBR with  $^{68}\text{Ga}$ -PSMA allows easier identification of even very small lesions.

The major limitation of this trial was that not all positive findings were confirmed histopathologically. Confirmation was impaired by the small volume of individual lesions and the high number of biopsy-inaccessible lymph node and bone recurrences. In patients whose biopsy was successful, we could confirm all  $^{68}\text{Ga}$ -PSMA findings as true-positive. At biopsy, one  $^{18}\text{F}$ -fluoromethylcholine-positive (and MR imaging-positive) lymph node that had been negative on  $^{68}\text{Ga}$ -PSMA was found. The aim of this trial was not to determine diagnostic accuracy but to assess the detection rate of the 2 tracers at low PSA levels. Many of these patients with disease identified on PET/CT will be undergoing targeted therapy as part of their routine clinical care. We intend to continue long-term follow-up of this cohort to document response to therapy and confirm diagnostic accuracy.

Histopathologic confirmation was obtained in only 24% of patients. However, it is remarkable that 100% of the  $^{68}\text{Ga}$ -PSMA-positive lesions that underwent biopsy were true-positive and that the single lesion positive with  $^{18}\text{F}$ -fluoromethylcholine and negative with  $^{68}\text{Ga}$ -PSMA was of a reactive nature. Although this study confirmed a high detection rate for  $^{68}\text{Ga}$ -PSMA at low PSA levels,



**FIGURE 5.** A 62-y-old man with Gleason 7 prostate cancer treated with radical prostatectomy and salvage radiation who presented with rising PSA level (0.4) and PSA doubling time of 8 mo.  $^{18}\text{F}$ -fluoromethylcholine (FMC) PET/CT findings were negative, whereas  $^{68}\text{Ga}$ -PSMA PET/CT scan demonstrated single positive left obturator lymph node (maximum standardized uptake value, 3.7). Subsequent biopsy confirmed prostate cancer recurrence.



**FIGURE 6.** A 70-y-old man with Gleason 7 prostate cancer treated with radical prostatectomy who presented with rising PSA (12.0) and PSA doubling time of 5.8 mo. Both  $^{18}\text{F}$ -fluoromethylcholine (FMC) PET/CT and  $^{68}\text{Ga}$ -PSMA PET/CT were positive for nodal disease (4 lesions positive on  $^{18}\text{F}$ -fluoromethylcholine imaging and 9 on  $^{68}\text{Ga}$ -PSMA). However, TBR was higher for  $^{68}\text{Ga}$ -PSMA than for  $^{18}\text{F}$ -fluoromethylcholine (25.0 vs. 7.0 in this image of positive paracaval lymph node). Biopsy confirmed nodal recurrence of prostate cancer.

further prospective trials addressing sensitivity and specificity are urgently needed.

A further limitation of this trial was the small number of men enrolled. Nevertheless, it is impressive that with such a small cohort there was a statistically significant difference in detection rates between  $^{68}\text{Ga}$ -PSMA and  $^{18}\text{F}$ -fluoromethylcholine on both a patient basis and a lesion basis. However, large, adequately powered prospective trials are needed to better evaluate  $^{68}\text{Ga}$ -PSMA.

Though previously reported in publications on  $^{11}\text{C}$ -choline (8,21) and more recently  $^{68}\text{Ga}$ -PSMA (22), a statistically significant correlation between PSA doubling time, Gleason score, and  $^{18}\text{F}$ -fluoromethylcholine or  $^{68}\text{Ga}$ -PSMA positivity was not found in our study. This discrepancy is probably related to the low mean PSA values of this patient cohort ( $<2.0$  ng/mL) and the small number of men enrolled. Calculation of the PSA doubling time was possible for only 31 patients, therefore limiting statistical analysis of this variable.

The development of  $^{68}\text{Ga}$ -PSMA is at an early stage. Currently, there are several different  $^{68}\text{Ga}$ -PSMA ligands in clinical use and under research (23), making extrapolation of these data across all clinical sites problematic. Further product development, comparative trials, and harmonization of tracer use are urgently needed.

## CONCLUSION

In patients who have a low, rising PSA level and are being evaluated for therapy with curative intent,  $^{68}\text{Ga}$ -PSMA PET/CT demonstrated a significantly higher detection rate for recurrent disease than  $^{18}\text{F}$ -fluoromethylcholine and had an impact on management in many patients. Although these findings need to be confirmed in larger trials, this prospective trial suggests that  $^{68}\text{Ga}$ -PSMA PET/CT will be an effective imaging tool for early detection of prostate cancer recurrence.

## DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this

fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. Funding was provided by St. Vincent’s Prostate Cancer Centre and the Australian Department of Health and Ageing through the Australian Prostate Cancer Research Centre—New South Wales (APCRC-NSW). No other potential conflict of interest relevant to this article was reported.

## REFERENCES

- Schwarz R, Graefen M, Krüll A. Therapy of treatment failure after curative treatment of prostate cancer. *EAU-EBU Update Series 4*. 2006;4:228–240.
- Ménard C, Lupati D, Publicover J, et al. MR-guided prostate biopsy for planning of focal salvage after radiation therapy. *Radiology*. 2015;274:181–191.
- Cochet A, Kanoun S, Humbert O, et al. Multimodality MRI and PET for restaging prostate cancer after biochemical failure of the treatment [in French]. *Cancer Radiother*. 2014;18:509–516.
- Bauman G, Belhocine T, Kovacs M, Ward A, Beheshti M, Rachinsky I. <sup>18</sup>F-fluorocholine for prostate cancer imaging: a systematic review of the literature. *Prostate Cancer Prostatic Dis*. 2012;15:45–55.
- Fuccio C, Rubello D, Castellucci P, Marzola MC, Fanti S. Choline PET/CT for prostate cancer: main clinical applications. *Eur J Radiol*. 2011;80:e50–e56.
- Beheshti M, Haim S, Zakavi R, et al. Impact of <sup>18</sup>F-choline PET/CT in prostate cancer patients with biochemical recurrence: influence of androgen deprivation therapy and correlation with PSA kinetics. *J Nucl Med*. 2013;54:833–840.
- Castellucci P, Fanti S. Prostate cancer: identifying sites of recurrence with choline-PET-CT imaging. *Nat Rev Urol*. 2015;12:134–135.
- Mamede M, Ceci F, Castellucci P, et al. The role of <sup>11</sup>C-choline PET imaging in the early detection of recurrence in surgically treated prostate cancer patients with very low PSA level <0.5 ng/mL. *Clin Nucl Med*. 2013;38:e342–e345.
- Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the <sup>68</sup>Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2015;42:197–209.
- Afshar-Oromieh A, Haberkorn U, Eder M, Eisenhut M, Zechmann CM. [<sup>68</sup>Ga] gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with <sup>18</sup>F-FECH. *Eur J Nucl Med Mol Imaging*. 2012;39:1085–1086.
- Afshar-Oromieh A, Zechmann CM, Malcher A, et al. Comparison of PET imaging with a <sup>68</sup>Ga-labelled PSMA ligand and <sup>18</sup>F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2014;41:11–20.
- Ross JS, Sheehan CE, Fisher HA, et al. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. *Clin Cancer Res*. 2003;9:6357–6362.
- Rajasekaran AK. Is prostate-specific membrane antigen a multifunctional protein? *Am J Physiol Cell Physiol*. 2005;288:C975–C981.
- Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014;65:467–479.
- Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid <sup>68</sup>Ga-PSMA-ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med*. 2015;56:668–674.
- Ceci F, Herrmann K, Castellucci P, et al. Impact of <sup>11</sup>C-choline PET/CT on clinical decision making in recurrent prostate cancer: results from a retrospective two-centre trial. *Eur J Nucl Med Mol Imaging*. 2014;41:2222–2231.
- Picchio M, Briganti A, Fanti S, Heidenreich A, Krause BJ, Messa C. The role of choline positron emission tomography/computed tomography in the management of patients with prostate-specific antigen progression after radical treatment of prostate cancer. *Eur Urol*. 2011;59:51–60.
- Mottet N, Bellmunt J, Bolla M, et al. Reply to Stefano Fanti, Bernd Krause, Wolfgang Weber, et al’s letter to the editor re: Nicolas Mottet, Joaquim Bellmunt, Michel Bolla, et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer [reply]. *Eur Urol*. 2011;60:e39–e41.
- Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol*. 2007;25:2225–2229.
- Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol*. 2007;25:2035–2041.
- Giovacchini G, Picchio M, Scattoni V, et al. PSA doubling time for prediction of [<sup>11</sup>C]choline PET/CT findings in prostate cancer patients with biochemical failure after radical prostatectomy. *Eur J Nucl Med Mol Imaging*. 2010;37:1106–1116.
- Ceci F, Uprimny C, Nilica B, et al. <sup>68</sup>Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? *Eur J Nucl Med Mol Imaging*. May 15, 201 [Epub ahead of print].
- Haberkorn U, Afshar-Oromieh A, Giesel F, et al. PSMA ligands for diagnosis and therapy of prostate cancer [abstract]. *Ann Oncol*. 2015;26(suppl 2):ii33.