Impact of $^{18}$F-Fluciclovine PET on Target Volume Definition for Postprostatectomy Salvage Radiotherapy: Initial Findings from a Randomized Trial

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The purpose of this study was to evaluate the role of the synthetic amino acid PET radiotracer $^{18}$F-fluciclovine in modifying the defined clinical and treatment-planning target volumes in postprostatectomy patients undergoing salvage radiotherapy and to evaluate the resulting dosimetric consequences to surrounding organs at risk. Methods: Ninety-six patients were enrolled in a randomized, prospective intention-to-treat clinical trial for potential salvage radiotherapy for recurrent prostate cancer after prostatectomy. The initial treatment plan was based on the results from conventional abdominopelvic CT and MRI. The 45 patients in the experimental arm also underwent abdominopelvic $^{18}$F-fluciclovine PET/CT, and the images were registered with the conventional images to determine whether the results would modify the initial treatment plan. The 51 patients in the control arm did not undergo $^{18}$F-fluciclovine PET/CT. For each patient, the clinical and treatment-planning target volumes that would have been treated before $^{18}$F-fluciclovine registration were compared with those after registration. For organs at risk (rectum, bladder, and penile bulb), the volumes receiving 40 Gy and 65 Gy before registration were compared with those after registration. Statistical comparisons were made using the paired t test. Acute genitourinary and gastrointestinal toxicity as defined by the Radiation Therapy Oncology Group was compared between the control and experimental arms using the χ² test. Results: In 24 cases, radiotherapy was planned to a clinical target volume consisting of the prostate bed alone (CTV) (64.8–66.6 Gy). In 21 cases, radiotherapy was planned to a clinical target volume consisting of the pelvis (CTV1) (45.0 Gy) followed by a boost to the prostate bed (CTV2) (19.8–25.2 Gy). In each case, the respective treatment-planning target volume expansion (PTV, PTV1, or PTV2) was 0.8 cm (0.6 cm posterior). With the exception of PTV2, all post-registration volumes were significantly larger than the corresponding preregistration volumes. Analysis of the rectum, bladder, and penile bulb volumes receiving 40 Gy and 60 Gy demonstrated that only the penile bulb volumes were significantly higher after registration. No significant differences in acute genitourinary or gastrointestinal toxicity were observed. Conclusion: Including information from $^{18}$F-fluciclovine PET in the treatment-planning process led to significant differences in the defined target volume, with higher doses to the penile bulb but no significant differences in rectal or bladder dose or in acute genitourinary or gastrointestinal toxicity. Longer follow-up is needed to determine the impact of $^{18}$F-fluciclovine PET on cancer control and late toxicity endpoints.

Key Words: molecular imaging; positron emission tomography; fluciclovine; radiotherapy; prostatectomy


DOI: 10.2967/jnumed.116.176057

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

Defining the postprostatectomy clinical target volume poses clinical challenges. The Radiation Therapy Oncology Group (RTOG) has published consensus guidelines for defining the prostate bed (8), but treatment failure still occurs 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 help define the target volume in the prostate bed (9). Though MR has a higher yield than CT and is useful for identifying the vesicourethral 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 to define the clinical target volume. Radioimmunoscintigraphy was explored as one such tool but did not translate to observed clinical benefit, partly because of low sensitivity, specificity, and resolution (11–15).

Molecular imaging is increasingly under development for use in metastatic, locally advanced, localized, and postprostatectomy prostate cancer. The investigational classes of radiotracers include fatty acid analogs (acetate), cell membrane analogs (choline), amino acid analogs (fluciclovine), and newer-generation prostate-specific membrane antigen ligands (16–21). In this context, $^{18}$F-fluciclovine (anti-1-amino-3-$^{18}$F-fluorocyclobutane-1-carboxylic acid), which is transported in a manner similar to glutamine, has shown promising
imaging characteristics for the detection of prostate cancer recurrence. $^{18}$F-fluciclovine PET/CT has been compared with radioimmunoscintigraphy in a randomized trial and has shown significantly higher accuracy (22,23).

In this randomized, prospective intention-to-treat clinical trial, we set out to determine whether incorporating information from $^{18}$F-fluciclovine PET into treatment planning significantly changes the volumes targeted for salvage therapy in patients with rising levels of PSA after prostatectomy and whether there is an effect on surrounding normal structures and acute toxicity. Our hypotheses were that the target volumes would be significantly modified and that acute toxicity would not increase.

**MATERIALS AND METHODS**

**Trial Design**

At our institution, we are conducting an ongoing National Institutes of Health–funded randomized trial (NCT 01666808) evaluating the use of $^{18}$F-fluciclovine PET/CT in the postprostatectomy setting. Figure 1 shows the schema of this trial. It was approved by the institutional review board, and all patients signed an informed consent form.

Eligible patients are those with detectable PSA after prostatectomy, no prior pelvic radiotherapy, negative bone scans, and abdominal or pelvic CT and MRI showing no extrapelvic disease. The patients are stratified by, first, preradiotherapy PSA; second, adverse pathologic features (i.e., positive margins, seminal vesicle invasion, extracapsular extension, or positive nodes); and third, intention to treat with androgen deprivation. Prepopulated worksheets generated using random numbers are then applied to randomize the patients 1:1 for treatment planned by standard imaging alone or treatment planned by standard imaging plus $^{18}$F-fluciclovine PET/CT. The providers and patients do not know the arm to which they have been assigned until the study coordinator reveals it immediately after randomization.

The patients in both arms are assessed during therapy weekly for toxicity and then at 1, 6, 12, 18, 24, 30, and 36 mo for toxicity (both provider-reported and patient-reported) and disease control. The primary endpoint of the study is 3-y disease-free survival. Failure is defined as a serum PSA value at least 0.2 ng/mL above the postradiotherapy nadir, followed by another higher value, a continued rise in serum PSA despite radiotherapy, initiation of systemic therapy after completion of radiotherapy, or clinical progression. The study accrual goal is 162 patients. Assuming a 10% dropout rate, the study is powered to detect a 20% difference in disease-free survival between the two arms at 3 y.

The current report is a planned analysis of two secondary endpoints: volumetric and dosimetric differences between the treatment plans with and without information from $^{18}$F-fluciclovine PET, and the acute toxicity differences seen thus far.

**$^{18}$F-Fluciclovine Production and Imaging**

The $^{18}$F-fluciclovine is produced under Investigational New Drug Application 72,437 via the FastLab Cassette System (GE Healthcare) or automated synthesis (21). The patients are imaged on a Discovery MV690 PET/CT scanner (GE Healthcare) after fasting for at least 4 h to normalize amino acid levels. An initial abdominalpelvic CT scan (80–120 mA and 120 kVp) is obtained with oral contrast medium. Afterward, $^{18}$F-fluciclovine (371.6 ± 12.4 MBq) is injected intravenously over 2 min, and after a 3-min window to allow the blood pool to clear, acquisitions from the pelvis to the diaphragm are obtained at 5–15.5 min and at 16–27.5 min. Data are then transferred to a MIMVista workstation (MIM Software) for analysis.

**$^{18}$F-Fluciclovine PET Positivity Criteria**

The positivity criteria for $^{18}$F-fluciclovine PET include persistent nonphysiologic moderate (greater than marrow) focal uptake in the prostate bed, lymph nodes, or bone (22,23).

**Treatment Planning (Radiotherapy Simulation)**

For each patient, a treatment-planning CT scan (Somatom Definition AS; Siemens Medical Solutions) is obtained at the time of radiotherapy simulation. The treatment-planning CT scan is obtained without intravenous or oral contrast medium, scanning from the top of the L2 vertebral body to the bottom of the ischial tuberosities using 5-mm spacing. Treatment-planning MR (at 3 tesla, using a T2-weighted pulse sequence) is also done for all patients, and prostate bed volumes are defined according to the RTOG consensus. For patients receiving nodal treatment, the RTOG pelvic atlas is used to define the nodal volume (24). At the time of radiotherapy simulation, the rectum, bladder (minus clinical treatment volume), penile bulb, and femoral heads are outlined for each patient in a manner that adheres with RTOG studies (8,24,25). In particular, the filled bladder is outlined from the apex to the dome, and the rectum is outlined from the ischial tuberosities to the rectosigmoid junction.

The clinical target volume consists of either the prostate bed alone (CTV) or the pelvis (CTV1) followed by a boost to the prostate bed (CTV2). Likewise, the respective treatment-planning target volumes are PTV or PTV1/PTV2.

**Treatment Planning Incorporating $^{18}$F-Fluciclovine PET Information**

Axial, sagittal, and coronal images for a representative patient who underwent an $^{18}$F-fluciclovine PET/CT scan and had iso-SUVs (SUVs using different definitions of volumes of interest with varying isocentours) transferred to the treatment-planning CT scan after image registration are displayed in Figure 2. Rigid registration and deformable registration were done to carry the regions of $^{18}$F-fluciclovine uptake (CTV$_{PET}$) into the treatment-planning CT scan (26,27). Registration was done using Velocity AI (Varian Medical Systems), and treatment planning was done using Eclipse (Varian Medical Systems). In each case, the clinically relevant CTV$_{PET}$ iso-SUV level, as determined by the nuclear medicine physician and radiation oncologist, was used to guide treatment planning.
Patients in the arm undergoing 18F-fluciclovine PET/CT had their final radiotherapy decisions determined by CTV PET. Specifically, there were 4 possible scenarios: extrapelvic uptake (no radiotherapy), pelvic uptake or pathologic node positivity (radiotherapy to pelvis plus prostate bed), prostate bed–only uptake (radiotherapy to prostate bed only), and no uptake (radiotherapy to prostate bed only).

The process of integrating CTV PET into the treatment-planning process to define the final volumes is displayed in Figure 3. CTV POST (the clinical target volume ultimately used for treatment planning) was defined to be the union of CTVPRE (the clinical target volume defined using standard contouring guidelines; i.e., without CTV PET) and CTVPET. Though Figure 3 shows the prostate bed portion (CTV), the same principle applies when the pelvic nodes are treated (CTV1/CTV2), so that if the nodes are treated, CTV1POST = (CTV1PRE plus CTVPET), and CTV2POST = (CTV2PRE plus CTVPET).

CTV PRE is uniformly expanded by 0.8 cm (0.6 cm posterior) to define PTVPRE, and CTV POST is uniformly expanded by 0.8 cm (0.6 cm posterior) to define PTVPRE. The expansion accounts for a 2- to 3-mm deformable registration uncertainty as well as setup uncertainty. Similar expansions are applied to CTV1PRE and CTV2PRE if the lymph nodes are treated (26,27). The PTVPRE prescription dose is 64.8–70.2 Gy. When the pelvic lymph nodes are treated, the PTV1PRE prescription dose is 45.0–50.4 Gy and the PTV2PRE prescription dose is 64.8–70.2 Gy. All patients are treated using volumetric modulated radiotherapy that applies the inhomogeneity and normal-tissue constraints defined in RTOG protocol 0534 (28).

Comparison of Preregistration and Postregistration Treatment Plans
For each patient, the absolute CTVPRE is compared with the corresponding absolute CTV POST. The preregistration volume for comparison in each case is chosen to be analogous to the postregistration volume (i.e., if the postregistration plan involves nodal treatment, it is compared with a preregistration plan that involves nodal treatment, not treatment to the prostate bed alone). Although the change in absolute volume serves as a measure of the impact of 18F-fluciclovine PET on definition of the clinical target volume, it does not take into account the shape or location of the clinical target volume. To address this issue, the treatment plans generated using CTVPRE were compared with those generated using CTV POST to quantitate the dosimetric effects of differences between the two on the rectum, bladder, and penile bulb dose–volume histograms. CTV POST (or, alternatively, CTV1POST/CTV2POST) was what was ultimately used for patient treatment. Dice similarity index, maximum surface distance, and the vector (direction and magnitude) of the volume centroid were also computed for each target comparison.

Descriptive statistics were used to summarize the patient, imaging, and treatment characteristics. Pre- and postregistration volumes for all targets (CTV and PTV, CTV1 and PTV1, CTV2 and PTV2) were tabulated. The 2-tailed paired t test was used to compare these volumes before and after registration (29).

Organs-at-Risk Analysis
Dosimetric endpoints (the volumes receiving 40 Gy and 65 Gy) for the rectum, bladder, and penile bulb were tabulated. The 2-tailed paired t test was used to compare the target volumes before and after registration (29).

Toxicity Analysis
χ² tests were used to compare maximum RTOG acute genitourinary and gastrointestinal toxicity between the control and experimental arms (29). The window for maximum toxicity was defined as the period from enrollment into
results

accrued patients

Table 1 shows the characteristics of the first 96 patients enrolled in this trial (47 in the control arm and 49 in the experimental arm). Also displayed in Table 1 are the treatment techniques, general fields, and final dose used for patients who have undergone treatment. One patient each in the control and experimental arms withdrew from the study, and radiotherapy was aborted in two patients in the experimental arm who had extrapelvic uptake, leaving 46 treated patients in each arm. For patients in the experimental arm, Table 1 also displays the general areas of 18F-fluciclovine uptake; volumetric analysis was done for these patients only (the 46 patients in the experimental arm, with the exception of one patient for whom there were technical difficulties in obtaining the 18F-fluciclovine scan). These patients had their treatment plans designed first in the absence of 18F-fluciclovine PET information and then with integration of the 18F-fluciclovine PET information to define final volumes, permitting accurate and unbiased assessment of the role of 18F-fluciclovine PET.

Comparison of preregistration and postregistration treatment plans

Table 2 displays the results of the volumetric analysis comparing CTVPRE with CTVPOST. For all targets, postregistration volumes were significantly larger than their corresponding preregistration volumes. Furthermore, whereas the Dice similarity index was close to unity, the maximum surface distance averaged 5–15 mm and the vector-of-volume-centroid comparison demonstrated an approximately 3-mm shift, with the greatest component of the shift being in the craniocaudal (z) direction. Figure 4, a waterfall plot of the maximum surface distance for each patient and target, demonstrates that in more than a third of patients the maximum surface distance was substantial (>10 mm).

organs-at-risk analysis

Table 2 also displays the organs-at-risk dosimetric analysis. The pre- and postregistration dose–volume histogram endpoints (the volumes receiving 40 Gy and 65 Gy) did not significantly differ.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control arm (n = 47)</th>
<th>Experimental arm (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (y)</td>
<td>61.6</td>
<td>62.3</td>
</tr>
<tr>
<td>Tumor stage</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>Node status</td>
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<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>Median pretreatment PSA level (ng/mL)</td>
<td>0.40 (0.06–27.14) to 0.43 (0.02–11.15)</td>
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<tr>
<td>Gleason score</td>
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<td></td>
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<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>
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<td>Hormone therapy</td>
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<td>19</td>
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<tr>
<td>No</td>
<td>31</td>
<td>30</td>
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<td>18F-fluciclovine findings</td>
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<td>Extrapelvic</td>
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</tr>
<tr>
<td>Pelvis alone</td>
<td>—</td>
<td>5</td>
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<td>Prostate bed alone</td>
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<td>Pelvis plus prostate bed</td>
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<tr>
<td>No uptake</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>Radiotherapy fields</td>
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<td></td>
</tr>
<tr>
<td>Prostate bed alone</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>Pelvis plus prostate bed</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Mean radiotherapy dose (Gy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate bed</td>
<td>67.53 (64.80–70.20)</td>
<td>67.09 (64.80–70.20)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>45.00 (45.00–45.00)</td>
<td>45.00 (45.00–45.00)</td>
</tr>
</tbody>
</table>

Data in parentheses are range.
for the rectum and bladder but did significantly differ for the penile bulb.

**Toxicity Analysis**

Table 3 shows the observed acute treatment toxicity using the grading criteria of the RTOG. The most common gastrointestinal toxicity was loose bowel movements or diarrhea, and the most common genitourinary toxicity was urinary frequency. A patient could experience toxicity in more than a single category (i.e., both gastrointestinal and genitourinary). The acute toxicity results did not significantly differ between the control and experimental arms. Furthermore, no acute grade 3, 4, or 5 toxicity—either gastrointestinal or genitourinary—was observed in the experimental arm.

**DISCUSSION**

The main hypothesis of this investigation, which was a planned analysis of secondary endpoints of an ongoing randomized controlled trial, was that the addition of 18F-fluciclovine PET/CT to conventional imaging in the postprostatectomy setting would influence the definition of target volume and, further, that the effect of these changes in target volume on dose would not be detrimental to the organs at risk or translate to increased toxicity. In general, our results supported this hypothesis.

Our analysis suggests that adding the 18F-fluciclovine PET/CT results to the prostatectomy pathologic results and the treatment-planning CT results is feasible, will assist in defining the prostate bed clinical target volume, and may significantly modify the postprostatectomy clinical target volume, in most cases causing CTVPOST to be larger on average than the corresponding CTVPRE. As the prostate bed (CTV and CTV2) and pelvis (CTV1) volumes significantly differed between the preregistration and postregistration scans, it can be inferred that the 18F-fluciclovine PET information significantly affected the target definition regardless of whether the lymph nodes were being treated. Although concerns may arise about whether treatment to these larger volumes would result in additional toxicity, the dosimetric consequences of the clinical target volume modifications on the rectum and bladder did not reach significance. Additionally, no grade 4 or 5 acute gastrointestinal or genitourinary toxicity was seen in either arm, and only one grade 3 event (which was in the control arm) was seen, suggesting that treatment to the modified clinical target volume was tolerable.
Furthermore, comparison of overall acute toxicity showed no differences between the control and experimental arms. Our findings are important in that they show a potential role for integration of molecular imaging into postprostatectomy guidance to the anatomic source of detectable PSA, a role not adequately met by conventional imaging. The usefulness of \( { }^{18} \mathrm{~F} \)-fluiclovine PET/CT in the diagnostic setting has been documented, particularly with respect to higher diagnostic accuracy than radioimmunooscintigraphy (22). The current report takes prior work on molecular imaging in general—and on \( { }^{18} \mathrm{~F} \)-fluiclovine PET in particular—and extends it in a different direction: to the use of \( { }^{18} \mathrm{~F} \)-fluiclovine PET to guide definition of the clinical target volume after prostatectomy. The current analysis suggests that \( { }^{18} \mathrm{~F} \)-fluiclovine PET information may be complementary to information provided by standard methods for clinical target volume definition.

Our results are consistent with those of other studies exploring the role of molecular imaging in prostate cancer (30–32). Specifically, earlier retrospective work did demonstrate the role of radioimmunooscintigraphy in influencing target volume definition without increasing toxicity (13–15). Other work has demonstrated a potential role for \( { }^{11} \mathrm{C} \)-choline PET/CT in guiding target volume delineation in the prostate bed and in extending treatment to targets outside the prostate bed, affecting the extent of the treatment-planning target volume (30,31). Furthermore, recent work has shown encouraging results with \( { }^{68} \mathrm{Ga} \)-labeled prostate-specific membrane antigen in identifying the source of PSA, particularly in recurrent prostate cancer (32). However, to our knowledge, our report is the only one that has evaluated the impact of molecular imaging on target definition in the setting of a randomized, prospective controlled trial.

There are several limitations to our study. First, the current report represents a planned analysis of secondary endpoints for the first 96 patients in the trial (the accrual goal is 162); thus, the sample size does not represent the full cohort. Nonetheless, significant differences in target volume have been demonstrated in the number of 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 \( \text{CTV}_{\text{PET}} \); however, in this particular study the same team of nuclear medicine physicians and radiation oncologists was 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, because our protocol defined \( \text{CTV}_{\text{POST}} \) to be the union of \( \text{CTV}_{\text{PRE}} \) and \( \text{CTV}_{\text{PET}} \), \( \text{CTV}_{\text{POST}} \) could not be any smaller than \( \text{CTV}_{\text{PRE}} \). In future versions of the protocol, we may be able to define \( \text{CTV}_{\text{POST}} \) more closely to \( \text{CTV}_{\text{PET}} \), particularly if cancer control endpoints become available suggesting a benefit to the incorporation of \( \text{CTV}_{\text{PET}} \) into the treatment-planning process. Fourth, the current follow-up on the study allows us to report only the acute toxicity endpoints, not the 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-y disease-free survival endpoint. In a similar vein, the acute toxicity currently consists only of provider-reported outcomes. After the study reaches its accrual goal and we have the necessary follow-up, we plan to report late toxicity (both patient-reported and provider-reported) and disease-free survival comparisons. By design, analysis of disease-free survival can be addressed only at study closure.

Within these limitations, however, the current investigation does provide preliminary data on the clinical use of molecular imaging to guide definition of clinical target volume after prostatectomy. It is hoped that the current communication can provide an initial framework on which molecular imaging can be tested and added to the existing consensus contouring guidelines to guide definition of the radiotherapy target.

**CONCLUSION**

In this planned analysis of secondary endpoints in an ongoing randomized trial, inclusion of \( { }^{18} \mathrm{~F} \)-fluiclovine PET information into the treatment-planning process led to significant differences in target definition, with higher doses to the penile bulb but no significant differences in rectal or bladder dose or in acute genitourinary or gastrointestinal toxicity. Longer follow-up is needed to determine how the incorporation of \( { }^{18} \mathrm{~F} \)-fluiclovine PET information will affect cancer control and late toxicity endpoints.

**DISCLOSURE**

This research was sponsored by the NIH (RO1 CA169188; principle investigators: Drs. Jani and Schuster) and Blue Earth Diagnostics Ltd. Emory University and Dr. Mark Goodman are eligible for royalties. No other potential conflict of interest relevant to this article was reported.

**ACKNOWLEDGMENT**

The work was communicated as a podium presentation at the annual meeting of the American Society of Radiation Oncology (ASTRO), San Antonio, Texas, October 2015.
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Published online: September 8, 2016.
Doi: 10.2967/jnumed.116.176057

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