Impact of Fluciclovine ($^{18}$F) Positron Emission Tomography on Target Volume Definition for Post-Prostatectomy Salvage Radiotherapy: Initial Findings from a Randomized Trial

Short Running Title: Fluciclovine ($^{18}$F) PET-CT for XRT Target

Ashesh B. Jani, M.D., M.S.E.E., Eduard Schreibmann Ph.D., Peter J. Rossi, M.D., Joseph Shelton, M.D., Karen Godette, M.D., Peter Nieh, M.D., Viraj A. Master, M.D., Ph.D., Omer Kucuk, M.D., Mark Goodman, Ph.D., Raghuveer Halkar, M.D., Sherrie Cooper, B.A., Zhengjia Chen, Ph.D., and David M. Schuster, M.D.

1. Winship Cancer Center of Emory University, Department of Radiation Oncology, Atlanta, USA
2. Department of Urology, Emory University, Atlanta, USA
3. Department of Hematology/Oncology, Emory University, Atlanta, USA
4. Dept. of Radiology & Imaging Sciences, Division of Nuclear Medicine & Molecular Imaging, Emory University, Atlanta, USA
5. Department of Biostatistics and Bioinformatics, Emory University, Atlanta, USA

Corresponding Author:
Ashesh B. Jani, MD, MSEE
Professor, Department of Radiation Oncology, Emory University
1365 Clifton Road, NE, Ste A 1300, Atlanta, GA 30322
Tel: 404-778-3827; Fax: 404-778-4139; Email: abjani@emory.edu

Word Count: 4999; Number of Figures: 4; Number of Tables: 3

This research was sponsored by the National Institutes of Health (R01 CA169188 – PI’s Dr. Ashesh Jani & Dr. David Schuster) and Blue Earth Diagnostics Ltd.
ABSTRACT

The purpose was to evaluate the role of the synthetic amino acid positron emission tomography (PET) radiotracer fluciclovine (18F) in modifying the clinical and planning target volume (CTV and PTV) definition in post-prostatectomy patients undergoing salvage radiotherapy and to evaluate the resulting dosimetric consequences to surrounding organs at risk.

Methods:

96 patients were enrolled in a randomized prospective intention to treat clinical trial for potential salvage radiotherapy for recurrent prostate cancer after prostatectomy. All patients underwent initial treatment planning based on results from conventional abdominopelvic imaging (computed tomography [CT] or magnetic resonance imaging). Patients in the experimental arm (n=45) underwent planning modification after additionally undergoing abdominopelvic fluciclovine (18F) PET/CT. For each patient, the target volume (CTV {prostate bed} [or CTV1 {pelvis}/CTV2 {prostate bed}] and PTV [or PTV1/PTV2]) that would have been treated prior to fluciclovine (18F) registration (PRE) was compared to that after registration (POST). The V40Gy and V65Gy of the organs at risk (Rectum, Bladder [minus CTV], and Penile Bulb) PRE and POST were compared. Statistical comparisons were made using the paired t-test.

Results:

Radiotherapy was planned either to the prostate fossa alone (CTV) [64.8-66.6 Gy] [n=24] or pelvis (CTV1) [45.0 Gy] followed by prostate fossa boost (CTV2) [19.8-25.2 Gy] [n=21]. In each case, the corresponding PTV expansion was 0.8 cm (0.6 cm posterior). For CTV, CTV1, CTV2, PTV, and PTV1, POST volumes were all significantly larger than the corresponding PRE volumes (only PTV2 PRE vs POST volumes were not significantly different). Analysis of Rectum, Bladder [minus CTV], and Penile...
Bulb V40Gy and V60Gy PRE vs POST demonstrated that only Penile Bulb endpoints were significantly higher after registration. No significant differences in acute GU or GI toxicity were observed.

Conclusions:

Inclusion of fluciclovine (^{18}F) PET information into the treatment planning process leads to significant differences in target definition with higher doses to the penile bulb but with no significant differences in bladder or rectal dose or acute GU/GI toxicity. Longer follow-up is needed to determine the impact of fluciclovine (^{18}F) on cancer control and late toxicity endpoints.

Keywords: molecular imaging, positron emission tomography, fluciclovine, radiotherapy, prostatectomy.
INTRODUCTION

Radical retropubic prostatectomy and radiotherapy (RT) are the two main curative options for localized prostate cancer (1,2). Failure can occur after surgery, and post-prostatectomy radiotherapy can be administered either as adjuvant or as salvage treatment (3-6). Salvage radiotherapy has been used with success, with factors such as pre-treatment prostate-specific antigen (PSA), Gleason Score, seminal vesicle invasion, PSA doubling time determining rate of success of outcome (7).

The design of the post-prostatectomy clinical target volume (CTV) poses clinical challenges; RTOG consensus guidelines have been published for definition of the prostate bed (8). However, treatment failures still occur and more advanced imaging is needed to guide treatment planning. The yield of conventional CT is often too low to identify areas of high risk. A bone scan is useful for excluding skeletal disease but generally cannot be used to assist in designing the prostate bed target volume (9). Though MR has a higher yield than CT and is useful for identifying the vesico-urethral anastomosis and penile bulb for treatment planning, the yield of MR in identifying the source of the PSA is still low (10). Thus, better imaging tools are needed for CTV definition. Radioimmunoscintigraphy was explored as one such tool but did not translate to observed clinical benefit due in part to low sensitivity, specificity, and resolution (11-15).

Molecular imaging is increasingly under development for use in metastatic, locally advanced, localized, and post-prostatectomy prostate cancer. Investigational classes of radiotracers include fatty acid analogs (acetate), cell membrane analogs (choline), amino acid analogs (fluciclovine), and newer generation PSMA ligands (16-21). In this context, fluciclovine (18F) (anti-1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid or FACBC), which is transported in a manner similar to glutamine, has been found to have promising imaging characteristics for the detection of prostate cancer recurrence. Fluciclovine (18F) has been explored in a randomized trial in comparison with radioimmunoscintigraphy, with fluciclovine (18F) showing significantly higher accuracy (22,23).
In this analysis from a randomized prospective intention to treat clinical trial, we set out to determine if incorporating fluciclovine ($^{18}$F) PET/CT in radiotherapy planning significantly changes target volumes for salvage therapy post prostatectomy in patients with PSA failure compared with intended radiotherapy planning based on conventional imaging, and to investigate the impact of this modification on surrounding normal structures and acute toxicity. Our hypotheses were that (a) inclusion of fluciclovine ($^{18}$F) results in significant modification of target volumes and (b) this modification will not result in increased acute toxicity compared to controls without this modification.

**MATERIALS AND METHODS**

**Trial Design**

At our institution, we have an ongoing National Institutes of Health-funded randomized trial (NCT 01666808) evaluating the use of fluciclovine ($^{18}$F) in the post-prostatectomy setting - the schema of this trial is shown in Figure 1. The study was approved by the institution review board and all subjects signed an informed consent form.

Eligible patients were those with detectable PSA after prostatectomy, no prior pelvic radiotherapy, and negative bone scan and CT or magnetic resonance imaging of abdomen/pelvis showing no extra-pelvic disease. Patients were stratified by 3 factors {(a) pre-radiotherapy PSA, (b) adverse pathological features [any of: margins positive, seminal vesical invasion, extracapsular extension, or positive nodes], and (c) androgen deprivation therapy intent}, and then randomized 1:1 (using pre-populated worksheets generated using random numbers) to receive treatment planning using only standard imaging (arm A), or standard imaging plus fluciclovine ($^{18}$F) scan (arm B). Both providers and subjects were blinded to the randomization until the study coordinator conveyed the randomized arm, at which point all parties were aware of the study arm.
Subjects on both arm had toxicity assessments weekly during radiotherapy. Patients are assessed for toxicity (including both provider and patient-reported outcomes) and disease control at 1, 6, 12, 18, 24, 30, and 36 months; the primary endpoint of the study is 3 year disease-free survival (with failure defined as serum PSA value of 0.2ng/mL or more above the post-radiotherapy nadir followed by another higher value, a continued rise in the serum PSA despite radiotherapy, initiation of systemic therapy after completion of radiotherapy, or clinical progression). The study accrual goal is 162 (assuming 10% dropout rate, the study is powered to detect a 20% difference in disease-free survival between the 2 arms at 3 years).

The current analysis represents a planned analysis of secondary endpoints: (1) volumetric and dosimetric differences [between pre- and post-fluciclovine (\(^{18}\text{F}\)) treatment plans] and (2) acute toxicity differences collected thus far on this trial.

**Fluciclovine Production and Imaging**

The production of fluciclovine (\(^{18}\text{F}\)) under Investigational New Drug Application 72,437 was completed via the GE FastLab Cassette System or via automated synthesis (21). Patients were imaged on a GE Discovery MV690 PET-CT scanner after at least 4 hours of fasting to normalize amino acid levels. An initial abdominopelvic CT scan was conducted with administration of oral contrast only at 80-120 mA and 120 kVp. Following this, fluciclovine (371.6 +/- 12.4 MBq) was injected intravenously over 2 minutes, with a 3-minute blood pool clearance window after which 5-15.5 minute and 16-27.5 minute acquisitions extending from the pelvis to the diaphragm were acquired. Data was then transferred to a MIMVista workstation (MIM Software; Cleveland, OH) for analysis.

**Fluciclovine Positivity Criteria**

As previously reported, positivity criteria on fluciclovine PET included persistent nonphysiologic moderate (greater than marrow) focal uptake in prostate bed, lymph nodes or bone (22,23).
Radiotherapy Simulation/Planning

For each patient, a planning CT scan (Somatom Definition AS, Siemens Medical Solutions USA, Malvern, PA) was obtained at the time of simulation. The planning CT scan was obtained without intravenous or oral contrast, scanning from the top of the L2 vertebral body (top border) to below the ischial tuberosities (lower border) using 5-mm spacing. Treatment planning MR (using 3-Tesla, T2 weighted pulse sequence) was done for all patients, and prostate bed volumes were defined using RTOG consensus definition. For patients receiving nodal treatment the RTOG pelvic atlas was used to define the nodal volume (24). At the time of simulation, outlining of the bladder, rectum, penile bulb, and femoral heads was performed on each patient in a manner that adhered to RTOG studies (8,24,25). In particular, the (filled) bladder was outlined from apex to dome, and the rectum was outlined from the level of the ischial tuberosities to the rectosigmoid junction.

Fluciclovine-Incorporated Treatment Planning

Axial, sagittal, and coronal images for a representative patient who underwent a fluciclovine (18F) scan and had iso-SUV’s transferred to the treatment planning CT after image registration are displayed in Figure 2. Rigid and deformable registrations were done to bring the regions of fluciclovine (18F) uptake (CTV_{PET}) into the treatment planning CT (26,27). Registrations were done using Velocity AI (Varian Medical Systems, Palo Alto, CA), and radiotherapy treatment planning was done using Eclipse (also Varian). In each case the clinically relevant CTV_{PET} iso-SUV level, as determined by the nuclear medicine physician and radiation oncologist, was used for guidance with treatment planning.

Patients on the arm receiving fluciclovine (18F) had their final radiotherapy treatment decisions determined by the fluciclovine (18F) uptake. Specifically there were one of four scenarios: (1) extrapelvic uptake: no radiotherapy, (2) pelvic uptake or pathological node positivity: radiotherapy to
prostate bed + pelvic lymph nodes, (3) prostate-bed only uptake: radiotherapy to prostate bed only, and (4) no uptake: radiotherapy to prostate bed only.

The process of integrating fluciclovine (^{18}F) PET into the planning process to define the final volumes is displayed in Figure 3. CTV_{POST} (the CTV ultimately used for treatment planning) was defined to be the union of CTV_{PRE} (the CTV defined using standard contouring guidelines [i.e., defined in the absence of fluciclovine (^{18}F) information]) and the added information provided from PET. Though Figure 3 shows prostate bed portion, the same principle applies when pelvic nodes were treated (in which case CTV1=prostate bed plus pelvic lymph nodes and CTV2= prostate bed), so that if nodes were treated, CTV1_{POST} = (CTV1_{PRE} plus PET data), and CTV2_{POST} = (CTV2_{PRE} plus PET data).

CTV_{PRE} was uniformly expanded by 0.8 cm (0.6 cm posterior) to define PTV_{PRE}, and CTV_{POST} was uniformly expanded by 0.8 cm (0.6 cm posterior) [which accounts for a 2-3 mm deformable registration uncertainty as well as setup uncertainty] to define PTV_{POST} (and similarly for CTV1_{PRE} and CTV2_{PRE} if lymph nodes were treated) (26,27). PTV_{POST} prescription dose was 64.8-70.2 Gy. For cases where pelvic LN’s were treated, PTV1_{POST} prescription dose was 45.0-50.4 Gy, and PTV2_{POST} prescription dose was 64.8-70.2 Gy. All patients were treated using volumetric modulated radiotherapy using inhomogeneity and normal tissue constraints defined on RTOG 0534 (28).

Comparison of Baseline and Post-fluciclovine Treatment Plans

For each patient, the absolute volume of CTV_{PRE} was compared with that of the corresponding CTV_{POST}. Note that the PRE volume for comparison in each case was chosen to be analogous to the POST volume (i.e., if the POST plan involved nodal treatment, it was compared to a PRE plan that involved nodal treatment, not prostate bed alone). Although the change in absolute volume served as a measure of the impact of fluciclovine (^{18}F) on the design of the CTV, it did not take into account the shape or location of the CTV. To address this issue, the radiotherapy treatment plans generated using
CTV_{PRE} were compared with those generated using CTV_{POST} to quantitate the dosimetric effects of these CTV differences on the bladder, rectum, and penile bulb dose volume histograms. As mentioned previously, CTV_{POST} (or alternatively CTV1_{POST}/CTV2_{POST}) was what was ultimately used for patient treatment. Dice similarity index, maximum surface distance, and vector (direction and magnitude) of volume centroid were also computed for each target comparison.

Descriptive statistics were used to summarize the patient, imaging, and treatment characteristics. Pre- and post-volumes for all targets (CTV & PTV, CTV1 & PTV1, CTV2 & PTV2) were tabulated. The two-tailed paired t-test was employed to compare the target volumes between PRE and POST (29).

**Organs at Risk (OAR)-related Analysis**

Dosimetric endpoints (V40Gy and V65Gy) for the Rectum, Bladder (minus CTV), and Penile bulb were tabulated. The two-tailed paired t-test was employed to compare the V40Gy and V65Gy of the organs at risk between PRE and POST (29).

**Toxicity Assessment/Analysis**

Chi-square tests were conducted to compare the RTOG maximum acute (with window defined from enrollment into the study through radiotherapy completion) GU and GI toxicity between those who had completed radiotherapy in the control group (Arm A) and experimental group (Arm B), respectively (29).

The significance level was set at 0.05 for all tests.
RESULTS

Trial Design Accrual

Table 1 shows the patient characteristics of the first 96 subjects enrolled on this trial (47 on arm A and 49 on arm B). Also displayed in Table 1 are the treatment techniques, general fields, and final dose used for patients who have undergone treatment. [One patient on arm A withdrew from the study, as did one subject on arm B. Furthermore, 2 subjects in arm B had extra-pelvic uptake and had their decision to undergo radiotherapy aborted. This leaves 46 treated patients in each arm]. For arm B patients, Table 1 also displays the general areas of fluciclovine (\(^{18}\text{F}\)) uptake. The volumetric analyses of these subjects were done for arm B patients only (46 patients on arm B minus 1 patient [subject #1, for whom there were technical difficulties in obtaining the fluciclovine (\(^{18}\text{F}\)) scan]). These subjects had their treatment plans designed first in the absence of fluciclovine (\(^{18}\text{F}\)) information, then the fluciclovine (\(^{18}\text{F}\)) information was integrated to define final volumes, permitting accurate and unbiased assessment of the role of fluciclovine (\(^{18}\text{F}\)).

Comparison of Baseline and Post-fluciclovine Treatment Plans

Table 2 displays the results of the volumetric analysis comparing \(\text{CTV}_{\text{PRE}}\) (the CTV designed without knowledge of the fluciclovine (\(^{18}\text{F}\)) findings) with \(\text{CTV}_{\text{POST}}\) (the prostate bed CTV designed after the fluciclovine (\(^{18}\text{F}\)) registration). As shown, for all targets, POST volumes were significantly larger than their corresponding PRE volumes. Furthermore, while Dice similarity index was close to unity, maximum surface distances averaged 5mm-15mm, and the vector of volume centroid comparison demonstrated ~3mm shift, with the greatest component of the shift in the cranio-caudal(z) direction. Figure 4 demonstrates a waterfall plot of the maximum surface distance for each patient and target, and demonstrates that in over a third of patients the maximum surface distance was substantial (> 10mm).

Organs at Risk (OAR)-related Analysis
Table 2 also displays the OAR dosimetric analyses. As displayed, PRE vs POST dose volume histogram endpoints (V40 and V65) for bladder and rectum were not significantly different, but were significantly different for penile bulb.

Toxicity Assessment/Analysis

Table 3 shows the observed treatment toxicity, using RTOG acute toxicity grading criteria. The most common GI toxicity was loose bowel movements / diarrhea, and the most common GU toxicity was urinary frequency. Note that a patient could belong to more than a single category (i.e., acute GI and acute GU toxicity could develop in the same patient). As shown, acute toxicity results were not significantly different between arms A and B. Furthermore, no acute grade 3, 4, or 5 (GI or GU) toxicity was observed in the fluciclovine (18F) arm B.
DISCUSSION

The main hypothesis of this investigation, which is a planned analysis of secondary endpoints of an ongoing randomized controlled trial, was that the addition of fluciclovine ($^{18}$F) to conventional imaging in the post-prostatectomy setting would influence target volume design, and further that these target volume changes would not result in detrimental effect on dose received by organs at risk and translate to increased toxicity. In general, our results support this hypothesis.

Our analysis suggests that incorporating fluciclovine ($^{18}$F) uptake results in significant modification in the volume of the post-prostatectomy CTV, with the incorporation of the fluciclovine ($^{18}$F) uptake in the majority of cases causing the volume of CTV$_{POST}$ to be larger on average than that of the corresponding CTV$_{PRE}$. This suggests that projecting the fluciclovine ($^{18}$F) findings into the planning CT scan was feasible and may serve as a tool (in addition to prostatectomy pathologic findings and planning CT) to assist in defining the prostate bed CTV. Of note, as the prostate bed (CTV and CTV2) and pelvis (CTV1) were all significantly different (PRE vs POST), it can be inferred that fluciclovine ($^{18}$F) significantly affected target design in both of these settings (i.e., whether lymph nodes were being treated or not). Although concerns may arise about whether treatment to these larger volumes would result in additional toxicity, the dosimetric consequences of the CTV modifications on the rectum and bladder did not reach significance. Additionally, no grade 4 or 5 (acute GI or GU) toxicities were seen in either arm, and only one grade 3 event (which was in the control arm) was seen, suggesting that treatment to the modified CTV was tolerable. Furthermore, comparison of overall acute toxicity showed no differences between the control and experimental arms.

Our findings are important as we have demonstrated a potential role for integration of molecular imaging to guide post-prostatectomy radiotherapy, an area where conventional imaging has a demonstrated low yield in identification of the anatomic location(s) of the source of detectable PSA. The role of fluciclovine ($^{18}$F) in the diagnostic setting has been documented, particularly with respect to the
higher diagnostic accuracy of fluciclovine ($^{18}$F) over radioimmunoscintigraphy (22). The current report extends prior work in molecular imaging in general, and fluciclovine ($^{18}$F) in specific, in a different direction to the use of fluciclovine ($^{18}$F) in guiding post-prostatectomy CTV definition. The current analysis suggests that fluciclovine ($^{18}$F) may provide information complementary to that provided using standard methods for the task of CTV definition.

Our results are consistent with other studies exploring the role of molecular imaging in prostate cancer (30-32). Specifically, earlier work did demonstrate the role of radioimmunoscintigraphy in influencing target volume design without increase in toxicity in the retrospective setting (13-15). Other recent work has demonstrated a potential role for $^{11}$C-Choline PET/CT in guiding target volume delineation in the prostate fossa and also for extension of targets outside of the prostate bed, affecting the extent of the planning target volume (30,31). Furthermore, recent work has shown encouraging results with $^{68}$Ga-labeled PSMA in identification of the source of the PSA, particularly in the recurrent prostate cancer setting (32). However, it should be noted that our study is the only report to date evaluating the impact of molecular imaging on target design in the prospective randomized controlled trial setting.

There are several limitations to our study. First, as mentioned above, the current report represents a planned analysis of secondary endpoints for the first 96 subjects on this trial [accrual goal is 162]), thus the sample size does not represent the full cohort; nonetheless, significant differences in target volume have demonstrated using patients enrolled thus far. Second, there is some variability in the iso-SUV level selected for registration, and consequently there is some operator dependence on the volume of CTV$_{PET}$; however in this particular study the same team of nuclear medicine physicians and radiation oncologists were involved in the selection of the clinically relevant iso-SUV level, so within the context of the clinical trial the operator dependence is likely to be small. Third, in our protocol CTV$_{POST}$ was
defined to be the union of CTV$_{\text{PRE}}$ and CTV$_{\text{PET}}$, so the CTV$_{\text{POST}}$ volumes could not by definition be any smaller than the original CTV$_{\text{PRE}}$ volumes. In future versions of the protocol we may be able to define CTV$_{\text{POST}}$ closer to CTV$_{\text{PET}}$, particularly if cancer control endpoints when available suggest a benefit to the incorporation of CTV$_{\text{PET}}$ into the treatment planning process. Fourth, with current follow-up on the study we are only able to report the acute toxicity endpoints, not late toxicity endpoints (particularly erectile function [despite the impact of modified treatment volumes on the penile bulb], as this was captured only at baseline and at follow-up, not during treatment) or the primary 3-year disease free survival endpoint. In a similar vein, the acute toxicity consists only of provider-reported outcomes. In a future report, after the study reaches its accrual goal and we have the necessary follow-up, we plan to report late toxicity (both patient- and provider-reported outcomes) and disease free survival comparisons. By design, analysis of disease free survival can only be addressed at study closure.

Within these limitations, however, the current investigation does provide preliminary data on the clinical use of molecular imaging (in this case fluciclovine($^{18}$F) PET/CT) in the setting of guiding post-prostatectomy CTV definition. It is hoped that the current communication can provide an initial framework on which molecular imaging can be tested and used to additionally guide radiotherapy target definition over existing consensus contouring guidelines.
CONCLUSIONS

In this planned analysis of secondary endpoints on an ongoing randomized trial, inclusion of fluciclovine (18F) information into the treatment planning process leads to significant differences in target definition with higher doses to the penile bulb but with no significant differences in bladder or rectal dose or acute GU/GI toxicity. Longer follow-up is needed to determine the incorporation of fluciclovine (18F) PET on cancer control and late toxicity endpoints.
DISCLOSURE / ACKNOWLEDGEMENTS

This research was sponsored by the NIH (R01 CA169188 – PI’s Dr. Ashesh Jani & Dr. David Schuster) and Blue Earth Diagnostics Ltd. Emory University and Dr. Mark Goodman are eligible for royalties.

The work was communicated as a Podium Presentation at the American Society of Radiation Oncology (ASTRO) Annual Meeting, San Antonio, TX, October 2015.
REFERENCES


tomography and (111)In-capromab pendetide single photon emission computerized tomography-computerized
24. Lawton CA, Michalski J, El-Naqa I, et al. RTOG GU Radiation oncology specialists reach consensus on
26. Liu F, Ahunbay E, Lawton C, Li XA. Assessment and management of interfractional variations in daily
28. Radiation Therapy Oncology Group (RTOG). A Phase III Trial of Short-Term Androgen Deprivation with
Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPORT) in Prostate Cancer with Rising PSA. After
30. Schwarzenböck SM, Kurth J, Gocke CH, et al. Role of choline PET/CT in guiding target volume delineation
32. Rai BP, Baum RP, Patel A, et al. The role of positron emission tomography with 68gallium(Ga)-labeled
prostate-specific membrane antigen (PSMA) in the management of patients with organ-confined and locally
advanced prostate cancer prior to radical treatment and after radical prostatectomy. *Urology.* 2016 (Epub ahead of
print).
**FIGURE LEGENDS**

**Patient consent/enrollment/eligibility:**
- Adenocarcinoma after radical retropubic prostatectomy
- Detectable PSA
- Negative bone-scan results
- Abdominal/pelvic CT or MRI showing no extrapelvic metastases
- Radiotherapy-decision attestation form completed by provider

**Stratification:**
- Presence of at least one pathologic risk factor (extracapsular extension, seminal vesicle invasion, positive margins, or positive nodes) vs. none
- Preradiotherapy PSA level ≤ 2.0 ng/mL vs. > 2.0 ng/mL
- Intent to use vs. not to use androgen deprivation therapy

**Randomization**

**Arm A:**
- Radiotherapy planning based on standard imaging

**Arm B:**
- Radiotherapy planning based on standard imaging plus $^{18}$F-fluciclovine scan

**Figure 1.** Schema for randomized trial.
Figure 2. Fluciclovine ($^{18}$F) PET-CT registration with planning CT (axial, coronal, and sagittal views).

After deformable image registration, the clinically relevant Iso-SUV level was selected (to define $\text{CTV}_{\text{PET}}$) and unioned with $\text{CTV}_{\text{PRE}}$ to define $\text{CTV}_{\text{POST}}$. 
Figure 3. Representative example of fluciclovine ($^{18}$F) to define target. CTV$_{\text{POST}}$ (red) = CTV$_{\text{PRE}}$ (yellow) union CTV$_{\text{PET}}$ (pink). Also shown (upper right corner) are the PRE (square) vs POST (triangle) dose volume histograms for PTV1, PTV2, Rectum, Bladder, and Penile bulb, showing minimal impact on target coverage or organs at risk dose with the modified targets.
Figure 4. Waterfall plot of patient number, target volume, and maximum surface distance.
**Table 1.** Patient, Imaging, and Treatment Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Arm A [no PET] (n=47)</th>
<th>Arm B [PET] (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (years)</strong></td>
<td>61.6</td>
<td>62.3</td>
</tr>
<tr>
<td><strong>T-stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2a/b</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>pT3a/b</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td><strong>N-status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0 or pNX</td>
<td>39</td>
<td>43</td>
</tr>
<tr>
<td>pN1</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td><strong>Pre-Treatment PSA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), ng/mL</td>
<td>0.40 (0.06, 27.14)</td>
<td>0.43 (0.02, 11.15)</td>
</tr>
<tr>
<td><strong>Gleason Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>≥ 8</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td><strong>Hormone therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td><strong>FACBC findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapelvic</td>
<td>n/a</td>
<td>2</td>
</tr>
<tr>
<td>Pelvis alone</td>
<td>n/a</td>
<td>5</td>
</tr>
<tr>
<td>Prostate bed alone</td>
<td>n/a</td>
<td>15</td>
</tr>
<tr>
<td>Pelvis + prostate bed</td>
<td>n/a</td>
<td>16</td>
</tr>
<tr>
<td>No uptake</td>
<td>n/a</td>
<td>8</td>
</tr>
<tr>
<td><strong>Radiotherapy fields</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate bed alone</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>Prostate bed + pelvis</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td><strong>Radiotherapy dose, Gy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate bed, mean (range)</td>
<td>67.53 (64.80, 70.20)</td>
<td>67.09 (64.80, 70.20)</td>
</tr>
<tr>
<td>Pelvis, mean (range)</td>
<td>45.00 (45.00, 45.00)</td>
<td>45.00 (45.00, 45.00)</td>
</tr>
</tbody>
</table>
Table 2. Target volumes and Volumes of OAR’s PRE and POST fluciclovine (\(^{18}\)F)PET registration for Arm B patients (n=46). All p values obtained using 2-tailed paired t-test.

<table>
<thead>
<tr>
<th>Target volumes</th>
<th>CTV (cc)</th>
<th>PTV (cc)</th>
<th>CTV1 (cc)</th>
<th>PTV1 (cc)</th>
<th>CTV2 (cc)</th>
<th>PTV2 (cc)</th>
<th>p-value</th>
<th>Dice Similarity Index</th>
<th>Maximum surface distance (range)[mm]</th>
<th>Vector centroid mean difference (x, y, z); overall magnitude [mm]</th>
<th>OAR’s V40 (%)</th>
<th>Rectum-V65 (%)</th>
<th>Bladder-minus-CTV-V40 (%)</th>
<th>Bladder-minus-CTV-V65 (%)</th>
<th>Penile-Bulb V40 (%)</th>
<th>Penile-Bulb V65 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE</td>
<td>137.7 ± 49.0</td>
<td>334.5 ± 79.4</td>
<td>472.8 ± 127.0</td>
<td>1114.8 ± 230.8</td>
<td>129.4 ± 42.9</td>
<td>320.8 ± 77.8</td>
<td>0.034</td>
<td>0.99467 ± 0.01164</td>
<td>6.02 (0, 17.99)</td>
<td>(0.00, 0.00, 1.56); 3.69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POST</td>
<td>139.6 ± 49.6</td>
<td>339.2 ± 81.4</td>
<td>487.2 ± 132.6</td>
<td>1147.2 ± 237.9</td>
<td>131.4 ± 42.4</td>
<td>324.6 ± 75.5</td>
<td>0.009</td>
<td>0.99279 ± 0.01099</td>
<td>5.94 (0, 17.27)</td>
<td>(0.02, -0.05, 2.50); 3.71</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.007</td>
<td>0.002</td>
<td>0.027</td>
<td>0.147</td>
<td></td>
<td></td>
<td></td>
<td>0.98402 ± 0.03041</td>
<td>16.51 (0, 31.33)</td>
<td>(-0.48, 0.22, 0.43); 2.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.98673 ± 0.01588</td>
<td>14.33 (0, 29.23)</td>
<td>(-0.48, 0.35, 0.99); 2.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.99735 ± 0.02878</td>
<td>7.25 (0, 34.44)</td>
<td>(0.25, 0.44, -1.04); 2.73</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.98118 ± 0.03793</td>
<td>6.99 (0, 34.26)</td>
<td>(-0.25, 0.19, 0.69); 2.74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45.8 ± 10.2</td>
<td>17.8 ± 8.1</td>
<td>61.7 ± 19.5</td>
<td>11.7 ± 16.0</td>
<td>44.9 ± 30.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45.9 ± 11.9</td>
<td>18.1 ± 8.1</td>
<td>61.7 ± 18.9</td>
<td>33.8 ± 16.8</td>
<td>55.9 ± 34.4</td>
</tr>
<tr>
<td></td>
<td>0.774</td>
<td>0.548</td>
<td>0.940</td>
<td>0.238</td>
<td>0.001</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

By on October 29, 2017. For personal use only. jnm.snmjournals.org Downloaded from
### Table 3. Toxicity Analysis (p-values obtained using chi-square test)

<table>
<thead>
<tr>
<th>GU</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>6/45 (13%)</td>
<td>30/45 (67%)</td>
<td>8/45 (18%)</td>
<td>1/45 (2%)</td>
<td>0.531</td>
</tr>
<tr>
<td>Arm B</td>
<td>4/44 (9%)</td>
<td>30/44 (68%)</td>
<td>10/44 (22%)</td>
<td>0/44 (0%)</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>Grade 0</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>p-value</td>
</tr>
<tr>
<td>Arm A</td>
<td>12/45 (27%)</td>
<td>27/45 (60%)</td>
<td>6/45 (13%)</td>
<td>0/45 (0%)</td>
<td>0.913</td>
</tr>
<tr>
<td>Arm B</td>
<td>12/44 (27%)</td>
<td>25/44 (57%)</td>
<td>7/44 (16%)</td>
<td>0/44 (0%)</td>
<td></td>
</tr>
</tbody>
</table>
Impact of Fluorine-18 Positron Emission Tomography on Target Volume Definition for Post-Prostatectomy Salvage Radiotherapy: Initial Findings from a Randomized Trial

Ashesh Jani, Eduard Schreibmann, Peter J Rossi, Joseph W Shelton, Karen Godette, Peter Nieh, Viraj A Master, Omer Kucuk, Mark Goodman, Raghuveer Halkar, Sherrie Cooper, Zhengjia Chen and David M Schuster

J Nucl Med.
Published online: September 8, 2016.
Doi: 10.2967/jnumed.116.176057

This article and updated information are available at:
http://jnm.snmjournals.org/content/early/2016/09/07/jnumed.116.176057

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml

JNM ahead of print articles have been peer reviewed and accepted for publication in JNM. They have not been copyedited, nor have they appeared in a print or online issue of the journal. Once the accepted manuscripts appear in the JNM ahead of print area, they will be prepared for print and online publication, which includes copyediting, typesetting, proofreading, and author review. This process may lead to differences between the accepted version of the manuscript and the final, published version.

© Copyright 2016 SNMMI; all rights reserved.