Impact of ^{18}F-fluciclovine PET/CT findings on failure-free survival in biochemical recurrence of prostate cancer following salvage radiation therapy

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Abstract

Purpose: We aimed to evaluate the impact of ^{18}F-fluciclovine PET/CT imaging on failure-free survival (FFS) post salvage radiotherapy (SRT) for prostate cancer (PCa) recurrence.

Methods: Seventy-nine patients were recruited in a phase 2/3 clinical trial to undergo ^{18}F-fluciclovine PET/CT prior to SRT for PCa. Four patients with extra-pelvic disease were excluded. All patients were followed at regular intervals up to 48 months. Treatment failure was defined as a serum prostate-specific antigen (PSA) level of ≥0.2ng/mL above the nadir after SRT, confirmed with an additional measurement, requiring systemic treatment or clinical progression. Failure-free survival (FFS) was computed and compared between patients grouped according to ^{18}F-fluciclovine PET/CT imaging findings.

Results: 80.0% (60/75) of patients had a positive finding on ^{18}F-fluciclovine PET/CT, of which 56.7% (34/60) had prostate bed-only uptake, while 43.3% (26/60) had pelvic nodal ± bed uptake. Following SRT, disease failure was detected in 36.0% (27/75) of patients. There was a significant difference in FFS between patients who had a positive vs negative scan (62.3% vs 92.9%; $p<0.001$) at 36 months and

(59.4% vs 92.9%; p<0.001) at 48 months. Similarly, there was a significant difference in FFS between patients with uptake in pelvic nodes ± bed vs prostate bed-only at 36 months (49.8% vs 70.7%; p=0.003) and at 48 months (49.8% vs 65.6%; p=0.040). FFS was also significantly higher in patients with either negative PET/CT or prostate bed-only disease versus those with pelvic nodal ± prostate bed disease at 36 (78.0% versus 49.8%, P<0.001) and 48 months (74.4% versus 49.8%, p<0.001).

Conclusions: Findings on pre-SRT ^{18}F-fluciclovine PET/CT imaging, even when acted upon to optimize the treatment decisions and treatment planning, are predictive of post-SRT failure-free survival in men who experience PCa recurrence after radical prostatectomy. A negative ^{18}F-fluciclovine PET/CT is most predictive of a lower risk of failure while the presence of pelvic nodal recurrence portends a higher risk of SRT failure.

Keywords: ^{18}F-fluciclovine PET/CT, Biochemical Recurrence, Prostate Cancer, Salvage Radiation Therapy, Failure-Free Survival

Introduction

Imaging has played a pivotal role in localizing recurrent lesions and guiding salvage therapy in men with biochemical recurrence (BCR) of prostate cancer (PCa) following definitive local therapy such as radical prostatectomy (RP) and external beam radiotherapy [1,2]. Conventional imaging (CI) utilized for localizing recurrence of PCa includes computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy [2]. The limited diagnostic sensitivity of CI, especially at low serum prostate-specific antigen (PSA) level has led to the interest in the application of molecular imaging techniques for localizing PCa recurrence [2-4]. The earlier molecular imaging techniques, mostly targeting fatty acid metabolism using fluorine-18 (^{18}F) or carbon-11-labeled radiopharmaceuticals, performed better than CI

but also suffer from a sub-optimal diagnostic performance at very low PSA levels [5]. Over the last few years, positron emission tomography (PET) radiopharmaceuticals targeting two molecular pathways in PCa, prostate-specific membrane antigen (PSMA) and amino acid transport, have been investigated and approved for localizing the site of PCa recurrence. Both categories of radiopharmaceuticals have shown superior diagnostic performance over earlier generations of molecular imaging modalities for PCa recurrence evaluation [6,7].

PSMA ligands labeled with either gallium-68 (^{68}Ga) or ^{18}F have gained widespread application globally for PET imaging of prostate cancer [8-10]. This popularity is due to their high lesion detection rate at lower serum PSA levels, as well as the possibility of in-house labeling of ^{68}Ga available from a long-live ^{68}Ge/^{68}Ga generator to PSMA to obtain ready-to-use ^{68}Ga[Ga]-PSMA. ^{18}F-fluciclovine is a synthetic amino acid trapped by prostate cancer cells via membrane-expressed amino acid transporters [11,12]. Beyond its high diagnostic sensitivity for PCa recurrence including at very low PSA levels [13-15], ^{18}F-fluciclovine does not have a significant early urinary excretion, allowing for better lesion detection in the prostate bed [16]. Currently, ^{18}F-fluciclovine PET/CT imaging is commenced after a 3-5 minute uptake time, which improves patient throughput.

Despite their high lesion detection rates across different PSA categories, radiolabeled PSMA ligands or ^{18}F-fluciclovine may not detect the site of PCa recurrence even at high PSA levels [17,18]. The goal of lesion detection in PCa recurrence is to guide salvage therapy. It is therefore, important to study the impact of both negative and positive imaging findings on patient survival post salvage radiotherapy (SRT). Emmett et al. reported a significant impact of ^{68}Ga-PSMA PET/CT findings on 3-year failure-free survival in men who had SRT for PCa recurrence [19]. No study has investigated the impact of ^{18}F-fluciclovine PET/CT imaging findings on the survival of patients who had SRT for PCa recurrence. The aim of this study was to evaluate the impact of ^{18}F-fluciclovine PET/CT imaging findings on post SRT failure-free survival in men with PCa recurrence post-RP who had ^{18}F-fluciclovine PET/CT guided SRT.

Methods

This study is a secondary analysis of the data from an open-label phase 2/3 randomized controlled trial (NCT0166680) that compared the treatment outcome of conventional imaging versus ^{18}F-fluciclovine PET/CT imaging-guided SRT of patients with detectable serum PSA post RP. The current study is an analysis of the ^{18}F-fluciclovine arm of the trial. The details regarding study design, participant selection, randomization and masking, therapy administration, and outcomes measurement have been previously reported [20]. Briefly, men with detectable serum PSA post RP for adenocarcinoma of the prostate gland who had no systemic metastasis on conventional imaging (bone scintigraphy and either CT or MRI of the abdomen and pelvis) and were eligible for SRT were randomized in a 1:1 ratio to no further imaging versus additional ^{18}F-fluciclovine PET/CT. Exclusion criteria were previous pelvic radiotherapy, presence of contraindications to pelvic radiotherapy including inflammatory bowel disease, active malignancy in the preceding three years prior to enrollment, European Co-operative Oncology Group (ECOG) performance status of 3 or higher, and severe concurrent illness. The institutional review board of Emory University approved the study and all trial participants gave written informed consent.

^{18}F-fluciclovine PET/CT Imaging

Details regarding ^{18}F-fluciclovine PET/CT acquisition have been previously published [21]. Briefly, ^{18}F-fluciclovine was synthesized as previously described [22]. A minimum of 4-hour fasting was observed by all patients. 10.0 ± 2.0 mCi ^{18}F-fluciclovine was injected intravenously as a bolus followed by PET/CT imaging from the level of the diaphragm to the pelvis at 2.5 minutes per bed position. Imaging was acquired at two-time points; 5-15.5 minute and 16-27.5 minutes post tracer injection. Imaging was acquired on a hybrid Discovery MV690 PET/CT scanner (GE Healthcare, IL, USA). Image reconstruction was done using iterative algorithm, 3 iterations and 24 subsets, with a filter applied at 6.4mm.

Image Interpretation

Image interpretation was done on a MIMVista Workstation (MIM Software Inc, OH, USA). Image interpretation was done independently by two experienced board-certified nuclear medicine physicians each with more than 20-year experience. Discrepancies were resolved by consensus read. The interpreters were blinded to the patients' clinical history including PSA level and findings on the prior conventional imaging modalities. Areas of increased ^{18}F-fluciclovine uptake above background activity not corresponding to typical physiological uptake or its variants were considered pathological and in favor of PCa recurrence. The maximum standardized uptake value (SUVmax) of the recurrent lesion and the diameter (long and short axis dimensions) of lymph nodal recurrent lesions were determined and recorded. The recurrent lesions were classified as prostate (prostate bed, seminal vesicles, lateral resection margins, or vesicourethral anastomosis), pelvic (pelvic lymph nodes) or extrapelvic (outside of the standard field of pelvic SRT including skeletal, visceral, and extra-pelvic lymph nodes) recurrence.

Salvage Radiotherapy

Patients with prostate bed-only findings and those with negative ^{18}F-fluciclovine PET/CT imaging findings received 64.8 – 70.2 Gy in 1.8 Gy fractions of radiation to the prostate bed only. Patients with ^{18}F-fluciclovine PET-positive pelvic nodes with or without positive prostate bed findings received 64.8 – 70.2 Gy in 1.8 Gy fractions to the prostate bed and 45.0 – 50.4 Gy in 1.8 Gy fractions of radiation to the pelvis with PET-positive nodes included in the clinical target volume. We excluded patients with extrapelvic sites of recurrence.

Follow-up and Outcome Measurement

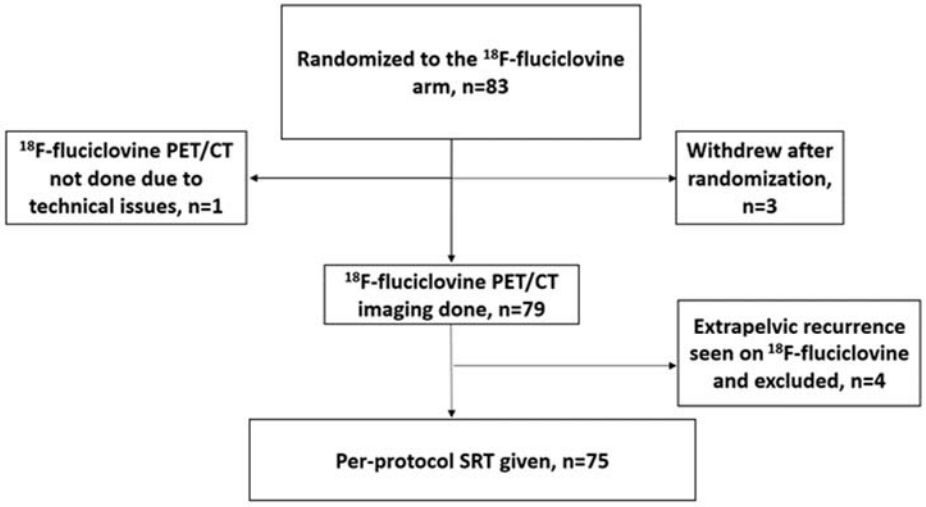
Patients were followed up with physical examination and serum PSA at 1, 6, 12, 18-, 24-, 30-, and 36-months post SRT. Longer follow-up (up to 48 months) was permitted in patients who had not experienced treatment failure at 36-month follow-up. We defined treatment failure as PSA of 0.2 ng/mL

and higher than the post-SRT nadir confirmed with a second measurement showing a further rise in PSA level, clinically detectable disease recurrence by digital rectal examination, imaging-based recurrence detection, and the need for systemic therapy [23]. We defined failure-free survival (FFS) rate as the proportion of patients who were failure-free at 36- and 48-month follow-ups.

Statistical Analysis

We performed statistical analysis using SAS (version 9.4) and set statistical significance at a p-value of <0.05. We performed descriptive statistics of the baseline clinical and demographic characteristics of the patients included in the study. Qualitative data were expressed as frequency (percentage). Quantitative variables were expressed as mean ± standard deviation (SD) if normally distributed or as median (range) if skewed. We grouped patients based on imaging findings and compared epidemiological and disease-related characteristics between groups using ANOVA for numerical covariates and Chi-Square test or Fisher's exact test for categorical covariates, as appropriate. We used the Z test to compare FFS between patients with positive versus negative ^{18}F-fluciclovine PET/CT imaging findings [24]. Similarly, we used the Z test to compare FFS between patients with prostate-only recurrence versus pelvic nodal ± prostate recurrence. Patients with a negative PET/CT or prostate bed-only recurrence were also compared with those with pelvic ± prostate bed recurrence using Z test. We generated Kaplan-Meier plots to compare FFS between patients with negative, prostate-only, pelvic ± prostate recurrence on ^{18}F-fluciclovine PET/CT imaging.

Figure 1: Flowchart showing recruitment of patients into the ^{18}F-fluciclovine arm of the phase 2/3 trial evaluated in the current study.



Results

A total of 83 patients were randomized to the ^{18}F-fluciclovine arm of the phase 2/3 randomized controlled trial analyzed in the current study (Figure 1). Of these, three patients withdrew from the study after randomization and ^{18}F-fluciclovine PET/CT imaging could not be obtained in one patient due to technical issues. We found extra-pelvic sites of PCa recurrence on ^{18}F-fluciclovine PET/CT images in four patients. These patients received out-of-protocol treatment and their results were not included in this analysis. The median age of the remaining 75 patients who received per-protocol SRT and whose FFS are presented here was 61 years (range=42 - 75 years) with a median pre-SRT PSA level of 0.32 ng/mL (range = 0.02 – 9.79). Gleason score was ≥8 in 17 patients (22.7%). Based on their pre-SRT risk categorization, there was an intention to add a short course of androgen-deprivation therapy (ADT) to SRT in 26 patients (34.7%). ADT was typically commenced during SRT and given for six months in most instances. Table 1 shows the detailed baseline clinical and demographic characteristics of the patients.

Table 1: Descriptive statistics of the baseline demographic and clinical variables

Variable	Value
Age, median (range), years	61.5 (42 - 75)
Race, n (%)	
Caucasian	48 (64.0)
African American/others	27 (36.0)
Gleason score, n (%)	
<8	58 (77.3)
≥8	17 (22.7)
Pre-SRT PSA level, median (range), ng/mL	0.32 (0.02 – 9.79)

SRT: Salvage Radiotherapy; **PSA**: Prostate-Specific Membrane Antigen

^{18}F-fluciclovine PET/CT Imaging Findings

At least one lesion consistent with PCa recurrence was seen on the ^{18}F-fluciclovine PET/CT images of 60 patients giving a positivity rate of 80.0%. Of these 60 patients, 56.7% (34/60) had prostate-only recurrence while 43.3% (26/60) had pelvic nodal ± bed recurrence. The mean SUVmax of the prostate recurrence was 3.6 ± 1.7. The mean SUVmax and the size of recurrent nodal lesions were 5.5 ± 3.1 and 1.1 ± 0.5 cm, respectively. Table 2 shows the details of the ^{18}F-fluciclovine PET/CT imaging findings in the trial patients.

Table 2: Summary of ^{18}F-fluciclovine PET/CT findings

Variable	Value
PET Results, n (%)	
Negative	15 (20.0)
Positive	60 (80.0)
Positive PET Results, n (%) = 60	
Prostate-only	34 (56.7)
Prostate ± pelvic lymph nodes	26 (43.3)
Prostate	
SUVmax, mean ± SD	3.6 ± 1.7
Pelvic node	
SUVmax, mean ± SD	5.5 ± 3.1
Long axis diameter (cm), mean ± SD	1.1 ± 0.5
Short axis diameter (cm), mean ± SD	0.7 ± 0.3

Table 3: Comparison of epidemiological and disease-related characteristics of patients grouped according to ^{18}F-fluciclovine PET/CT findings

Covariate	Level	Negative N=15	Prostate bed-only N=34	Pelvic nodes ± Prostate bed N=26	P-value*
Race, n (%)	Caucasian	8 (53.3)	20 (58.8)	20 (76.9)	0.221
	African American/Other	7 (46.7)	14 (41.2)	6 (23.1)	
Gleason score, n (%)	<8	11 (73.3)	28 (82.4)	19 (73.1)	0.639
	≥8	4 (26.7)	6 (17.7)	7 (26.9)	
ADT intent, n (%)	No	10 (66.7)	25 (73.5)	14 (53.9)	0.282
	Yes	5 (33.3)	9 (26.5)	12 (46.2)	
Presence of adverse pathology, n (%)	No	3 (20.0)	10 (29.4)	10 (38.5)	0.456
	Yes	12 (80.0)	24 (70.6)	16 (61.5)	
ECE, n (%)	No	7 (46.7)	17 (50.0)	10 (38.5)	0.669
	Yes	8 (53.3)	17 (50.0)	16 (61.5)	
SV invasion, n (%)	No	3 (20.0)	10 (29.4)	8 (30.8)	0.738
	Yes	12 (80.0)	24 (70.6)	18 (69.2)	
Positive Margin, n (%)	No	9 (60.0)	16 (47.1)	8 (30.8)	0.171
	Yes	6 (40.0)	18 (52.9)	18 (69.2)	
Positive Node at RP, n (%)	No	3 (20.0)	5 (14.7)	5 (19.2)	0.788
	Yes	12 (80.0)	29 (85.3)	21 (80.8)	
Age, median (range), years		62.0	60.5	61.5	0.522
		(53.0 – 72.0)	(42.0 – 75.0)	(43.0 – 74.0)	
PSA pre-RP, median (range), ng/mL		7.8	6.4	9.4	0.354
		(3.3 – 16.9)	(3.9 – 114.0)	(2.6 – 76.6)	
PSA pre-RT, median (range), ng/mL		0.3	0.3	0.5	0.095
		(0.03 – 1.8)	(0.02 – 6.0)	(0.1 – 9.8)	

ADT: Androgen-Deprivation Therapy; **ECE**: Extra-Capsular Extension; **SV**: Seminal Vesicle; **RP**: Radical Prostatectomy; **PSA pre-RP**: Prostate-Specific Antigen level prior to Radical Prostatectomy; **PSA pre-RT**: Prostate-Specific Antigen level prior to Salvage Radiotherapy; *****: p-value<0.05; Presence of Adverse Pathology is defined as the presence of one or more of extra-capsular extension, seminal vesicle invasion, positive margin, and positive lymph node at prostatectomy.

We compared epidemiological (race and age) and disease-related characteristics (Gleason score, ADT intent, presence of adverse pathology, pre-RP PSA, and pre-RT PSA) between patients grouped according to ^{18}F-fluciclovine PET/CT imaging findings (table 3). We found no significant differences in any of the epidemiologic or disease-related characteristics between patients with negative, prostate bed-only, or pelvic ± bed recurrence. When categorized into two groups as positive versus negative ^{18}F-fluciclovine PET/CT imaging findings, we also found no significant difference in any of the epidemiological or disease-related characteristics evaluated between groups (supplementary table).

Salvage Radiotherapy (SRT) outcome and Failure-Free Survival (FFS)

Following SRT and during follow-up, SRT failure occurred in 36.0% of patients (27/75). FFS rate was 92.9% and 62.3% in patients with negative and positive ^{18}F-fluciclovine PET/CT findings at 36-month follow-up, respectively, p<0.001. At 48-month follow-up, FFS remained significantly higher in patients with negative ^{18}F-fluciclovine PET/CT findings versus positive findings, 92.9% versus 59.4%, p<0.001 (figures 2 and 3). Among patients with positive ^{18}F-fluciclovine PET/CT findings, those with prostate-only recurrence had a significantly higher FFS compared with those with pelvic nodal ± prostate recurrence at 36-month (70.7% versus 49.8%, p=0.003) and 48-month (65.6% versus 49.8%, p=0.040) (Figure 4).

Figure 2: Axial CT (A), axial PET (B) and axial fused ^{18}F-fluciclovine PET/CT (C) images of a patient with biochemical recurrence of prostate cancer show no radiotracer uptake in the prostatectomy bed (arrows) or elsewhere in the PET/CT and the patient had a failure-free survival of approximately 48 months.

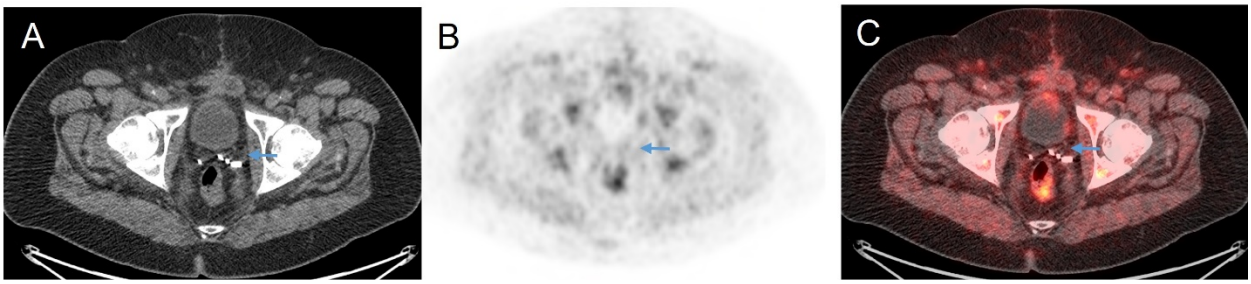


Figure 3: Axial fused (A) and sagittal fused (B) ^{18}F-fluciclovine PET/CT images of a patient with biochemical recurrence of prostate cancer show focal radiotracer uptake adjacent to the vesicourethral anastomosis (arrows) suggestive of local recurrence. The patient had a failure-free survival of approximately 24 months.

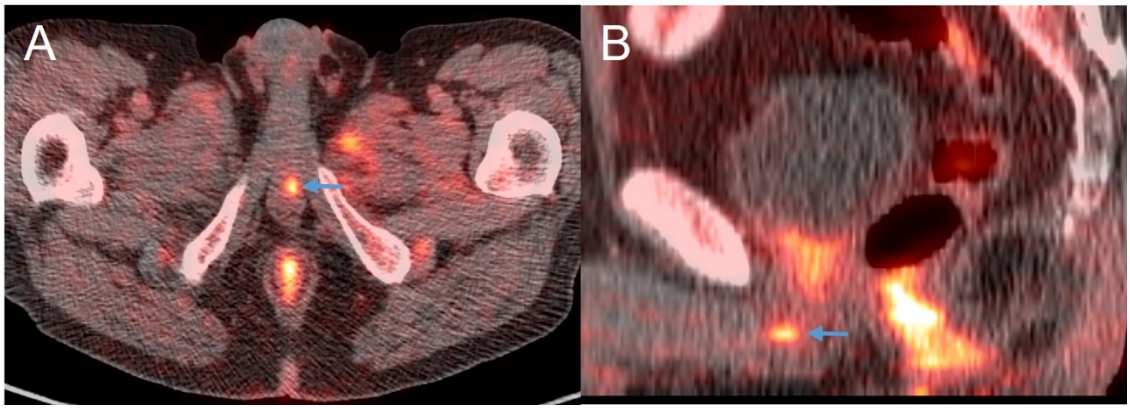


Figure 4: Axial CT (A, D), axial PET (B, E) and axial fused ^{18}F-fluciclovine PET/CT (C, F) images of a patient with biochemical recurrence of prostate cancer demonstrate focal radiotracer uptake in the prostatectomy bed (arrows in A, B, and C) and within pelvic nodes (arrows in D, E, and F) suggestive of recurrent disease. The patient had a failure-free survival of approximately 1.2 months.

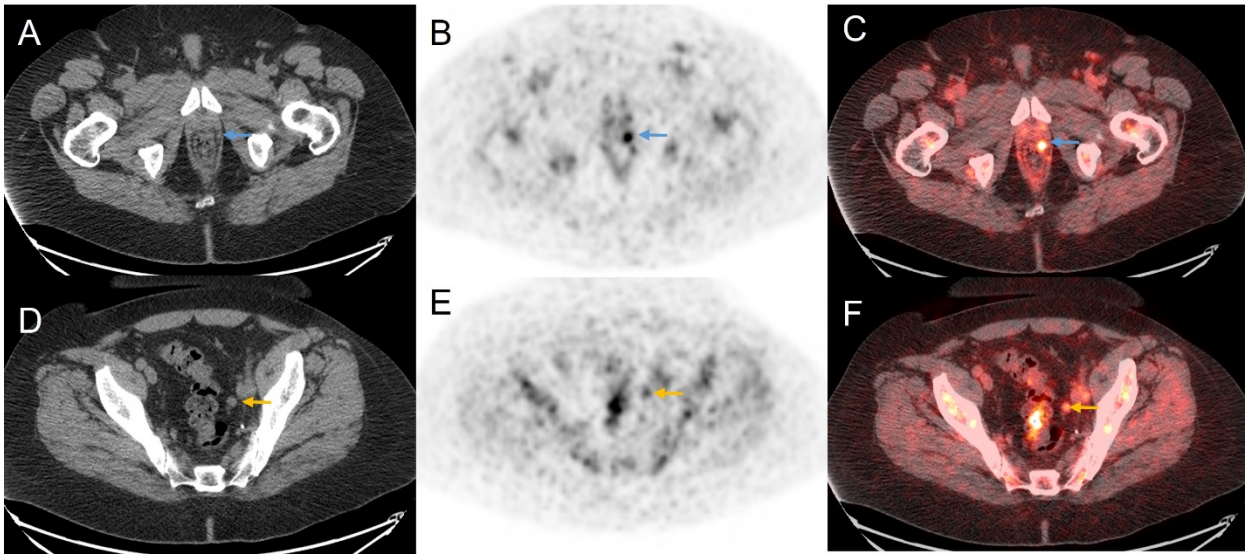


Figure 5: Kaplan-Meier failure-free survival curves showing (a) the differences in failure-free survival in patients with either a negative PET or prostate bed-only recurrence (top curve) compared with those with pelvic nodal ± prostate-bed recurrence (lower curve) and (b) the differences in the failure-free survival in patients with negative PET/CT findings (top curve), prostate bed only ^{18}F-fluciclovine uptake (middle curve), and patients with pelvic nodal ± prostate bed uptake (lower curve).

Figure 5a:

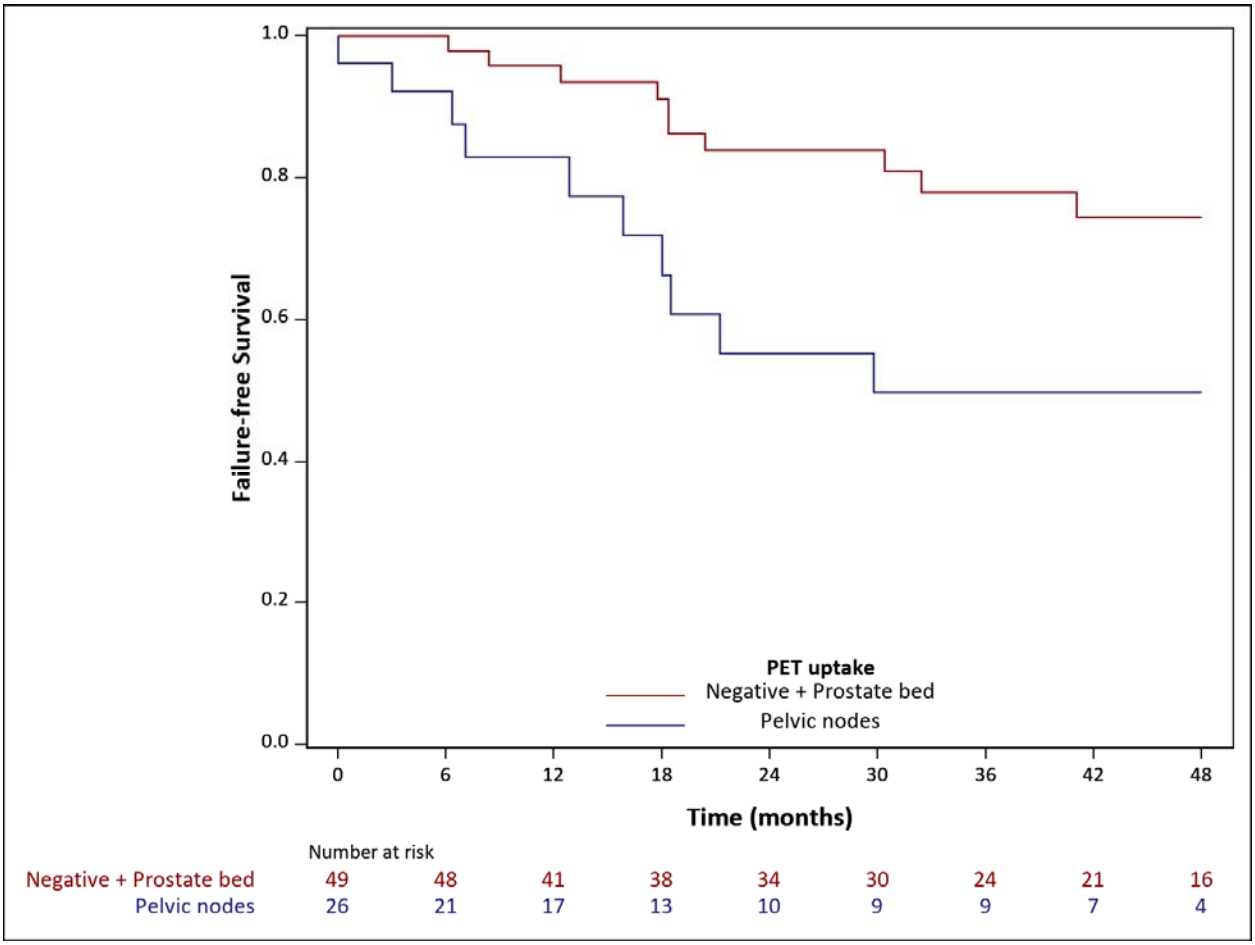
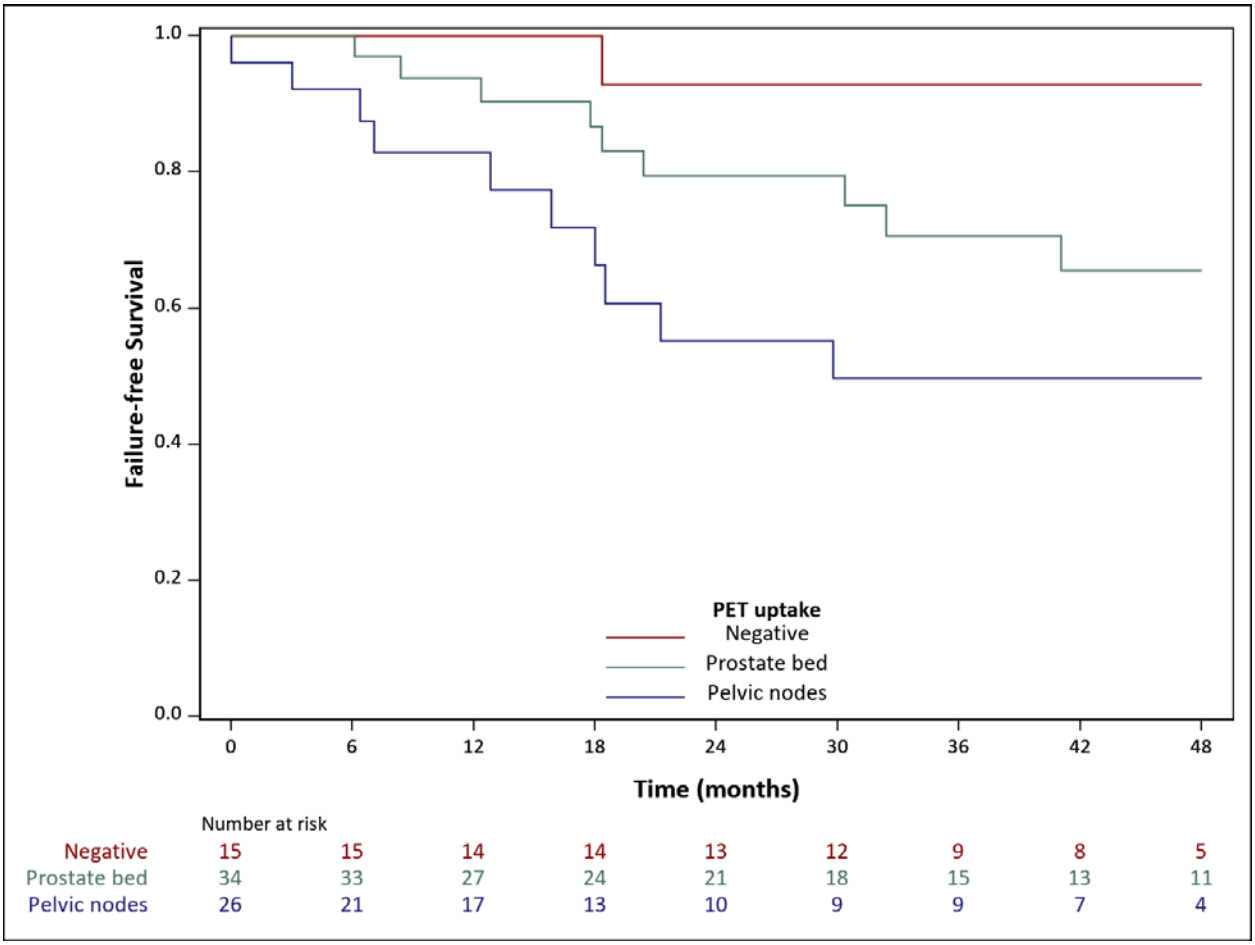


Figure 5b:



We also evaluated the differences in FFS between patients who either had a negative PET or prostate-only recurrence versus patients with pelvic nodal ± prostate bed recurrence and found significantly higher FFS in those with negative or prostate-only recurrence than those with pelvic nodal ± prostate bed recurrence at 36- (78.0% versus 49.8%, p<0.001) and 48-month (74.4% versus 49.8%, p<0.001) (Figure 5a). Table 4 shows the differences in FFS according to ^{18}F-fluciclovine PET/CT findings. Figure 5b is a Kaplan-Meier curves of FFS up to 48-month follow-up between patients with negative, prostate-only, and pelvic nodal ± prostate recurrence on ^{18}F-fluciclovine PET/CT imaging.

Table 4: Differences in failure-free survival according to ^{18}F-fluciclovine PET/CT imaging findings

Follow-up time	**Negative PET**	**Positive PET**	**p-value**
FFS at 36 months, % (95% CI)	92.9 (59.1 – 99.0)	62.3 (46.7 – 74.6)	<0.001*
FFS at 48 months, % (95% CI)	92.9 (59.1 – (99.0))	59.4 (43.5 – 72.2)	<0.001*
Follow-up time	**Prostate bed-only recurrence**	**Pelvic node ± prostate bed recurrence**	**p-value**
FFS at 36 months, % (95% CI)	70.7 (49.3 – 84.3)	49.8 (26.3 – 69.4)	0.003*
FFS at 48 months, % (95% CI)	65.6 (43.6 – 80.8)	49.8 (26.3 – 69.4)	0.040*
Follow-up time	**Negative PET + Prostate bed-only recurrence**	**Pelvic node ± prostate bed recurrence**	**p-value**
FFS at 36 months, % (95% CI)	78.0 (61.7 – 88.0)	49.8 (26.3 – 69.4)	<0.001*
FFS at 48 months, % (95% CI)	74.4 (57.1 – 85.6)	49.8 (26.3 – 69.4)	<0.001*

FFS: Failure-free survival; *****: p-value<0.005; **Positive PET**: ^{18}F-fluciclovine PET/CT imaging localizes the site of recurrence in either the prostate bed, pelvic nodes, or a combination of both; **Negative PET**: ^{18}F-fluciclovine PET/CT imaging did not localize the site of prostate cancer recurrence.

Among the 26 patients with pelvic nodal ± prostate recurrence on ^{18}F-fluciclovine PET/CT imaging, 18 patients had one or two nodal sites of recurrence while 8 patients had three or more nodal sites of recurrence. FFS was significantly different between these two groups. At 36-month follow-up, FFS was 61% in the patients with 1-2 nodal sites of recurrence versus 29% in those with three or more nodal recurrence, p=0.007. No further events occurred in both groups beyond 36-month follow-up as FFS remained 61% for patients with 1-2 sites of nodal recurrence and 29% for patients with three or more sites of nodal recurrence at 48-month follow-up.

Discussion

Imaging is often done as part of the work-up of patients with biochemical recurrence of PCa. Beyond localizing the site of PCa recurrence, imaging may provide additional prognostic information, which may be useful in guiding the intensity of management. In the current study, we evaluated the impact of ^{18}F-

fluciclovine PET/CT imaging findings acquired for SRT management guidance on the time to treatment failure in patients with rising serum PSA post-RP. We recruited patients early after experiencing a rise in their serum PSA post RP as evidenced by a median serum PSA of 0.32 ng/mL. The overall detection rate was 80% (57% with prostate-only recurrence and 43% with pelvic nodal ± prostate bed recurrence). Patients received SRT, with the radiation field guided by imaging findings. On follow-up, patients with negative imaging findings had the highest rate of FFS followed by patients with prostate bed-only recurrence, with patients who had pelvic nodal ± prostate bed recurrence having the lowest rate of FFS at both 36- and 48-month follow-ups. Among the patients with pelvic nodal recurrence, those with more than two foci of recurrence had a significantly lower FFS compared with those with 1-2 foci of recurrence reflecting the ability of ^{18}F-fluciclovine PET/CT to accurately depict the burden of disease recurrence and the impact of this on patient outcome. Our results not only emphasize the diagnostic sensitivity of ^{18}F-fluciclovine PET/CT at fairly low PSA levels but report, for the first time, the prognostic ability of imaging findings of ^{18}F-fluciclovine PET/CT on the time to failure in patients treated with SRT for PCa recurrence. The implication of this in clinical practice is that the findings on pre-SRT ^{18}F-fluciclovine have a strong impact on the time to SRT failure, even when such imaging findings are acted upon for guiding the treatment decisions and treatment planning during SRT for PCa recurrence post RP.

A multicenter prospective Australian study by Emmett et al. has recently reported the impact of ^{68}Ga[Ga]PSMA PET/CT on 3-year FFS in men with serum PSA of 0.5 – 5.0 ng/mL post RP who were treated with SRT [19]. The overall PET positivity rate was 65.4% compared with 80% in our study. FFS at 3-year follow-up was 82.5%, 79.0%, and 55% in men with negative, prostate bed-only, and pelvic nodal recurrence, respectively. The corresponding FFS rates at 3-year follow-up in our study were 92.9%, 70.7%, and 49.8%, respectively. Another recent prospective multicenter Australian study has reported an 84.8% FFS at 3-year follow-up in patients with negative ^{68}Ga[Ga]PSMA PET/CT prior to SRT for PCa recurrence [25]. When comparing results from studies that utilized different tracers for imaging, an

important consideration to bear in mind is the differences in the tumor biology that drives radiotracer uptake in the lesions. PSMA expression in PCa cells is a marker of receptors that are upregulated in prostate cancer, and the level of expression may be higher with certain types of tumor progression. Conversely, ^{18}F-fluciclovine targets metabolism that are reflected in amino acid transporters that are overexpressed in different phases of PCa [11,12,26]. Inherent differences in the study population may also be important contributors to differences in lesion detection rates and FFS between studies. Our study was a single-center phase 2/3 clinical trial, a study design that ensured uniformity in the image interpretation criteria, treatment approach, and follow-up schedule of patients included in the study compared with the variability in populations that may be present in multicenter studies. Despite these differences, overall, a negative PET (either with ^{18}F-fluciclovine or ^{68}Ga[Ga]PSMA) portends a good prognosis while a positive PET, especially with disease beyond the prostate bed, is predictive of a shorter time to SRT failure.

In the current trial, patients with negative PET imaging findings and those with prostate bed-only disease were treated in a similar manner, receiving 64.8 – 70.2 Gy in 1.8 Gy fractions to the prostate bed only. In view of this similarity in treatment approach, we combined these two groups of patients and compared their FFS with patients who had pelvic nodal ± prostate bed disease. FFS was significantly higher at 36- and 48-month follow-up in the former group (78.0% and 74.4%, respectively) and compared with the latter group (49.8% at both time points). Imaging findings from a new generation of molecular imaging techniques are playing an increasing role in influencing SRT approach for PCa recurrence management [27,28]. One such role is radiation boost to imaging-identified positive lesions. This approach allows for the delivery of high radiation doses to the recurrent lesions without increasing the dose to normal tissues [29-31]. In view of this improved dose delivery to PCa recurrence lesions without increasing normal tissue toxicity from molecular imaging-guided radiotherapy boosting, patients in another ongoing trial (NCT03762759) receive a total of 64.8 to 70.2 Gy at 1.8 Gy per fraction to the

prostate bed with a boost to 70.2 - 76.0 Gy to areas of radiotracer uptake on PET/CT imaging. The results of this trial, when concluded, will advance knowledge regarding the comparative impact of these two imaging modalities on FFS post-SRT in men who are diagnosed with PCa recurrence post-RP.

To ensure that the FFS differences seen between groups were due to the burden of disease (as demonstrated by imaging findings), we compared the prevalence of different epidemiological and disease-related characteristics known to influence treatment outcomes in the patients grouped according to PET imaging findings (table 3 and supplementary table). We have found no significant differences in any of these variables between patients grouped according to the ^{18}F-fluciclovine PET/CT findings. While this may represent a true lack of significant differences between groups, the smaller number of patients in each group is a limitation.

There are a few limitations to this study. The current study is a secondary analysis of one arm of a phase 2/3 clinical trial. The trial was not powered to detect differences in FFS within this study arm based on ^{18}F-fluciclovine PET/CT imaging findings. Despite this, we found significant differences in FFS between patients with negative, prostate-only, and pelvic ± prostate sites of PCa recurrence on pre-SRT ^{18}F-fluciclovine PET/CT. These differences compare well with findings from studies that have evaluated the prognostic utility of ^{68}Ga[Ga]PSMA PET/CT in a similar setting.

Conclusion

Findings on pre-SRT ^{18}F-fluciclovine PET/CT imaging, even when acted upon to optimize the treatment decisions and treatment planning, are predictive of post-SRT failure-free survival in men who experience PCa recurrence after radical prostatectomy. A negative ^{18}F-fluciclovine PET/CT is most predictive of a lower risk of failure while the presence of pelvic nodal recurrence portends the highest risk of SRT failure. Among patients with pelvic nodal recurrence of PCa, recurrence in more than two nodes on imaging carries a higher risk of failure.

References

1. Magnetta MJ, Casalino D, Heller MT. Imaging assessment of local recurrence of prostate cancer after radical prostatectomy. Abdom Radiol (NY). 2020;45:4073-4083.
2. Zaorsky NG, Calais J, Fanti S, et al. Salvage therapy for prostate cancer after radical prostatectomy. Nat Rev Urol. 2021;18:643-668.
3. Kane CJ, Amling CL, Johnstone PA, et al. Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. Urology. 2003;61:607-611.
4. De Visschere PJL, Standaert C, Fütterer JJ, et al. A Systematic Review on the Role of Imaging in Early Recurrent Prostate Cancer. Eur Urol Oncol. 2019;2:47-76.
5. Evangelista L, Briganti A, Fanti S, et al. New Clinical Indications for (18)F/(11)C-choline, New Tracers for Positron Emission Tomography and a Promising Hybrid Device for Prostate Cancer Staging: A Systematic Review of the Literature. Eur Urol. 2016;70:161-175.
6. Nanni C, Zanoni L, Pultrone C, et al. (18)F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging. 2016 Aug;43:1601-10.
7. Ma W, Mao J, Yang J, et al. Comparing the diagnostic performance of radiotracers in prostate cancer biochemical recurrence: a systematic review and meta-analysis. Eur Radiol. Epub ahead of print on Apr 29, 2022.
8. Fendler WP, Calais J, Eiber M, et al. Assessment of ^{68}Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. JAMA Oncol. 2019;5:856-863.
9. Giesel FL, Knorr K, Spohn F, et al. Detection Efficacy of ^{18}F-PSMA-1007 PET/CT in 251 Patients with Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy. J Nucl Med. 2019;60:362-368.

10. Rowe SP, Campbell SP, Mana-Ay M, et al. Prospective Evaluation of PSMA-Targeted ^{18}F-DCFPyL PET/CT in Men with Biochemical Failure After Radical Prostatectomy for Prostate Cancer. J Nucl Med. 2020;61:58-61.
11. Oka S, Okudaira H, Yoshida Y, et al. Transport mechanisms of trans-1-amino-3-fluoro[1-(14)C]cyclobutanecarboxylic acid in prostate cancer cells. Nucl Med Biol. 2012;39:109-119.
12. Ono M, Oka S, Okudaira H, et al. [(14)C]Fluciclovine (alias anti-[(14)C]FACBC) uptake and ASCT2 expression in castration-resistant prostate cancer cells. Nucl Med Biol. 2015;42:887-892.
13. Marcus C, Abiodun-Ojo OA, Jani AB, et al. Clinical utility of ^{18}F-Fluciclovine PET/CT in recurrent prostate cancer with very low (≤0.3 ng/mL) prostate-specific antigen levels. Am J Nucl Med Mol Imaging. 2021;11:406-414.
14. Bulbul JE, Grybowski D, Lovrec P, et al. Positivity Rate of [^{18}F]Fluciclovine PET/CT in Patients with Suspected Prostate Cancer Recurrence at PSA Levels Below 1 ng/mL. Mol Imaging Biol. 2022;24:42-49.
15. Salavati A, Gencturk M, Koksel Y, et al. A bicentric retrospective analysis of clinical utility of ^{18}F-fluciclovine PET in biochemically recurrent prostate cancer following primary radiation therapy: is it helpful in patients with a PSA rise less than the Phoenix criteria? Eur J Nucl Med Mol Imaging. 2021;48:4463-4471.
16. Schuster DM, Nanni C, Fanti S, et al. Anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid: physiologic uptake patterns, incidental findings, and variants that may simulate disease. J Nucl Med. 2014;55:1986-1992.
17. Perera M, Papa N, Roberts M, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol. 2020;77:403-417.

18. Alberts IL, Seide SE, Mingels C et al. Comparing the diagnostic performance of radiotracers in recurrent prostate cancer: a systematic review and network meta-analysis. Eur J Nucl Med Mol Imaging. 2021;48:2978-2989.
19. Emmett L, Tang R, Nandurkar R, et al. 3-Year Freedom from Progression After ^{68}Ga-PSMA PET/CT-Triaged Management in Men with Biochemical Recurrence After Radical Prostatectomy: Results of a Prospective Multicenter Trial. J Nucl Med. 2020;61:866-872.
20. Jani AB, Schreibmann E, Goyal S, et al. ^{18}F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial. Lancet. 2021;397:1895-1904.
21. Abiodun-Ojo OA, Jani AB, Akintayo AA, et al. Salvage Radiotherapy Management Decisions in Postprostatectomy Patients with Recurrent Prostate Cancer Based on ^{18}F-Fluciclovine PET/CT Guidance. J Nucl Med. 2021;62:1089-1096.
22. McConathy J, Voll RJ, Yu W, et al. Improved synthesis of anti-[18F]FACBC: improved preparation of labeling precursor and automated radiosynthesis. Appl Radiat Isot. 2003;58:657-66.
23. Tendulkar RD, Agrawal S, Gao T, et al. Contemporary Update of a Multi-Institutional Predictive Nomogram for Salvage Radiotherapy After Radical Prostatectomy. J Clin Oncol. 2016;34:3648-3654.
24. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York, NY: Springer, 2003.
25. Ong S, Pascoe C, Kelly BD, et al. PSMA PET-CT Imaging Predicts Treatment Progression in Men with Biochemically Recurrent Prostate Cancer-A Prospective Study of Men with 3 Year Follow Up. Cancers (Basel). 2022;14:2717.

26. Chu CE, Alshalalfa M, Sjöström M, et al. Prostate-specific Membrane Antigen and Fluciclovine Transporter Genes are Associated with Variable Clinical Features and Molecular Subtypes of Primary Prostate Cancer. Eur Urol. 2021;79:717-721.
27. Calais J, Czernin J, Cao M, et al. ^{68}Ga-PSMA-11 PET/CT Mapping of Prostate Cancer Biochemical Recurrence After Radical Prostatectomy in 270 Patients with a PSA Level of Less Than 1.0 ng/mL: Impact on Salvage Radiotherapy Planning. J Nucl Med. 2018;59:230-237.
28. Rogowski P, Trapp C, von Bestenbostel R, et al. Outcome after PSMA-PET/CT-based salvage radiotherapy for nodal recurrence after radical prostatectomy. Eur J Nucl Med Mol Imaging. 2022;49:1417-1428.
29. Vogel MME, Dewes S, Sage EK, et al. Feasibility and Outcome of PSMA-PET-Based Dose-Escalated Salvage Radiotherapy Versus Conventional Salvage Radiotherapy for Patients With Recurrent Prostate Cancer. Front Oncol. 2021;11:715020.
30. Eade T, Kneebone A, Hruby G, et al. Early Outcomes and Decision Regret Using PSMA/MRI-Guided Focal Boost for Prostate Cancer SBRT. Pract Radiat Oncol. 2022;12:e201-e206.
31. Gawish A, Walke M, Röllich B, et al. Nodal and osseous oligometastatic prostate cancer: a cohort including the introduction of PSMA-PET/CT-guided stereotactic and hypofractionated radiotherapy with elective nodal therapy. J Cancer Res Clin Oncol. 2022 Aug 27. doi: 10.1007/s00432-022-04229-1. Epub ahead of print.