F-18-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

Ashesh Jani, Emory University
Eduard Schreibmann, Emory University
Subir Goyal, Emory University
Raghuveer Halkar, Emory University
Bruce Hershatter, Emory University
Peter J Rossi, Emory University
Joseph Shelton, Emory University
Pretesh Patel, Emory University
Karen M Xu, Emory University
Mark Goodman, Emory University

Only first 10 authors above; see publication for full author list.

Journal Title: LANCET
Volume: Volume 397, Number 10288
Publisher: ELSEVIER SCIENCE INC | 2021-05-22, Pages 1895-1904
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/S0140-6736(21)00581-X
Permanent URL: https://pid.emory.edu/ark:/25593/vxfck

Final published version: http://dx.doi.org/10.1016/S0140-6736(21)00581-X

Copyright information:
This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (https://creativecommons.org/licenses/by-nc-nd/4.0/rdf).

Accessed July 29, 2023 8:46 PM EDT
Corresponding Author: Ashesh B. Jani, MD, MSEE, FASTRO, Professor, Department of Radiation Oncology, Winship Cancer Institute of Emory University, 1365 Clifton Road, NE; Suite A1300, Atlanta, GA 30322, USA, +1-404-778-3827, abjani@emory.edu.

* Indicates contributor is a Full Professor

Contributors

**ABJ** was co-principal investigator on the NIH grant that was the main funding source for the work, and was the lead principal investigator on the IRB protocol used to conduct the randomized trial that is the core of this investigation; was responsible for funding acquisition, study design, patient recruitment, data collection, management of regulatory items on radiation oncology side of the trial, data interpretation, data analysis, and writing.

**ES** was the lead research physicist who did the image registrations for radiotherapy treatment planning on Arm 2 of the trial; was responsible for imaging and radiotherapy data collection and data interpretation.

**SG** was the lead biostatistician who performed all statistical analyses for this manuscript; was responsible for data interpretation, data analysis, and writing.

**RH** was one of the two board-certified nuclear medicine physicians interpreting the PET studies; was responsible for image data interpretation.

**BH** was a community affiliate radiation oncologist; was responsible for patient recruitment and treatment, data collection, and data interpretation.

**PJR** was a community affiliate radiation oncologist; was responsible for patient recruitment and treatment, data collection, and data interpretation.

**JWS** was a community affiliate radiation oncologist; was responsible for patient recruitment and treatment, data collection, and data interpretation.

**PRP** was a community affiliate radiation oncologist; was responsible for patient recruitment and treatment, data collection, data interpretation, and writing.

**KMX** is a radiation oncologist in training and assisted with tabulation of the survival data; was responsible for data collection and data interpretation.

**MG** is laboratory scientist - the radiotracer that is main subject of this investigation – fluciclovine – was developed in his laboratory; was responsible for study design and data interpretation.

**VAM** is director of the clinical trials unit in urology at our center; was responsible for coordination of patient recruitment and data interpretation.

**SSJ** is urology co-investigator; was responsible for data interpretation and writing.

**BCC** is a genitourinary medical oncology unit and; was responsible for patient recruitment and data interpretation.

**MAB** is a genitourinary medical oncologist; responsible for patient recruitment and data interpretation.

**OAA** is a nuclear medicine research fellow; responsible for imaging data collection, data interpretation, and writing.

**AAA** is a nuclear medicine research fellow; responsible for imaging data collection and data interpretation.

**VRD** is a radiation oncologist in training and assisted with tabulation of the toxicity data; responsible for data interpretation and writing.

**DMS** was co-principal investigator on the NIH grant that was the main funding source for the work; was the responsible for directing all of the major imaging components of the work - imaging data collection, management of regulatory items on radiology/nuclear medicine side of the grant, data interpretation, data analysis, and writing.

Although all authors above are ultimately responsible for the data, the main authors who have verified the underlying data are **ABJ, SG, and DMS**.

Data Sharing

<table>
<thead>
<tr>
<th>Will individual participant data be available (including data dictionaries)?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>What data in particular will be shared?</td>
<td>Individual participant data that underlie the results reported in this article, after de-identification (text, tables and figures)</td>
</tr>
<tr>
<td>What other documents will be available?</td>
<td>Study protocol, statistical analysis plan</td>
</tr>
<tr>
<td>When will data be available (start and end dates)?</td>
<td>Immediately following publication; no end date</td>
</tr>
<tr>
<td>With whom?</td>
<td>Researchers who provide a methodologically sound proposal</td>
</tr>
<tr>
<td>For what types of analyses?</td>
<td>Any purpose</td>
</tr>
<tr>
<td>By what mechanism will data be made available?</td>
<td>Proposals should be directed to <a href="mailto:abjani@emory.edu">abjani@emory.edu</a> or (for imaging-specific queries) <a href="mailto:dschust@emory.edu">dschust@emory.edu</a> To gain access, data requestors will need to sign a data access agreement that requires approval by Emory’s Office of Technology Transfer</td>
</tr>
</tbody>
</table>

Declaration of Interests

**ABJ** reports personal fees from Blue Earth Diagnostics, Ltd. in the role of advisory board service outside the submitted work.

**ES** - none
EMPIRE-1: Randomized Trial Comparing Conventional- vs Conventional plus Fluciclovine (18F) PET/CT Imaging-Guided Post-Prostatectomy Radiotherapy for Prostate Cancer

Ashesh B. Jani, MD1,*; Eduard Schreibmann, PhD1; Subir Goyal, PhD2; Raghveer Halkar, MD3,*; Bruce Hershatter, MD1; Peter J. Rossi, MD1; Joseph W. Shelton, MD1; Preesh R. Patel, MD1; Karen M. Xu, MD1; Mark Goodman, PhD3,*; Viraj A. Master, MD4,*; Shreyas S. Joshi, MD4; Omer Kucuk, MD5,*; Bradley C. Carthon, MD5; Mehmet A. Bil, MD5; Olayinka A. Abiodun-Ojo, MD3; Akinyemi A. Akintayo, MD3; Vishal R. Dhere, MD1; David M. Schuster, MD3,*

1Department of Radiation Oncology, Winship Cancer Institute of Emory University
2Biostatistics Shared Resource, Winship Cancer Institute of Emory University
3Department of Radiology and Imaging Sciences, Emory University
4Department of Urology, Emory University
5Department of Medical Oncology, Winship Cancer Institute of Emory University

Abstract

**Background:** Molecular imaging is increasingly used to guide prostate cancer decisions and treatment planning. The specific aim was to evaluate the role of fluciclovine (18F) PET/CT in improving cancer control over conventional imaging (bone scan and either CT or magnetic resonance imaging) alone for post-prostatectomy radiotherapy.
**Methods:** Patients with prostate cancer with detectable PSA post-prostatectomy and negative conventional imaging (no extra-pelvic or bone findings) were randomized to radiotherapy directed by conventional imaging (Arm 1) alone vs conventional imaging+PET (Arm 2). The treatment setting was an academic medical center with community affiliates. In Arm 2, radiotherapy decisions were rigidly determined by PET, which was also used for target delineation. Using a standard post-radiotherapy failure definition, failure rates at 3 years (primary study endpoint) were compared. Univariate and multivariable analyses were performed for demographic, disease, and treatment factors. Secondary endpoints included provider-reported gastrointestinal and genitourinary toxicities. Enrollment was done under [ClinicalTrials.gov](https://clinicaltrials.gov) registration (NCT01666808) which is closed to new participants.

**Findings:** From September 18, 2012 to March 4, 2019, 165 patients were randomized. PET findings resulted in a 35·4% rate of decision changes, including 4 patients having radiotherapy aborted. Median follow-up was 3·52 years. Three-year failure-free survival rate for Arm 1 vs Arm 2 was 63·0 vs 75·5% (difference,12·5; 95% CI:4·3–20·8; p=0·0028) and at 4-years was 51·2 vs 75·5% (difference,24·3; 95% CI:15·6–33·0; p<0·0001). On multivariable analysis, Arm (HR=2·04[95%CI: 1·06–3·93], p=0·0327), extracapsular extension, pelvic field, and prostate-specific antigen (PSA) reached significance. Toxicity was similar in both Arms.

**Interpretation:** Inclusion of fluciclovine (\(^{18}\)F) PET into post-prostatectomy radiotherapy decisions and planning resulted in a significant improvement in failure rate. Integration of novel PET radiotracers into radiotherapy decisions and planning for prostate cancer patients warrants further study.

**Funding:** NIH R01 CA169188 [major source]; Blue Earth Diagnostics, Ltd. [cassette arrangement with Emory].

---

**Introduction**

Prostate cancer is among the most common malignancies worldwide. Primary, localized (non-metastatic) prostate cancer can be treated using several different approaches, including active surveillance, surgery and radiotherapy.\(^1\)\(^2\) For patients undergoing prostatectomy, particularly those with unfavorable features, biochemical failure can occur in 20–40% of patients and is strongly associated with metastases and prostate-cancer related death.\(^3\)

Radiotherapy is often delivered post-prostatectomy, either shortly after surgery based on adverse features (adjuvant radiotherapy)\(^4\)\(^–\)\(^6\) or at a later date based on documented recurrence (salvage radiotherapy).\(^7\) The decision of whether and when to offer radiotherapy is complex and dependent on many features including pre-prostatectomy risk group, pathologic findings, and post-surgery prostate-specific antigen (PSA) trajectory. Randomized comparisons of adjuvant radiotherapy vs observation\(^1\)\(^–\)\(^6\) as well as adjuvant vs salvage radiotherapy\(^8\)\(^–\)\(^11\) have been undertaken. The role of androgen deprivation therapy (ADT)\(^12\)\(^–\)\(^14\) and pelvic lymph node radiation\(^14\) on post-prostatectomy radiotherapy outcomes have also been studied.

While there remains considerable controversy in many aspects of post-prostatectomy radiotherapy, failure rates remain quite high and range from 20–60% depending on the study population.\(^3\)\(^–\)\(^14\) In addition to PSA and physical examination (including digital rectal
examination [DRE]), imaging plays a central role in guiding radiotherapy decisions and treatment planning. Conventional imaging studies such as computed tomography (CT) and bone scan have low diagnostic yield, especially at lower PSA levels. Magnetic resonance imaging (MRI) is useful in the detection of local recurrence in the surgical bed and is particularly advantageous for delineation of soft tissue anatomy for radiation treatment planning, but also has limitations in the detection of metastatic disease.

Molecular imaging has an emerging role in prostate cancer due to a higher diagnostic yield than conventional imaging. While earlier attempts with \(^{111}\)Indium-capromab pendetide (ProstaScint) yielded substandard results, newer positron emission tomography (PET) radiotracers are assuming an important role in the staging and restaging of prostate cancer.

Fluciclovine \((^{18}\text{F})\) is a synthetic amino acid PET radiotracer which was developed at our center, and is FDA-approved for prostate cancer recurrence imaging. Fluciclovine \((^{18}\text{F})\) PET/CT has been reported to have better diagnostic performance than CT and MRI for restaging biochemically recurrent prostate cancer. We have also previously reported that the incorporation of fluciclovine \((^{18}\text{F})\) PET/CT into treatment planning results in a 35.4% change in salvage radiotherapy management in biochemically recurrent post-prostatectomy patients who first underwent conventional imaging.

For salvage radiotherapy, molecular imaging has the potential to increase accuracy in decision making and target definition. Most reports evaluating imaging studies focus on diagnostic accuracy (comparing findings against a standard of truth) and/or decision changes. Very few, if any, imaging trials have used cancer control as a primary endpoint in a prospective, randomized manner compared to standard imaging. We hypothesized that if patients are appropriately selected for salvage radiotherapy with the aid of more advanced molecular imaging with fluciclovine \((^{18}\text{F})\) PET/CT, and if this molecular imaging information is further integrated into radiotherapy treatment planning, a significantly higher proportion will achieve failure-free survival compared to conventional treatment algorithms. We now report the results of a prospective randomized trial designed to test this hypothesis.

**Methods**

**Study Design**

To reach the primary aim of the study, a randomized trial was conducted. This trial – the Emory Molecular Prostate Imaging for Radiotherapy Enhancement (EMPIRE-1) was National Institutes of Health-funded (NIH R01 CA169188) and registered at ClinicalTrials.gov (NCT01666808). Signed informed consent was obtained from every trial participant. The treatment setting was at Winship Cancer Center of Emory University (academic medical center with community affiliates); institution review board approval was through Emory University.

The trial schema is shown in Figure 1. Of note, a radiotherapy decision attestation sheet was completed before randomization documenting provider intent as to whether radiotherapy was offered or not, the general treatment fields (whole pelvis vs prostate bed alone), and androgen deprivation intent/duration such that pre- vs post-PET decisions could be
compared systematically. As shown in Figure 1, patients were stratified by (a) PSA (< 2.0 vs \geq 2.0 ng/mL), (b) adverse pathology [extracapsular extension, seminal vesicle invasion, positive margin, and/or pathologically positive lymph node(s)] (none vs any), and (c) ADT intent (yes vs no), and then randomized to radiotherapy directed by conventional imaging only (Arm 1) vs conventional imaging plus fluciclovine (18F) PET/CT (Arm 2).

Participants

Patients with adenocarcinoma of the prostate who had detectable PSA post-prostatectomy and absence of systemic metastasis on conventional imaging (bone scan and either CT or MRI of abdomen/pelvis) were eligible. Patients who had prior pelvic radiotherapy, ECOG performance status \geq 3, contraindications to radiotherapy (including inflammatory bowel disease), prior invasive malignancy (unless disease-free for a minimum of 3 years), and severe acute morbidity were ineligible.

Randomization and masking

Randomization was 1:1 between the two Arms - patients were randomly assigned their Arm by the study statistician using a computer generated randomization schedule. Clinical research associates had access to this schedule, and notified both provider and patient to the arm immediately after randomization. Treatment was started within one month of randomization.

Procedures

ADT, if administered, was typically 6-months in duration and started concurrently with radiotherapy after PET was obtained; however, patients who were on ADT prior to randomization (but still had detectable PSA at time of enrollment) were eligible. Patients were followed at 1, 6, 12, 18, 24, 30, and 36 months post-treatment with PSA and physical examination (including DRE) performed at each of these time-points (no DRE was performed at the 1-month visit, however); longer-follow-up beyond 36 months was permitted. For those receiving ADT, serum testosterone and liver function tests were obtained pre-treatment and during follow-up time-points that spanned the ADT administration; serum testosterone was optional on later follow-ups.

Acquisition and interpretive details of the fluciclovine (18F) PET/CT have been previously reported and also summarized in Supplemental Table 1.20 Two board-certified nuclear medicine physicians interpreted the studies blinded to clinical details or other imaging. The study was performed in accordance with investigational new drug (IND) application 72,437 as the radiotracer had not yet been FDA approved when the study began. PET was obtained after randomization but before start of radiotherapy.

In Arm 2, radiotherapy decisions were rigidly determined by PET: (A) extra-pelvic or skeletal uptake (no radiotherapy); (B) pelvic nodal uptake (radiotherapy to pelvis [45.0–50.4 Gy in 1.8 Gy fractions] + prostate [surgical] bed [64.8–70.2 Gy in 1.8 Gy fractions]); (C) prostate bed-only uptake (radiotherapy to prostate bed); & (D) no uptake (radiotherapy to prostate bed). Note that patients in category (A) above were included in the intention to treat analysis but, as they did not receive radiotherapy nor follow-up, they effectively dropped out
of the Kaplan-Meier curve as an intentional consequence of improved patient selection for radiotherapy. Also, pathologic node positive patients were treated as in category (B) above [i.e., PET could not be used to reduce field size from pelvis+prostate bed to prostate bed alone if there were surgically positive lymph node(s)].

In Arm 2, PET was also registered with planning CT for target delineation. The final radiotherapy clinical target volume (CTV) was defined as the union of the standardized prostate bed (and, if applicable, pelvic lymph node) volume\(^1\) with the region of PET uptake, without escalating the radiation dose to regions of PET uptake beyond that listed above. The process of PET-guided radiotherapy planning used for this trial has been described previously.\(^2\),\(^2\)

**Outcomes**

The primary endpoint of the study was failure-free survival rate at 3 years. Failure was defined as any of: PSA > 0.2 ng/mL from nadir followed by another rise, persistent PSA, imaging or DRE failure, or initiation of systemic therapy.\(^7\) Follow-up was measured from end of radiotherapy (time=0). Secondary endpoints included provider-reported (acute & late) gastrointestinal (GI) and genitourinary (GU) toxicity rates.

**Statistical Analysis**

We calculated that a sample of 146 patients (73 in each arm) were needed to test a 20% difference in 3-year failure-free survival [50% vs 70%] between arms at a 0.05 level of significance with 80% power.\(^2\) The basis of an expected difference between the two arms was (a) excluding patients in Arm 2 for whom pelvic radiotherapy would likely be futile, and (b) improved radiotherapy by integrating the PET information into the treatment field decision as well as the final radiotherapy target volume design. Assuming a withdrawal/dropout rate of 10%, the overall target enrollment was a minimum of 162 subjects.

Pre- vs post-PET decision changes were assessed using the Clopper-Pearson (exact) binomial method. The univariate association between each variable and the two arms was assessed with a chi-square test for categorical covariates and with an analysis of variance (ANOVA) for numerical covariates. Failure-free survival rate at 3 years (primary endpoint) and at 4 years was compared between the two arms using the Z-test.\(^2\) Kaplan-Meier curves were generated up to 4 years from end-radiotherapy (time=0) and compared using the log-rank test. The median follow-up was calculated using the reverse Kaplan-Meier method. Univariate and multivariable analyses were performed for demographic, disease, and treatment factors using the Cox proportional hazards model. Provider-reported (acute and late, GI and GU) toxicities were compared between Arms using chi-square or Fisher's exact test. The statistical analysis was conducted with SAS 9.4 (SAS, Cary, North Carolina).

**Role of the funding source**

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Results

The CONSORT flow diagram for this trial is shown in Figure 2. From September 18, 2012 to March 4, 2019, 165 patients were randomized (Arm 1: 82; Arm 2: 83). In Arm 1, one patient withdrew from the trial after randomization but before radiotherapy. In Arm 2, three patients withdrew from the trial post-randomization, and one patient had technical difficulties in being able to undergo the PET scan (but this patient did receive radiotherapy and was followed on Arm 2 on an intention-to-treat basis).

Patient characteristics are shown in Table 1. The Arms were balanced on age, race, PSA, Gleason score, extracapsular extension, seminal vesicle invasion, margin positivity, lymph node involvement, and ADT use (including ADT duration).

PET uptake in Arm 2 (79 patients) was: extra-pelvic: 4; pelvic lymph nodes +/- prostate bed: 27; prostate bed only: 32; none: 16. As shown in Supplemental Table 2, this resulted in 35.4% rate of decision changes [which was statistically significant (p<0.001)], including 4 patients having radiotherapy aborted (note that this was a protocol mandate). Of these 4, one had histologic proof of retroperitoneal nodal metastasis, two with skeletal metastasis had definitive confirmation on follow-up correlative imaging, and one had a classic imaging presentation with extensive nodal disease in the pelvis ascending into the retroperitoneum though too small to biopsy. Ultimately, 81 patients in Arm 1 received radiotherapy (56 to prostate bed alone and 25 to prostate bed and pelvic nodes) and 76 patients (including the 1 patient listed above who had technical difficulties obtaining the PET scan) in Arm 2 received radiotherapy (41 to prostate bed alone and 35 to prostate bed and pelvic nodes).

Supplemental Figure 1 shows examples for illustrative purposes for whom a PET was used to define the final target volume used for radiotherapy. Within Arm 2, volumetric and dosimetric changes were also charted – a planned interim review of these changes has been previously reported.23

Median length of follow-up for the whole cohort was 3.52 years. During the study period (4 years from end-radiotherapy), there were 42 total failures; there were 12 more failures in Arm 1 (27 failures) than Arm 2 (15 failures).

Failure-free survival curves are shown in Figure 2. The 3-year failure-free survival rate for Arm 1 vs Arm 2, the primary endpoint of the study, was 63.0 vs 75.5% (difference, 12.5; 95% CI: 4.3–20.8; p=0.0028). A difference in failure-free survival between Arms 1 and 2 was also seen at 4 years, where it was found to be 51.2 vs 75.5% (difference, 24.3; 95% CI, 15.6–33.0; p<0.0001).

The results of the univariate analysis for failure-free survival are shown in Table 2. Variables found to be significant predictors for failure-free survival in the univariate analysis included: Gleason Score ≥ 8 (HR, 2.15; 95% CI, 1.17–3.96; p=0.012), absence of extra-capsular extension (HR, 0.44; 95% CI, 0.23–0.83; p=0.009), absence of seminal vesicle invasion (HR, 0.49; 95% CI, 0.27–0.91; p=0.022), whole pelvic treatment field (HR, 2.77; 95% CI, 1.50–5.11; p<0.001), and PSA ≥ 1.0 ng/mL (HR, 3.18; 95% CI, 1.73–5.85; p<0.001). Arm 1 (HR, 1.85; 95% CI, 0.98–3.47; p=0.0540) trended towards significance.

---

*Lancet. Author manuscript; available in PMC 2022 May 22.*
Multivariable analysis for failure-free survival revealed significantly higher risk of failure in Arm 1 (HR, 2.04; 95% CI, 1.06–3.93; p=0.0327) (Table 3). The absence of extra-capsular extension (HR, 0.45; 95% CI, 0.21–0.95; p=0.035), whole pelvic treatment field (HR, 2.09; 95% CI, 1.07–4.08; p=0.031), and PSA ≥1.0 ng/mL (HR, 3.49; 95% CI, 1.76–6.90; p<0.001) remained significant predictors of failure-free survival on multivariable analysis.

Of the 27 patients who failed in Arm 1, all 27 had biochemical failure, which was the time-point used for the failure event in the Kaplan-Meier curve. Thirteen also had imaging failure (eight at time of biochemical failure, five at a later date). Virtually all who had imaging failure received salvage therapy (ADT and/or salvage radiotherapy and/or salvage lymph node dissection). Two patients who had no imaging failure started ADT immediately at time of PSA failure. Of the 15 patients who failed in Arm 2, all had biochemical failure. Ten also had imaging failure (nine at time of biochemical failure, one at a later date). As with the case in Arm 1, virtually all who had imaging failure received salvage therapy (ADT and/or salvage radiotherapy and/or salvage lymph node dissection). One patient who had no imaging failure started ADT immediately at time of PSA failure.

Note that in those patients receiving ADT, serum testosterone measurements were optional beyond the period where ADT was administered. In those patients for whom serum testosterone was available at 3 years (primary study endpoint interval), testosterone had recovered in virtually all cases, which is to be expected in a population where those that received ADT typically received short-term ADT.

The results of the provider-reported toxicity analysis are listed in Supplemental Table 3. GI toxicity was typically diarrhea or proctitis, and GU toxicity was typically urinary frequency, urinary urgency, cystitis (non-infective), or dysuria. As displayed, acute and late GI and GU toxicity rates were similar in both Arms. Notably, grade 3 toxicity rates were low in both Arms and no grade 4/5 toxicity was seen in either Arm.

Discussion

The main finding of our study was that inclusion of fluciclovine (¹⁸F) PET into post-prostatectomy radiotherapy decisions and planning resulted in a significant improvement in failure rate.

Virtually all imaging studies, particularly in the oncology setting, are appropriately focused on diagnostic accuracy and/or decision changes. For fluciclovine (¹⁸F) specifically, several such trials have been done, including a secondary endpoint analysis of the current study²⁰ and also the LOCATE and FALCON studies.²⁵,²⁶

Randomized trials of imaging tests with primary cancer control endpoints are vitally important but uncommonly completed. Even well-established routine imaging studies such as bone scans were integrated into clinical practice without randomization against existing conventional imaging. Challenges in conducting such studies include (a) compliance (both patient and provider) with randomization to a new technology, (b) large numbers of patients needed to prove a difference in cancer control, (c) long follow-up required to see a clinical
impact, (d) difficulties in interpreting the impact of a diagnostic study from stage migration, and (e) lack of controlled therapy in imaging arms.

The post-prostatectomy radiotherapy setting is an ideal site for introduction of new imaging studies due to (a) the documented limitations of conventional imaging, (b) the high potential clinical impact of increased precision in decision making and treatment guidance (due to high failure rates with current techniques), and (c) the availability of a sensitive serum biomarker (PSA) for follow-up. The current era represents a renaissance in development of novel PET radiotracers that can be exploited for improvement in clinical outcomes. However, virtually all reports to date have focused on diagnostic parameters and decision changes, without addressing the true cancer control impact in a randomized setting.

To the best of our knowledge, our report is the first such prospective randomized trial of molecular imaging with cancer control as the primary endpoint in prostate cancer. Our study indicates that incorporation of fluciclovine (\(^{18}\)F) resulted in significant improvement in failure rate at 3 years, and with available follow-up this difference persists at 4 years. The likely reasons for the differences observed are: (a) better selection of patients likely to benefit from radiotherapy by excluding patients with extra-pelvic disease on PET, (b) field-size changes (i.e., inclusion of pelvic lymph node volume instead of prostate bed volume alone in cases where PET uptake was seen in the pelvic lymph nodes), and (c) integrating PET registration in the treatment planning process for finalization of target volumes that include regions of PET uptake.

In addition to other known prognostic factors, univariate and multivariable analyses identified Arm 2 as an important favorable prognostic factor for failure-free survival. The strength of this association is underscored by the fact that Arm 2 had a greater proportion of patients treated with prostate bed and pelvic radiotherapy and this larger field size, compared to prostate bed alone, was itself an adverse prognostic factor on multivariable analysis (as pelvic nodal treatment is typically used for patients with more aggressive disease).

As Supplemental Table 3 shows, provider-reported toxicity rates were similar between arms, suggesting PET-guided treatment was well-tolerated. One potential reason for this finding is that the PET was used to decrease field size (from pelvis + prostate bed to prostate bed alone, when no PET uptake was seen in the pelvic nodes) in addition to the converse (as displayed in Supplemental Table 2). Note that patient-reported toxicity outcomes across Arms will be the subject of a separate communication.

Our study does have some limitations. First, there was some variability in pre-PET decisions, particularly with respect to general target volumes; however, as mentioned, post-PET decisions were rigidly followed per protocol. Second, the role of ADT is difficult to interpret in our study – though not analyzed formally and not shown explicitly in Supplemental Table 2, ADT was offered for 6- months in 3 patients post-PET (pre-PET decision was no ADT), and was extended to 18-months in 2 patients (pre-PET decision was 6-months). However, Arm remained significant in multivariable analysis even with ADT and field size incorporated into the model. Third, this is a single center study; however, it should be noted that our study was carried out at multiple sites and involved multiple treating
radiation oncologists within our enterprise. Fourth, although median follow-up is long enough to report our primary study endpoint, confirmation of failure-free survival with longer follow-up interval is warranted. Fifth, based on the results of several recent studies, salvage radiotherapy is currently being offered at PSA’s in the 0.1–0.2 ng/mL range, whereas the median PSA in our study was 0.34 ng/mL; thus the reported impact of PET imaging may be higher in our study population over the current practice. Sixth, our study accrued over an approximately seven year period, and the standard of care (with respect to ADT use, radiation field size, and treatment of oligometastatic disease with radiotherapy) did change during this period. Finally, we utilized a dual time point PET-CT protocol which did not scan above the diaphragm and employed interpretative criteria tailored to this acquisition. While this research protocol is the progenitor of the clinical single time point whole body fluciclovine (18F) PET and consensus interpretative criteria, its use likely disadvantaged the PET arm in terms of sensitivity and may affect immediate generalizability of results.

The strengths of the reported study are (a) the randomized design – as described above this is a difficult endeavor and a high standard for any imaging study on a cancer control endpoint, (b) the rigid adherence to pre-specified treatment decisions based on PET findings, (c) conventional imaging was done on all patients with both bone imaging (bone scan) and soft tissue imaging (with either CT or MRI of abdomen/pelvis); thus, the true impact of PET is only incremental to conventional imaging and was still found to be impactful on cancer control, and (d) the high enrollment of under-represented minorities in our study, and resulting generalizability of our study findings due to this diversity.

Androgen deprivation therapy is being using more commonly in the post-prostatectomy radiotherapy setting due to randomized trial results. Additionally, the results of RTOG 0534 (randomized trial showing significant incremental improvements going from prostate bed radiotherapy only [Arm 1] to prostate bed radiotherapy + short-term ADT [Arm 2] to prostate bed + pelvic lymph node radiotherapy + short-term ADT [Arm 3]) may be used to justify both ADT and pelvic lymph node radiotherapy to a high percentage of patients, particularly those with PSA ≥0.34 ng/mL. Failure-free survival rates in RTOG 0534 were higher than those reported herein (3-year failure-free survival of approximately 80% in Arm 3, compared with 63% in Arm 1 of our trial), likely due to the higher mean PSA and inclusion of surgically positive lymph node patients in our study and also due to the nadir +2.0 ng/mL definition of failure in RTOG 0534. Of note, GI toxicity in RTOG 0534 increased with pelvic lymph node treatment over prostate bed only radiotherapy, suggesting a potential role for PET to reduce toxicity by a more individualized approach to treatment of pelvic lymph nodes.

While a number of studies have examined the impact of PET restaging on clinical decision making, few have reported on outcomes. For example, Schmidt-Hegemann and coworkers reported in a retrospective analysis of a 272 patient matched cohort undergoing radiotherapy planning after either Choline or 68Ga-PSMA-11 PET that there was no significant difference in 3-year biochemical-recurrence free survival with PSMA PET-based vs. choline PET-based planning (55% vs. 63%, p = 0.197). Emmett and coworkers in a prospective non-randomized trial of 68Ga-PSMA PET–triaged management in biochemical recurrence after

Lancet. Author manuscript; available in PMC 2022 May 22.
radical prostatectomy reported 64.5% failure-free survival at 3 years.\textsuperscript{28} Importantly, these studies either were not randomized nor prospective, did not include protocol-specified PET-directed therapy, or did not have failure-free survival as a primary endpoint such as the trial presented here, in which all these elements are present.

Several studies have formally compared diagnostic accuracy of fluciclovine (\textsuperscript{18}F) vs \textsuperscript{68}Ga-PSMA, suggesting relative benefits in different settings.\textsuperscript{29,30} \textsuperscript{68}Ga-PSMA is now FDA approved for use at limited academic medical centers. Both \textsuperscript{68}Ga-based and fluorinated PSMA radiotracers will likely be commercially available in the near future and will assume a prominent role in the imaging of prostate cancer. A formal trial is currently underway at our institution - the EMPIRE-2 study (NIH R01 CA226992, ClinicalTrials.gov registration: NCT03762759), which is fundamentally similar to the current investigation in using failure-free survival as a primary endpoint, but now randomizes to fluciclovine (\textsuperscript{18}F) or PSMA, and allows for dose-escalation to regions of PET uptake (which was not permitted in the present study).

The modern management of post-prostatectomy failures with radiotherapy continues to improve. Advances in systemic therapy are being studied in this setting in several randomized studies, including the ongoing NRG Oncology GU 002 (docetaxel), GU 006 (apalutamide), GU 008 (abiraterone + apalutimide), and RTOG 3506 (enzalutamide) trials. In addition, there is great interest to use genomic classifiers to guide treatment. The current study shows that, complementary to efforts in these other areas, integration of novel PET radiotracers into radiotherapy decisions and planning is clinically impactful and warrants further study.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgements**

We wish to thank the following individuals at Emory University for their support and assistance:

Walter J. Curran, MD, Mark McDonald, MD, and Sherrie Cooper, BA, and the entire radiation oncology clinical trials team.

Bridget Fielder, RN, MSN; Fenton G. Ingram, RT(R), CNMT, PET, and the entire imaging team; Ronald J. Crowe, RPh, BCNP, and the entire cyclotron and synthesis team from Emory University Center for Systems Imaging.

Martin Sanda, MD, Mehrdad Alemozaffar, MD, and the entire urology clinical enterprise and clinical trials team.

Also, research reported in this publication was supported in part by the Biostatistics Shared Resource of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We thank all participating patients.

**References**


167 patients without systemic or skeletal metastasis (as detected by bone scan, CT, or MRI) assessed for eligibility

2 not meeting inclusion criteria excluded

165 patients enrolled and randomly assigned

82 allocated to conventional imaging group

1 withdrew from study

81 had radiotherapy planning using bone scan and either CT or MRI imaging

81 received radiotherapy

66 followed up
15 lost to follow-up
13 non-compliant
1 moved
1 had insurance problem

81 included in intention-to-treat and modified intention-to-treat analyses

79 had ¹⁸F-fluciclovine-PET/CT scanning to guide treatment decision and radiotherapy planning
1 had no PET scanning due to technical issues

4 with extrapelvic or skeletal uptake on ¹⁸F-fluciclovine-PET/CT not appropriate for radiotherapy, not followed up further

76 received radiotherapy

67 followed up
9 lost to follow-up
4 non-compliant
3 moved
2 had insurance problem

76 included in modified intention-to-treat analysis

3 withdrew from study

83 allocated to ¹⁸F-fluciclovine-PET/CT group

80 included in intention-to-treat analysis

Jani et al. Lancet. Author manuscript; available in PMC 2022 May 22.
Figure 2.

The 3-year failure-free survival rate for Arm 1 vs Arm 2, the primary endpoint of the study, was 63.0 vs 75.5% (difference, 12.5; 95% CI: 4.3–20.8; p=0.0028). A difference in failure-free survival between Arms 1 and 2 was also seen at 4 years, where it was found to be 51.2 vs 75.5% (difference, 24.3; 95% CI, 15.6–33.0; p<0.0001). Overall logrank p-value shown as well.
**Table 1.**

Baseline characteristics of the intention-to-treat population.

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 (no PET) [n=82]</th>
<th>Arm 2 (PET) [n=83]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 (12)</td>
<td>61 (11)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race, White</td>
<td>N=52 (63·4%)</td>
<td>N=52 (62·6%)</td>
</tr>
<tr>
<td>Race, AA/other</td>
<td>N=30 (36·6%)</td>
<td>N=31 (37·4%)</td>
</tr>
<tr>
<td>Pre-XRT PSA – ng/mL</td>
<td>0·34 (0.82)</td>
<td>0·34 (0.92)</td>
</tr>
<tr>
<td>Extracapsular Extension</td>
<td>N=43 (52·4%)</td>
<td>N=39 (47·0%)</td>
</tr>
<tr>
<td>Seminal Vesicle Invasion</td>
<td>N=22 (26·8%)</td>
<td>N=24 (28·9%)</td>
</tr>
<tr>
<td>Margin Positive</td>
<td>N=41 (50·0%)</td>
<td>N=37 (44·6%)</td>
</tr>
<tr>
<td>Node Positive</td>
<td>N=14 (17·1%)</td>
<td>N=16 (19·3%)</td>
</tr>
<tr>
<td>Gleason Score ≥8</td>
<td>N=29 (35·4%)</td>
<td>N=23 (27·7%)</td>
</tr>
<tr>
<td>Androgen Deprivation Therapy (ADT) use (total)</td>
<td>N=28 (34·6%)</td>
<td>N=30 (38·0%)</td>
</tr>
<tr>
<td>Long-term (18–24 months) use</td>
<td>N=8 (9·8%)</td>
<td>N=9 (10·8%)</td>
</tr>
</tbody>
</table>
Table 2.
Univariate analysis. Results obtained using the Cox proportional hazards model.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Hazard Ratio (95% CI)</th>
<th>Logrank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>157</td>
<td>0.99 (0.94–1.03)</td>
<td>0.473</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA/Other</td>
<td>57</td>
<td>0.56 (0.28–1.15)</td>
<td>0.109</td>
</tr>
<tr>
<td><strong>PSA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1.0 ng/mL</td>
<td>39</td>
<td>3.18 (1.73–5.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;1.0 ng/mL</td>
<td>118</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extra-capsular extension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>81</td>
<td>0.44 (0.23–0.83)</td>
<td>0.009</td>
</tr>
<tr>
<td>Yes</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SV Invasion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>114</td>
<td>0.49 (0.27–0.91)</td>
<td>0.022</td>
</tr>
<tr>
<td>Yes</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Margin positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>84</td>
<td>0.69 (0.38–1.27)</td>
<td>0.228</td>
</tr>
<tr>
<td>Yes</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Node positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>130</td>
<td>0.73 (0.34–1.57)</td>
<td>0.419</td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gleason Score ≥8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47</td>
<td>2.15 (1.17–3.96)</td>
<td>0.012</td>
</tr>
<tr>
<td>No</td>
<td>110</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Androgen Deprivation Therapy (ADT) use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>55</td>
<td>1.61 (0.87–2.97)</td>
<td>0.124</td>
</tr>
<tr>
<td>No</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate Bed+Pelvis</td>
<td>60</td>
<td>2.77 (1.50–5.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prostate Bed Alone</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 [Conv. Imaging (CT) alone]</td>
<td>81</td>
<td>1.85 (0.98–3.47)</td>
<td>0.0540</td>
</tr>
<tr>
<td>2 [CI+Fluciclovine (18F) PET]</td>
<td>76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.
Multivariable analysis. Note that all covariates with p < 0.10 on univariate analysis (Table 3) were included. Results were obtained using the Cox proportional hazards model.

<table>
<thead>
<tr>
<th>Level</th>
<th>Hazard Ratio (HR) (95% CI)</th>
<th>HR p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1.0 ng/mL vs &lt; 1.0 ng/mL</td>
<td>3.49 (1.76–6.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Extra-capsular extension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs Yes</td>
<td>0.45 (0.21–0.95)</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>SV Invasion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs Yes</td>
<td>0.82 (0.40–1.68)</td>
<td>0.595</td>
</tr>
<tr>
<td><strong>Gleason Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 8 vs &lt; 8</td>
<td>0.98 (0.49–1.98)</td>
<td>0.955</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate Bed+Pelvis vs Prostate Bed Alone</td>
<td>2.09 (1.07–4.08)</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>Field</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 [Conv. imaging (CI) alone] vs 2 [CI + Fluciclovine (18F) PET]</td>
<td>2.04 (1.06–3.93)</td>
<td>0.0327</td>
</tr>
</tbody>
</table>