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Differences in Failure-free Survival Post Salvage Radiotherapy Guided by Conventional Imaging Versus ^{18}F-fluciclovine PET/CT in Post-prostatectomy Patients: a *Post-hoc* Sub-stratification Analysis of the EMPIRE-1 Trial

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ABSTRACT

The EMPIRE-1 (Emory Molecular Prostate Imaging for Radiotherapy Enhancement-1) trial reported a survival advantage in recurrent prostate cancer salvage radiotherapy (SRT) guided by ^{18}F-fluciclovine PET/CT versus conventional imaging. We performed a post-hoc analysis of the EMPIRE-1 cohort stratified by protocol-specified criteria, comparing failure-free survival (FFS) between study arms.

Methods: EMPIRE-1 randomized patients to either conventional imaging (Bone scan plus abdominopelvic CT or MRI) only SRT planning (arm A) or conventional imaging plus ^{18}F-fluciclovine PET/CT (arm B). Randomization was stratified by PSA (<2.0 ng/mL versus ≥2.0 ng/mL), adverse pathology, and androgen-deprivation treatment (ADT) intent. We sub-divided patients in each arm using the randomization stratification criteria and compared FFS between patients' sub-groups across study arms.

Results: Eighty-one and 76 patients received per-protocol SRT in study arms A and B, respectively. The median follow-up duration was 3.5 years (95% CI: 3.0 – 4.0). FFS was 63.0% and 51.2% at 36- and 48-months, respectively, in arm A and 75.5% at both 36- and 48-month follow-ups in arm B. Among patients with PSA <2ng/mL (mean=0.42 ± 0.42), significantly higher FFS was seen in arm B than arm A at 36-months (83.2%, 95%CI: 70.0-91.0 versus 66.5%, 95%CI: 51.6-77.8, p<0.001) and 48-months (83.2%, 95%CI: 70.0-91.0 versus 56.2%, 95%CI: 40.5-69.2, p<0.001). No significant difference in FFS between study arms in patients with PSA ≥2ng/mL was observed. Among patients with adverse pathology, significantly higher FFS was seen in arm B than in arm A at 48-months (68.9%, 95%CI: 52.1-80.8 versus 42.8%, 95%CI: 26.2-58.3, p<0.001) though not at 36-months follow-up. FFS was higher in patients without adverse pathology in arm B vs arm A; 90.2%, 95%CI: 65.9-97.5 versus 73.1%, 95%CI: 42.9-89.0, p=0.006, at both 36- and 48-months. Patients in whom ADT was intended in arm B had higher FFS than those in arm A with the difference reaching statistical significance at 48-months (65.2%, 95%CI: 40.3-81.7 versus 29.1, 95%CI: 6.5-57.2, p<0.001). Patients without ADT intent in arm B had significantly higher FFS than patients in arm A at 36-months (80.7%, 95%CI: 64.9-90.0 versus 68.0%, 95%CI: 51.1-80.2) and 48-months (80.7%, 95%CI: 64.9-90.0 versus 58.6%, 95%CI: 41.0-72.6).

Conclusion: The survival advantage due to the addition of ^{18}F-fluciclovine PET/CT into SRT planning is maintained regardless of the presence of adverse pathology or ADT intent. Including ^{18}F-fluciclovine PET/CT into SRT leads to survival benefits in patients with PSA <2 ng/mL, but not in patients with PSA≥ 2 ng/ml.

Keywords: ^{18}F-fluciclovine PET/CT, Salvage Radiotherapy, EMPIRE-1 trial, Prostate Cancer, Adverse Pathology, Prostate-Specific Antigen, Androgen-Deprivation Therapy, Failure-Free Survival

INTRODUCTION

Radical prostatectomy (RP) is one of the treatment choices offered to patients with localized prostate cancer (PCa) (1). Following RP, recurrence manifests as rising serum prostate-specific antigen (PSA) (2). Early detection of recurrence followed by salvage therapy is crucial for a favorable outcome (3). Salvage radiotherapy (SRT) with or without androgen-deprivation therapy (ADT) is recommended for biochemical recurrence (BCR) of PCa (4). SRT can be curative if the irradiation volume encompasses all the sites of PCa recurrence (5). Imaging for lesion localization, therefore, plays a critical role in SRT planning.

Conventional imaging with magnetic resonance imaging (MRI), computed tomography (CT), and radionuclide bone scintigraphy has traditionally been used for restaging and SRT planning. The performance of these conventional imaging modalities is heterogeneous across studies with low lesion detection rates at PSA <2.0 ng/mL, a level where SRT may be curative (5,6). Several radionuclide probes targeting different epitopes in the prostate cancer cells were subsequently developed to address the limited diagnostic performance of conventional imaging at low PSA levels and improve the lesion detection rate in BCR of PCa prior to SRT. ^{18}F-fluciclovine is a radio-fluorinated synthetic amino acid transported into prostate cancer cells (7,8). One of the strengths of ^{18}F-fluciclovine positron emission tomography (PET) imaging of PCa recurrence is its lack of significant early bladder excretion allowing for the detection of recurrence in the prostate bed (9,10). Our group and others have shown the high diagnostic performance of ^{18}F-fluciclovine PET/CT, even at low PSA levels (11-13). We have also reported a high impact of ^{18}F-fluciclovine PET/CT imaging on therapy decisions during SRT planning (14).

The ability of SRT to lead to a decline in serum PSA level to below detectable limits and maintain disease control is the ultimate measure of the correctness of treatment decisions made during radiotherapy planning. Unfortunately, most studies have focused on lesion detection rate and management change rather than the outcome of such decisions. Recently, the EMPIRE-1 (Emory Molecular Prostate Imaging for Radiotherapy Enhancement-1) study, a phase 2/3 trial that randomized patients with detectable serum PSA post-RP to either conventional imaging-only or conventional imaging plus ^{18}F-fluciclovine PET/CT to guide SRT reported a significantly longer time to failure (failure-free survival, FFS) in the conventional imaging plus ^{18}F-fluciclovine PET/CT arm compared with the conventional imaging-only arm (15). The difference in the time to failure between

arms was the primary aim for which the study was prospectively powered. Yet, the EMPIRE-1 trial also stratified patients' using three criteria (serum PSA level below versus ≥ 2 ng/mL; presence or absence of adverse pathologic features including extracapsular extension, seminal vesicle invasion, and presence of lymph node metastases at RP; and ADT intent) that are known to influence SRT outcomes in patients with PCa recurrence (16,17). This stratified randomization afforded the opportunity to evaluate the impact of these characteristics known to affect SRT outcomes in post-SRT patients with PCa. We, therefore, performed a secondary analysis of the EMPIRE-1 trial cohort stratified by protocol-specified criteria and compared failure-free survival between study arms.

MATERIAL AND METHODS

This is a secondary analysis of data from the EMPIRE-1 trial (NCT01666808). The EMPIRE-1 is a phase 2/3 controlled trial that randomized patients with detectable serum PSA post-RP to SRT guided by conventional imaging-only or conventional imaging plus abdominopelvic ^{18}F-fluciclovine PET/CT imaging. Details regarding inclusion and exclusion criteria, randomization and masking, imaging protocols for conventional imaging and ^{18}F-fluciclovine PET/CT, and outcome assessment have been published in detail (15). Briefly, patients with detectable serum PSA post-RP for adenocarcinoma of the prostate gland without evidence of systemic metastases on conventional imaging were randomized to undergo no additional imaging (arm A) versus additional ^{18}F-fluciclovine PET/CT imaging for guiding SRT decision. Systemic metastasis was defined as any site of metastasis outside the pelvic field of SRT. Conventional imaging includes whole-body planar bone scintigraphy and abdominopelvic CT or MRI. Exclusion criteria were history of previous pelvic radiotherapy, European Co-operative Oncology Group performance status of ≥3, presence of contraindications to radiotherapy, history of previous invasive malignancy within the three years preceding enrollment, and severe concurrent illness. All trial subjects signed a written informed consent. The institutional review board of Emory University approved the study.

Randomization

Randomization into the study arms was in a ratio of 1:1. Randomization into arms was stratified by serum PSA level (<2.0 ng/mL versus ≥2.0 ng/mL), presence of adverse pathology at RP (extra-capsular extension, seminal vesicle invasion, lymph node metastasis; none versus any), and ADT intent (yes versus no).

Image Analysis

Conventional imaging and ^{18}F-fluciclovine PET/CT images were read by two experienced readers independently. ^{18}F-fluciclovine PET/CT images were read on a MIMVista Workstation (MIM Software Inc, OH, USA) by two readers blinded to imaging findings on conventional imaging and the clinicopathologic history of the patients. Disagreements between the two readers were resolved by consensus.

Treatment

In the conventional imaging-only arm, SRT decisions were based on the standard-of-care practice and were guided by the pre-surgical disease features, pathological features of the RP specimen, and the PSA trajectory. In the conventional imaging plus ^{18}F-fluciclovine PET/CT arm, SRT decision was guided by ^{18}F-fluciclovine PET/CT imaging findings. No on-trial radiotherapy was given to patients with extrapelvic findings. Patients with pelvic findings had 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 to the pelvis. Patients with prostate-only findings and those with negative ^{18}F-fluciclovine PET/CT imaging findings had 64.8 – 70.2 Gy in 1.8 Gy fractions to the prostate bed only.

Follow-up and Outcome Determination

Following SRT, all patients were followed-up at 1-month, 6-month, and 6-monthly intervals thereafter for 36 months post SRT. Longer follow-up was permitted for patients who had not experienced treatment failure at 36 months post SRT. During each follow-up visit, treatment failure was evaluated clinically with physical examination and biochemically with serum PSA level determination. We defined treatment failure as a rise in serum PSA by 0.2 ng/mL above the nadir achieved post SRT, followed by another rise in a subsequent measurement; failure of decline in serum PSA post SRT; imaging- or clinical examination (including digital rectal examination)-based failure;

or the initiation of systemic therapy (18). We defined failure-free survival (FFS) as the duration from the completion of SRT to the date that failure was confirmed.

Statistical Analysis

For the primary endpoint of the RCT, a sample of 146 patients, including 73 patients in each treatment arm, was calculated to detect a 20% difference in 3-year FFS between the study arms at a 0.05 level of confidence with 80% power. We set an overall enrollment target of 162 participants assuming a 10% dropout rate. We used the Z test to compare FFS between arms (15).

For the current investigation, we subsequently stratified patients in the two arms by the protocol-specified stratification criteria (PSA <2.0 ng/mL versus ≥2.0 ng/mL, presence versus absence of any adverse pathology at RP, and yes versus no to ADT intent) and compared FFS between study arms at 3 years and 4 years using Z test (19). In addition to dichotomizing each study arm by a PSA cut-off of 2 ng/mL for comparison, we performed exploratory comparisons between study arms using the Z test at different PSA levels of <0.5 ng/mL, <1.0 ng/mL, and < 2.0 ng/mL. We set statistical significance at a *p*-value of less than 0.05. We performed statistical analysis using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

A total of 167 patients without systemic metastasis on conventional imaging were screened for inclusion. Two patients failed screening while 165 patients were randomized, 82 patients were allocated to arm A (conventional imaging-only) while 83 patients were allocated to arm B (conventional imaging plus ^{18}F-fluciclovine PET/CT imaging). One patient in arm A and three in arm B withdrew from the study after randomization. The remaining 81 patients in arm A received SRT without additional imaging. Of the remaining 80 patients in arm B, 79 had an additional ^{18}F-fluciclovine PET/CT imaging, while PET/CT could not be obtained in one patient due to technical issues. Four patients in arm B had extra-pelvic sites of metastasis and were excluded from undergoing SRT. Finally, 81 patients in arm A and 76 in arm B received SRT, and their data are presented in this work (Figure 1).

Table 1 compares the patients in both arms according to the baseline clinicopathologic characteristics and the criteria applied in stratifying patients to study arms. Baseline PSA, presence of any adverse pathology, and ADT intent were stratification criteria, hence, similar between arms. Age and Gleason scores at RP were also similar between groups.

In arm A, 56 patients (69.1%) received radiation to the prostate bed alone, while 25 (30.9%) received radiation dose to the prostate bed and pelvis. Among patients in arm B whose SRT decision was guided by findings on ^{18}F-fluciclovine PET/CT imaging, 41 patients (53.9%) received radiation dose to the prostate bed alone, while 35 (46.1%) received radiation dose to the prostate bed and the pelvis.

The median follow-up duration was 3.5 years (95% CI: 3.0 – 4.0). At the 36-month follow-up, 22 and 15 patients had experienced treatment failure in arms A and B, respectively. In arm A, FFS was 63.0% and 51.2% at 36- and 48-month follow-ups, respectively, while in arm B, FFS was 75.5% at both 36- and 48-month follow-ups.

66.5% and 83.2% of patients with PSA < 2 ng/mL were failure-free at 36-month follow-up in arm A and arm B, respectively, P<0.001, while 56.2% and 83.2% were failure-free at 48-month follow-up in arms A and B, respectively (Table 2). At 36-month follow-up, 40.4% and 26.3% of patients with PSA ≥ 2 ng/mL were failure-free in arms A and B, respectively, while at 48 months post SRT, no patients with PSA ≥ 2 ng/mL in arm A and 26.3% of patients in arm B remained failure-free.

In our exploratory comparison of FFS between study arms at different PSA thresholds, we found significant differences between study arms (table 3). At a PSA below 0.5 ng/mL, there was no significant difference in the FFS between arm A and arm B at 36-month follow-up, 79.3% versus 85.3%, respectively, p=0.184. At 48-month, however, FFS was significantly higher in arm B than in arm A, 85.3% versus 63.2, respectively, p<0.001. Among patients with PSA < 1 ng/mL, FFS was significantly higher in arm B than in arm A at 36-month (84.7% versus 72.8%, p=0.005) and 48-month (84.7% versus 60.5%, p<0.001).

We dichotomized the patients in each arm based on the presence of any of extracapsular extension, seminal vesicle invasion, or lymph node metastasis in the surgical specimen evaluated at pathology post-RP. Among patients with any of the adverse pathologic features, 59.9% and 68.9% of patients were failure-free at 36-

month follow-up in arms A and B, respectively, p=0.085 and at 48-month FFS remained significantly higher in arm B than in arm A (68.9% versus 42.8%, p<0.001). Amon patients without any of these adverse pathologic features, FFS was also significantly higher in arm B than in arm A at both 36- and 48-month (Table 2).

Based on their disease-associated risk, there was ADT intent for 28 and 27 patients in arms A and B, respectively. At 36-month follow-up, FFS was not significantly different between study arms (52.3% for arm A and 65.2% for arm B, p=0.113). At 48-month follow-up, FFS was significantly higher in arm B (65.2%) compared with arm A (29.1%), p<0.001. In the cohorts of patients without ADT intent, FFS was significantly higher in arm B compared with arm A at 36-month (80.7 versus 68.0, p=0.008) and 48-month (80.7 versus 58.6, p<0.001).

DISCUSSION

The EMPIRE-1 trial, which stratified patients into study arms based on pre-SRT serum PSA, presence or absence of adverse pathologic features, and the intent to add ADT in management, reported that SRT decision guided by findings on ^{18}F-fluciclovine PET/CT results in a favorable FFS (15). The benefit of ^{18}F-fluciclovine PET/CT on FFS reported in the EMPIRE-1 study was at a group level. In the current study, we performed a sub-stratification posthoc analysis of the EMPIRE-1 data to determine if the FFS advantage conferred by adding ^{18}F-fluciclovine PET/CT to SRT planning is maintained across different patients' strata. In this study, FFS was significantly higher in patients with serum PSA below 2 ng/mL who had an additional ^{18}F-fluciclovine PET/CT (arm B) for SRT planning compared with patients whose SRT planning was based on conventional imaging only. At a PSA above 2 ng/mL, we found no significant difference in FFS between study arms. This finding may be related to the limited number of patients with PSA > 2 ng/mL (22 patients) in the EMPIRE-1 cohort, but requires further study before definitive conclusions can be made.

SRT at low serum PSA levels has been recommended (20), usually at PSA below 0.5 ng/mL, due to the decrease in its benefits as PSA rises (21). Given this, we performed an explorative analysis to see if the FFS benefit conferred by ^{18}F-fluciclovine PET/CT is retained at lower PSA levels. Indeed, FFS remains significantly higher in arm B versus arm A at PSA < 1 ng/mL both at 36- and 48-month follow-ups. Among patients with PSA level < 0.5 ng/mL,

FFS was significantly higher for patients in arm B than in arm A, with the difference reaching statistical significance at 48-month follow-up. This finding suggests that while the use of ^{18}F-fluciclovine PET/CT for SRT planning is beneficial in patients with PSA < 0.5 ng/mL, this benefit reaches significance in the long-term, and this finding may be related to the more sustained disease control seen in patients who had ^{18}F-fluciclovine PET/CT as part of SRT planning compared with the progressive increase in failure rate over time in patients who did not.

Adverse pathologic features such as extra-prostate extension, seminal vesicle invasion, and the presence of nodal metastases in the pathology specimen obtained during radical prostatectomy are suggestive of advanced disease (17). The EMPIRE-1 trial, therefore, stratified patients during randomization into study arms according to the presence or absence of these adverse pathologic features. The FFS benefit conferred by incorporating ^{18}F-fluciclovine PET/CT into SRT planning was maintained in patients with and without adverse pathologic features at 36 and 48-month follow-ups. In patients with adverse pathology present, the higher FFS rate seen in arm B compared with arm A at 36-month follow-up showed a trend towards statistical significance while a clear significance was seen at 48-month follow-up, again highlighting the long-term tumor control afforded by SRT decision guided by ^{18}F-fluciclovine PET/CT imaging.

Adding ADT to SRT improves progression-free survival, especially in patients with high-risk disease phenotypes (16,22). To remove the confounding effect of additional ADT on SRT outcome, ADT intent was balanced between study arms. Among patients with no ADT intent, FFS was significantly higher at 36- and 48-months follow-ups in arm B compared with arm A. Among patients in whom additional ADT was planned, there was a higher FFS in arm B than in arm A at 36-month follow-up, with the difference reaching statistical significance at 48-months follow-up. The improvement in FFS due to SRT conferred by ^{18}F-fluciclovine PET/CT is more prominent at 48-months follow-up compared with 36-months follow-up, a finding that is consistently seen across different patients' strata. Fifteen patients experienced SRT failure in arm B, all of which occurred within 36-month of SRT. There was no further event during the 36 to 48-month follow-up interval. Conversely, among arm A patients, 22 events occurred within 36 months of SRT and a further five events occurred between the 36-month and 48-month follow-ups. It is notable and expected that patients with higher PSA, adverse histology, and ADT

intent generally have lower FFS than those with lower PSA, no adverse histology, and no ADT intent regardless of arm.

Among patients randomized to arm B, four patients did not receive SRT due to the detection of extrapelvic metastases on ^{18}F-fluciclovine PET/CT. In these patients, ^{18}F-fluciclovine PET/CT prevented futile SRT. In arm A, 30.9% of patients received pelvic radiotherapy in addition to radiotherapy to the prostate bed. This rate is lower than the 46.1% of patients in arm B who had pelvic radiotherapy in addition to radiotherapy to the prostate bed, a decision guided by the findings on ^{18}F-fluciclovine PET/CT. Put together, the higher FFS brought about by the incorporation of ^{18}F-fluciclovine PET/CT imaging during SRT decision-making is a result of a combination of better patient selection and a more accurate radiotherapy target delineation. We have previously reported that ^{18}F-fluciclovine PET/CT had a greater impact on SRT management decisions than conventional imaging in the EMPIRE-1 cohort (14). A more favorable survival outcome in patients with an additional ^{18}F-fluciclovine PET/CT compared with patients whose SRT was guided by conventional imaging only suggests that the change in management decision brought about by ^{18}F-fluciclovine PET/CT led to a favorable treatment outcome.

The detection of additional lesions on ^{18}F-fluciclovine PET/CT compared to conventional imaging is often associated with an increase in the pre-treatment defined target volume (23). The higher rate of radiotherapy to the pelvis in the ^{18}F-fluciclovine PET/CT arm in the current study, therefore, has the potential to expose such patients to radiotherapy-induced toxicities. A recent report which evaluated provider- and patient-reported SRT-induced toxicities in the EMPIRE-1 cohort did not find significant differences in the incidence of treatment-induced toxicities between study arms despite a significant increase in target volumes due to the incorporation of ^{18}F-fluciclovine PET/CT into SRT planning (24). This finding confirms that the improvement in lesion detection, SRT management decision, and favorable SRT outcomes brought about by the incorporation of ^{18}F-fluciclovine PET/CT into SRT planning occur without exposing the patients to a higher rate or severity of treatment-induced toxicities.

Several studies have reported the diagnostic performance of ^{18}F-fluciclovine PET/CT in patients with PCa recurrence (25-28). These studies have primarily evaluated the diagnostic performance of ^{18}F-fluciclovine PET/CT or its effects on management decisions rather than the impact of imaging findings on patients' survival. Imaging studies that randomized patients into study arms and evaluated the impact of imaging findings on survival are rare.

The strength of this study, therefore, lies in its design and the choice of FFS as the study endpoint. In the EMPIRE-1 trial design, power and sample size calculations were performed for the primary aim (i.e. to detect a 20% difference in 3-year FFS between study arms). The current subgroup investigation is purely exploratory. Despite not being powered to detect differences between study arms stratified according to protocol-specified criteria, we found that the survival benefit from adding ^{18}F-fluciclovine PET/CT was maintained across most of the strata evaluated.

Of note, though there has been a recent expansion in the use of ^{68}Ga-PSMA PET/CT with a few prospective single-arm trials reporting the time to failure as a study endpoint in patients whose SRT was guided by this novel imaging modality (29,30), there have been no randomized controlled trials of PSMA versus conventional imaging reported as yet in this post-prostatectomy radiotherapy space. An ongoing phase III trial at the University of California Los Angeles (NCT03582774), when completed, will fill this void (31). We have an ongoing phase III trial at our institution comparing ^{68}Ga-PSMA PET/CT versus ^{18}F-fluciclovine PET/CT (R01CA226992, NCT03762759) for guiding SRT of PCa recurrence. The results from this trial may provide further insights on the comparative benefits of these two approved imaging modalities for PCa recurrence for SRT management decision guidance.

CONCLUSION

The addition of ^{18}F-fluciclovine PET/CT to CI in SRT management planning reduces the occurrence of treatment failure. This benefit is seen across different PSA levels below 2 ng/mL. This benefit is also maintained regardless of the presence versus absence of adverse disease pathologic features or the intention to add ADT to SRT or not in the treatment of PCa recurrence post-RP.

DISCLOSURE

ABJ reports personal fees from Blue Earth Diagnostics for advisory board services outside the submitted work. MG is entitled to a royalty derived from sale of products related to the research described in this report. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies. The research consent forms state that he is entitled to a share of sales royalty received by Emory University from Nihon MediPhysics under that agreement. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies. DMS participates through the Emory University Office of Sponsored Projects in sponsored grants including those funded or partially funded by Blue Earth Diagnostics, Nihon MediPhysics, Telix Pharmaceuticals (US), Advanced Accelerator Applications, FUJIFILM Pharmaceuticals USA, and Amgen. DMS also reports consultant fees outside the submitted work from Syncona, AIM Specialty Health, Global Medical Solutions Taiwan, and Progenics Pharmaceuticals. The other authors declare no competing interests.

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KEY POINTS

QUESTION: Is the survival advantage imparted by the addition of ^{18}F-fluciclovine PET/CT to salvage radiotherapy planning of prostate cancer recurrence reported in the EMPIRE-1 trial maintained in different patients subpopulations?

PERTINENT FINDINGS: The incorporation of ^{18}F-fluciclovine PET/CT in SRT management decision led to an improvement in failure-free survival across different PSA strata below 2 ng/mL. The survival benefit is also retained regardless of the presence or absence of adverse pathologic features or whether concomitant androgen-deprivation therapy is planned with SRT or not.

IMPLICATIONS FOR PATIENT CARE: The addition of ^{18}F-fluciclovine PET/CT SRT planning improves failure-free survival in patients with disease recurrence after radical prostatectomy, and the benefit is retained across different patient categories.

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Table 1: Baseline characteristics of the patients randomized into study arms

	Arm A, CI-guided SRT, n=81	**Arm B, CI plus ^{18}F-fluciclovine PET/CT-guided SRT, n=76**
Age, median (IQR)	61 (55 - 68)	61 (57 - 68)
Baseline PSA, median (IQR)	0.34 (0.8)	0.34 (0.9)
<2 ng/mL, n (%)	69 (85.2)	66 (86.8)
≥2 ng/mL, n (%)	12 (14.8)	10 (13.2)
Any adverse pathology, n (%)		
Present	61 (75.3)	53 (69.7)
Absent	20 (24.7)	23 (13.2)
ADT intent		
Yes, n (%)	28 (34.6)	27 (35.5)
No, n (%)	53 (65.4)	49 (64.5)
Gleason score		
<8, n (%)	52 (64.2)	53 (69.7)
≥8, n (%)	29 (35.8)	23 (30.3)

CI: Conventional Imaging; **SRT**: Salvage Radiotherapy; **PSA**: Prostate-Specific Antigen; **ADT**: Androgen Deprivation Therapy

Table 2: Comparison of failure-free survival rates between arms stratified according to PSA, adverse pathology, and ADT intent

Stratification criteria	Follow-up Time (months)	Arm A, % (95% CI)	Arm B, % (95% CI)	p-value
PSA				
<2 ng/mL	36	66.5 (51.6 – 77.8)	83.2 (70.0 – 91.0)	<0.001*
	48	56.2 (40.5 – 69.2)	83.2 (70.0 – 91.0)	<0.001*
≥2 ng/mL	36	40.4 (9.8 – 70.2)	26.3 (4.0 – 57.5)	0.231
	48	0.0 (NA - NA)	26.3 (4.0 – 57.5)	NA
Adverse Pathology				
Present	36	59.9 (43.7 – 72.8)	68.9 (52.1 – 80.8)	0.085
	48	42.8 (26.2 – 58.3)	68.9 (52.1 – 80.8)	<0.001*
Absent	36	73.1 (42.9 – 89.0)	90.2 (65.9 – 97.5)	0.006*
	48	73.1 (42.9 – 89.0)	90.2 (65.9 – 97.5)	0.006*
ADT intent				
Yes	36	52.3 (27.7 – 72.1)	65.2 (40.3 – 81.7)	0.113
	48	29.1 (6.5 – 57.2)	65.2 (40.3 – 81.7)	<0.001*
No	36	68.0 (51.1 – 80.2)	80.7 (64.9 – 90.0)	0.008
	48	58.6 (41.0 – 72.6)	80.7 (64.9 – 90.0)	<0.001*

PSA: Prostate-Specific Antigen; *****: *P*-value <0.005; **ADT**: Androgen Deprivation Therapy; **NA**: Not Applicable.

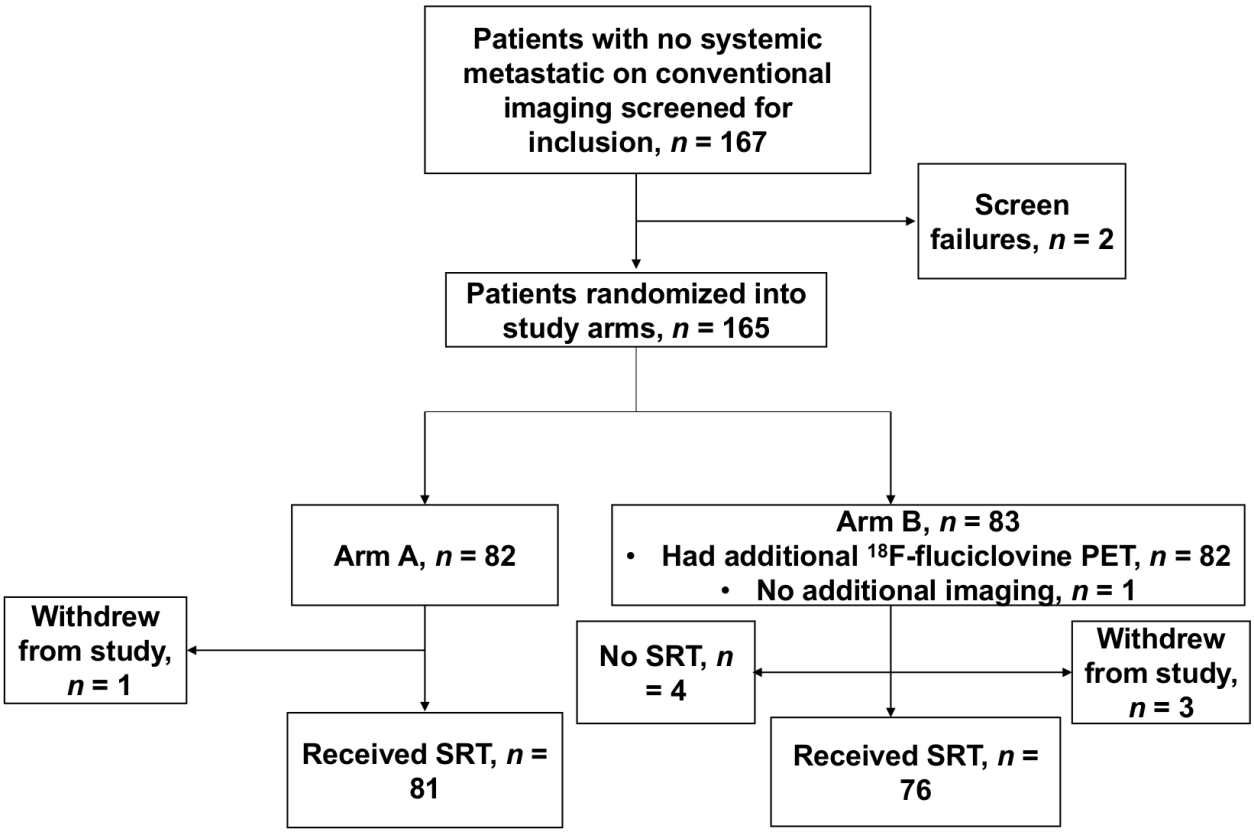
Adverse Pathology Considered: extra-prostate extension, seminal vesicle invasion, and the presence of nodal metastases in the pathology specimen obtained during radical prostatectomy.

Table 3: Differences in failure-free survival between patients who had conventional imaging only (arm A) versus patients who had conventional imaging plus ^{18}F-fluciclovine-PET/CT (arm B) for salvage radiotherapy planning

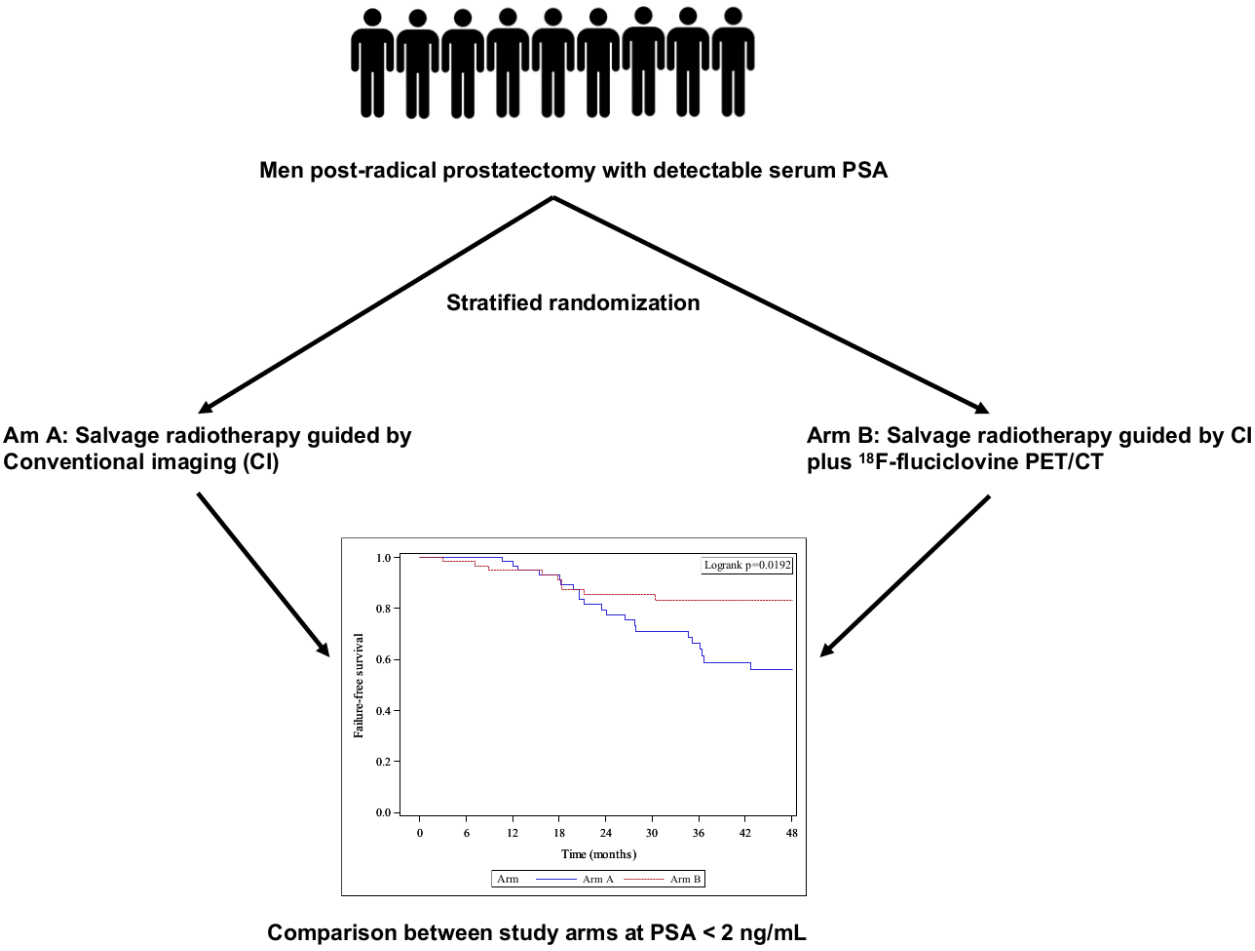
	Arm 1, % (95% CI)	**Arm 2, % (95CI)**	***P*-value**
PSA < 0.5 ng/mL			
	N=48	N=51	
	Mean ± = 0.19 ± 0.13	Mean ± = 0.23 ± 0.12	
FFS at 36 months	79.3 (61.3 – 89.6)	85.3 (69.7 – 93.2)	0.184
FFS at 48 months	63.2 (42.8 – 78.1)	85.3 (69.7 – 93.2)	<0.001*
PSA < 1 ng/mL			
	N=61	N=57	
	Mean ± = 0.29 ± 0.24	Mean ± = 0.29 ± 0.20	
FFS at 36 months	72.8 (56.8 – 83.6)	84.7 (70.3 – 92.5)	0.005*
FFS at 48 months	60.5 (43.2 – 74.0)	84.7 (70.3 – 92.5)	<0.001*
PSA < 2 ng/mL			
	N=69	N=66	
	Mean ± = 0.41 ± 0.41	Mean ± = 0.43 ± 0.43	
FFS at 36 months	66.5 (51.6 – 77.8)	83.2 (70.0 – 91.0)	<0.001*
FFF at 48 months	56.2 (40.5 – 69.2)	83.2 (70.0 – 91.0)	<0.001*

PSA: Prostate-Specific Antigen; **FFS:** Failure-Free Survival; *****: P-value < 0.05

Figure 1: A flowchart showing patient recruitment and randomization into study arms



Graphical abstract



Comparison between study arms at PSA < 2 ng/mL