Prostate-Specific Antigen and Prostate-Specific Antigen Velocity as Threshold Indicators in $^{11}$C-Acetate PET/CTAC Scanning for Prostate Cancer Recurrence

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**Purpose:** The aim of this study was to identify which patient characteristics are associated with the highest likelihood of positive findings on $^{11}$C-acetate PET/computed tomography attenuation correction (CTAC) (PET/CTAC) scan when imaging for recurrent prostate cancer.

**Methods:** From 2007 to 2011, 250 $^{11}$C-acetate PET/CTAC scans were performed at a single institution on patients with prostate cancer recurrence after surgery, brachytherapy, or external beam radiation. Of these patients, 120 met our inclusion criteria. Logistic regression analysis was used to examine the relationship between predictability of positive findings and patients’ characteristics, such as prostate-specific antigen (PSA) level at the time of scan, PSA kinetics, Gleason score, staging, and type of treatment before scan.

**Results:** In total, 68.3% of the 120 $^{11}$C-acetate PET/CTAC scans were positive. The percentage of positive scans and PSA at the time of scanning and PSA velocity (PSAV) had positive correlations. The putative sensitivity and specificity were 86.6% and 65.8%, respectively, when a PSA level greater than 1.24 ng/mL was used as the threshold for scanning. The putative sensitivity and specificity were 74% and 75%, respectively, when a PSA level greater than 1.32 ng/mL/y was used as the threshold. No significant associations were found between scan positivity and age, PSA doubling time, Gleason score, staging, or type of treatment before scanning.

**Conclusions:** This retrospective study suggests that threshold models of PSA greater than 1.24 ng/mL or PSAV greater than 1.32 ng/mL per year are independent predictors of positive findings in $^{11}$C-acetate PET/CTAC imaging of recurrent prostate cancer.

**Key Words: $^{11}$C-acetate PET, prostate cancer recurrence, prostate cancer imaging, PSA, $^{11}$C-choline PET

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In the United States, aside from nonlethal skin cancers, prostate cancer is the most common cancer among men and is the second leading cause of cancer death.¹ In 2014, prostate cancer will be newly diagnosed in approximately 233,000 men.² Three quarters of these patients will choose potentially curative surgery or radiation therapy; unfortunately, up to 40% of those treated with curative intent will experience recurrent disease.³ Accurately identifying sites of recurrence is important in making treatment decisions to achieve remission or amelioration of the disease.³

The primary difficulty in locating recurrent sites lies within the limitations of standard imaging modalities such as bone and CT scans.⁴ However, newer PET radiopharmaceuticals, such as $^{11}$Carbon (¹¹C) acetate,¹¹C-choline, and $^{18}$Fluorine (¹⁸F) choline, have shown efficacy for imaging recurrent prostate cancer, demonstrating superiority over $^{18}$FDG PET/CT attenuation correction (CTAC) (PET/CTAC) and $^{11}$In in capromab SPECT.⁵–⁸ Rapidly proliferating prostate cancer cells use acetate and choline as substrates in building bilipid cell membranes. By transforming these substrates into radiochemicals through the incorporation of $^{11}$C and $^{18}$F, respectively, they become imaging markers of tissue sites undergoing rapid cell membrane synthesis (Figs. 1 and 2).⁹,¹⁰ Since questions remain about the ability of these 2 agents to distinguish between malignant and inflammatory tissue within an intact gland, their best application lies in the detection of prostate cancer after recurrence or in detecting extraprostatic spread before surgery.¹¹,¹² A number of recent studies have provided powerful evidence that there is a significant survival benefit to using these new PET scans to target salvage therapy.¹³,¹⁴

Although the effectiveness of $^{11}$C-acetate,¹¹C-choline, and $^{18}$F-choline PET/CTAC is well supported for recurrent disease, there is reduced sensitivity when scanning patients with prostate-specific antigen (PSA) values less than 1 ng/mL.¹⁵ On the other hand, studies examining progression rates for patients receiving salvage radiotherapy for biochemical recurrence after prostatectomy show no significant difference between the progression rates for patients with preradiotherapy PSA levels ≤ 1.0 ng/mL and patients with preradiotherapy PSA levels > 1.0 but ≤ 2.0 ng/mL. Patients with PSA levels of ≤ 2.0 ng/mL had a 4-year progression-free probability (PFP) of 77% if there were no adverse features. Those with PSA levels ≤ 2.0 ng/mL but with rapid PSA doubling times (PSADT) had 4-year FPFPs of 64% and 22% when the surgical margins were negative and positive, respectively. Patients with pretreatment PSA levels greater than 2.0 ng/mL had 4-year FPFPs of 20%, regardless of PSADT, surgical margin status, or Gleason score.¹⁶,¹⁷

Therefore, our aim was to identify which patients’ characteristics are associated with the highest likelihood of positive findings on $^{11}$C-acetate PET/CTAC imaging of recurrent prostate cancer, ideally at a PSA level low enough to preserve the greatest PFP if salvage therapy is undertaken.

**PATIENTS AND METHODS**

**Patients**

This study was performed in accordance with the rules and guidelines set forth by the Human Subjects Committee at the University of Kansas Medical Center. Patients who received $^{11}$C-acetate PET/CTAC scans were referred from both local and national sources. Between July 2007 and September 2011, 250 scans were evaluated.
for inclusion in the study. Prior definitive treatments included radical prostatectomy, brachytherapy, and external beam radiation.

For patients who had surgery, PSA values were required to reach a nadir of less than 0.1 ng/mL for inclusion in this study. Recurrence in this population was defined as a PSA level greater than 0.2 ng/mL on the 2 most recent PSA tests.18 For patients who received external beam radiation or brachytherapy, recurrence was determined by the American Society for Radiation Oncology’s (ASTRO’s) Phoenix definition, which is the first time PSA increases by 2 ng/mL above the nadir PSA after completion of treatment.19 When combination therapies included surgery followed by radiation, recurrence was determined by the Phoenix definition. For patients who received multiple separate treatments, the definition of recurrence was determined by the most recent definitive treatment modality.

Patients who received only hormone therapy, chemotherapy, or nonstandard treatments, such as cryotherapy or supplements, were not included in the study. Patients who did not have a PSA level within 3 months of the 11C-acetate PET/CTAC scan, patients who did not achieve a nadir in PSA level after treatment, and patients with known metastatic disease before treatment, as established by the criteria of the American Joint Committee on Cancer, were also excluded.20 Of the 250 patients with available scans, 120 patients met inclusion criteria for this analysis. Characteristics of the study population are summarized in Table 1.

### Radiopharmaceuticals

The 11C-acetate was produced by a Siemens RDS 111 cyclotron housed at the University of Kansas Hospital in Kansas City, KS. After producing 11C-CO2, a General Electric TRACERlab FX chemistry module was used to convert 11C-CO2 to 11C-acetate by the Grignard reaction. A mean of 40 mCi of the radioisotope was available for intravenous injection at the time of the scan. Although this dosage is higher than some 11C-acetate PET studies, it is congruent with the midrange of activity used in the dosimetry studies performed by Seltzer et al.21

### Imaging

All patients had their 11C-acetate PET/CTAC imaging performed at the University of Kansas Hospital using a General Electric Discovery ST 16 PET/CTAC scanner, which has an integrated 16-slice CT scanner. All images were interpreted by radiologists board certified by both the American Board of Nuclear Medicine and the American Board of Radiology, with more than 5 years of experience in 11C-acetate PET/CTAC interpretation. All positive findings were correlated with coregistered CT images and confirmed findings by biopsy (n = 3), disease progression on follow-up imaging (n = 61), lesion improvement after treatment on follow-up imaging (n = 14), or PSA value improvement after treatment of lesion(s) (n = 4).

### PSA Kinetics

Prostate-specific antigen kinetics results were calculated using all PSA values starting from the time of recurrence up to the time of the 11C-acetate PET imaging. Prostate-specific antigen doubling time was calculated in 2 ways: best-line fit and first and last observation methods. The formula used to calculate PSADT in months is

$$\text{PSADT} = \ln(2)/b$$

in which \(\ln(2)\) is the natural logarithm of 2, and \(b\) is the slope of all the log-scale PSA measurements collected from the aforementioned time frame. In the best-line fit method popularized by Memorial Sloan-Kettering Cancer Center, \(b\) is given by fitting the least-squares regression line to that data. In the first and last observation method, \(b\) is given by

$$b = \frac{\ln(\text{PSA}_{\text{final}}) - \ln(\text{PSA}_{\text{initial}})}{t_{\text{final}} - t_{\text{initial}}}$$

in which \(\ln(\text{PSA}_{\text{final}})\) is the natural logarithm of the last recorded PSA before the 11C-acetate PET scan, \(\ln(\text{PSA}_{\text{initial}})\) is the natural logarithm of the PSA at the time of recurrence, and \(t_{\text{final}} - t_{\text{initial}}\) is the number of months between scan and recurrence.

The calculation of PSA velocity (PSAV), in ng/mL per year, is defined by the slope of the least-squares regression line of the raw PSA data.

### Statistics

Chi-squares, 2-sample \(t\) tests, and nonparametric tests were used to examine the differences of parameters of interest between those with positive and negative scans. Whereas distinct PSA or PSA kinetics values highly correlate with patient outcomes after recurrence, continuous scales are clinically more useful if split into cutoff ranges. Therefore, we grouped PSA or PSA kinetics values into deciles or quintiles to create equal-ordered categorical subgroups of

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**TABLE 1. Characteristics of Study Cohort**

| Entire Cohort |
|----------------|
| No. patients | 120 |
| Age at scan, mean ± SD, yrs | 67.0 ± 9.15 |
| Age at scan, median, yrs | 67 |
| PSA at scan, mean ± SD, ng/mL | 7.6 ± 17.43 |
| PSA at scan, median, ng/mL | 3.48 |
| Gleason score at surgery | 7.0 |
| Unknown | 72 |

**TNM** stage—clinical

| T1c | 11 |
| T2 | 25 |
| T3 | 8 |
| T4 | 1 |
| Unknown | 75 |

**Type of treatment**

| Surgery | 35 |
| XRT† | 38 |
| Brachytherapy | 21 |
| Surgery + XRT‡ | 7 |
| Brachytherapy + XRT‡ | 19 |

| Use of ADT‡ at time of scan | Yes | 49 |
| No | 69 |
| Unknown | 2 |

**Locations of recurrence**

| Local only | 15 |
| Local with lymph nodes | 19 |
| Distant lymph nodes | 41 |
| Bony metastases | 33 |

*n = 120.
†Tumor Node Metastasis classification.
‡External beam radiotherapy.
§Androgen deprivation therapy.
patients to describe prostate cancer progression. Subsequently, a PSA or PSA kinetics cutoff (or cutoffs, when appropriate) was established using χ² tests and logistic regression models. Both the sensitivity and specificity associated with the identified PSA or PSA kinetics threshold were calculated. Sensitivity is the percentage of patients who had a positive ¹¹C-acetate PET/CTAC scan with the immediate pretest PSA or PSA kinetics above the threshold, whereas specificity is the percentage of patients who had a negative ¹¹C-acetate PET/CTAC scan with the immediate pretest PSA or PSA kinetics below the threshold. To determine the discriminatory ability of PSA or PSA kinetics in association with the ¹¹C-acetate PET/CTAC scan, we calculated the receiver operating characteristic (ROC) curves and the associated area under the curves (AUC), which is estimated by the C-statistic, of the models using a logistic regression technique.

RESULTS

PSA at Time of Scan

In total, 68.3% (82 of 120 available PSA values at the time of scan) of the ¹¹C-acetate PET/CTAC scans were positive. Table 2 summarizes the characteristics of all scans. There was a statistically significant difference of PSA values between the positive and negative scans (P < 0.001 for both median and mean differences). In our analysis, PSA values were categorized into 10 equal groups (or deciles). The characteristics of each decile are summarized in Table 3. The ROC curve is shown in Figure 3 (C-statistic, 0.76). The putative specificity and sensitivity were 86.6% and 65.8%, respectively, when a PSA value greater than 1.24 ng/mL was used as the threshold for determining the optimal time to perform ¹¹C-acetate PET/CTAC imaging.

PSA Kinetics

Of the 47 patients with calculable PSA kinetics data, 74.5% (35) of 47 scans were positive. When 3 patients who had stable PSA over time were included in the analysis, the median and mean PSADT in log scale were 6.0 months (range, 768–3555 months) and 75.0 months (± 532.59 months). On the other hand, the median and mean PSADT were 6.6 months (range, 1.3–270 months) and 17.0 months (± 40.68 months) when the same 3 cases were excluded from the calculation. Since these 3 patients met the study eligibility criteria and were included in all the analyses, only median value PSADT was reported for the comparison between positive and negative scans.

The median PSADT was 7.08 and 5.58 for those with positive and negative scans, respectively (P = 0.9323). The PSADT results were grouped by PSADT ≤ 2 months, PSADT > 2 months but ≤ 4 months, PSADT > 4 months but < or > 6 months, and PSADT > 6 months. In each respective group, there were positive scans in 66.7% of 6 patients, 80% of 10 patients, 57% of 7 patients, and 79% of 24 patients. There was no statistical significance in the proportion of positive scans across the PSADT subgroups.

The median and mean PSAV were 3.5 ng/mL per year (range, 0.8–506.4 ng/mL per year) and 18.7 ng/mL per year (±74.53 ng/mL per year), respectively. The median PSAV of positive scans was 4.4 ng/mL per year, and the median of negative scans was 0.61 ng/mL per year, respectively (P = 0.0034). In our analysis, using 5 equal groups (quintiles) of PSAV (≤0.564 ng/mL per year, 0.564 < PSAV ≤ 1.32 ng/mL per year, 1.32 < PSAV ≤ 3.96 ng/mL per year, 3.96 < PSAV ≤ 7.92 ng/mL per year, and PSAV > 7.92 ng/mL per year), the proportion of patients with a positive scan ranged from 33% to 60% in the first 2 quintiles and 89% to 90% in the last 3 quintiles. The ROC curve corresponding to these cutoffs is shown in Figure 4 (C-statistic, 0.75). The putative sensitivity and specificity were 74% and 75% when a PSAV value greater than 1.32 ng/mL per year was used as the cutoff for positive scans.

Androgen Deprivation Therapy

Hormone data for 119 patients were available, with immediate pretest PSA values recorded for nearly all patients (n = 118). Of the 118 PSA-available patients, 68.4% had positive scans. Median and mean PSA values were 3.52 ng/mL and 7.67 ± 17.56 ng/mL, respectively (range, 0.20–127.32 ng/mL). From this same group, 49 (41.5%) of the 188 patients had androgen deprivation therapy within 1 year of ¹¹C-acetate PET/CTAC imaging. For patients treated with androgen deprivation therapy, the median and mean PSA values from positive scans were 4.17 ng/mL and 12.38 ± 23.18 ng/mL, respectively, whereas the median and the mean values for negative scans were 0.30 ng/mL and 2.3 ± 6.13 ng/mL, respectively. Both median and mean PSA values between positive and negative scans were statistically significant (P < 0.0001 and P = 0.0263, respectively). In these patients, 25.0%, 66.7%, 81.8%, and 93.8% had positive scans in the subgroups defined as PSA ≤ 1 ng/mL, PSA > 1 ng/mL but ≤ 2 ng/mL, PSA greater than 2 ng/mL but ≤ 5 ng/mL, and PSA > 5 ng/mL, respectively. In patients not treated with androgen deprivation therapy in the previous year, positive scans were 26.7%, 50%, 77.3%, and 92.9%, respectively. There was no significant difference in correlations and trends between the androgen-deprived and androgen-intact patients.

Logistic Regression Analysis

Our analysis demonstrated that PSA value at the time of scan was significantly associated with a positive ¹¹C-acetate PET/CTAC scan (OR, 12.2: 95% confidence interval, 3.980–37.661). The associations between ¹¹C-acetate PET/CTAC positivity and selected risk factors, including age at time of scan, type of definitive treatment, and androgen deprivation therapy, were not statistically significant. Results from this logistic regression analysis are shown in Table 4 (C-statistic, 0.812). PSA doubling time and PSA velocity were also examined for possible association with positive ¹¹C-acetate PET/CTAC scans. Of these factors, only PSA velocity was significantly associated with scan results. Table 5 summarizes the PSA and PSA velocity at our chosen thresholds. Data were separated into postprostatectomy and postradiotherapy groups, and each group was analyzed separately for PSA threshold, velocity, doubling time, and presence of androgen deprivation therapy. No statistically significant results were found for either group.

DISCUSSION

The results of this analysis demonstrate that the positivity of a ¹¹C-acetate PET/CTAC scan is strongly correlated with absolute PSA value at the time of image acquisition. Our calculated optimal PSA threshold value for obtaining a ¹¹C-acetate PET/CTAC scan is 1.24 ng/mL, with a putative sensitivity and specificity of 86.6% and 65.8%, respectively. These results are similar to the findings of European studies that used ¹¹C-choline or ¹⁸F-choline. A large-scale investigation of ¹¹C-choline by Giovacchini et al²² calculated a PSA threshold value of 1.4 ng/mL, with a sensitivity and specificity of 73% and 72%, respectively. Castellucci et al²³ found a higher optimal PSA threshold value of 2.43 ng/mL when examining ¹¹C-choline for imaging, with

| TABLE 2. Median and Mean PSA of Positive and Negative ¹¹C Acetate PET/CTAC Scans |
|---------------------------------|-----------------|
| Median PSA* | Mean PSA* |
| All scans | 3.5 | 7.6 |
| Positive scans | 4.8 | 10.0 |
| Negative scans | 0.8 | 2.1 |

*ng/mL

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comparable sensitivity and specificity of 73% and 69%, respectively. Similarly, Graute et al\textsuperscript{24} established a PSA threshold value of 1.74 ng/mL for \textsuperscript{18}F-choline that was associated with a sensitivity and specificity of 82% and 74%, respectively.

Our PSA V threshold of 1.32 ng/mL per year also supports many recent studies that have correlated PSA kinetics and rate of scan positivity. For example, a meta-analysis of PSA kinetics data compiled before July 2013 calculated a 65% detection rate for PSADT of less than 6 months and a 71% detection rate for PSA V greater than 1 ng/mL per year.\textsuperscript{25} More recently, Mamede et al\textsuperscript{26} demonstrated that even with recurrence at PSA of less than 0.5 ng/mL, low PSADT values were associated with high scan positivity rates. Thus, many have come to view PSA kinetics as the prime indicators for guiding the use of \textsuperscript{11}C-choline PET/CTAC scans.

Despite the value of PSADT and PSA V, defining a PSA threshold is also clinically valuable. Determining the optimal time to perform a \textsuperscript{11}C-acetate PET/CTAC scan after biochemical recurrence in prostate cancer should ideally maximize the likelihood of detection.

### TABLE 3. Decile Characteristics of PSA at the Time of \textsuperscript{11}C-Acetate Scan

| Decile | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  |
|--------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| PSA*   | ≤0.26 | 0.26–0.59 | 0.60–1.24 | 1.25–2.60 | 2.61–3.48 | 3.49–4.28 | 4.29–5.64 | 5.65–8.0 | 8.1–12.3 | >12.3 |
| No. scans | 13 | 11 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Percent positive | 23.1 | 45.5 | 25.0 | 66.7 | 75.0 | 91.7 | 83.3 | 83.3 | 100 | 91.7 |

*ng/mL.*
localizing recurrent tumor sites at a point in time early enough to allow for the successful use of salvage therapies. As mentioned previously, PFP is significantly improved for preradiotherapy PSA levels less than 2.0 ng/mL. According to our analysis, this would imply that the optimal time to detect foci of recurrence after a failed radical prostatectomy is between PSA greater than 1.24 ng/mL but ≤ 2.0 ng/mL. Although PSADT and PSA V could also offer this benefit, using a single, prescan PSA level to determine when to scan has the compelling advantage that it does not require the gathering of sequential PSA samples to calculate a PSA doubling time or velocity.

### TABLE 4. Logistic Regression Model With Positive 11C Acetate PET Outcomes and PSA at Scan (n = 120)

| Predictor                  | Odds Ratio | 95% CI     | P    |
|----------------------------|------------|------------|------|
| Age at scan (1 year increment) | 1.02       | 0.967–1.080 | 0.4379 |
| Type of treatment          |            |            |      |
| Surgery+XRT* (reference)   | 1.00       |            |      |
| XRT*                       | 0.94       | 0.109–8.128 | 0.8344 |
| Brachytherapy              | 0.81       | 0.078–8.419 | 0.9246 |
| Brachy+XRT*                | 0.81       | 0.080–8.311 | 0.9295 |
| Surgery                    | 0.74       | 0.087–6.258 | 0.7591 |
| ADT†                       | 0.87       | 0.327–2.232 | 0.7908 |

*External beam radiotherapy.
†Androgen deprivation therapy.

### TABLE 5. Logistic Regression Models With Outcomes Being Positive 11C Acetate PET/CTAC Scans

| Predictor                  | Odds Ratio (95% CI) | AUC/C-Statistic (95% CI) |
|----------------------------|---------------------|-------------------------|
| Entire cohort (n = 120)    |                |                        |
| PSA > 1.24*               | 12.4 (4.93–31.25)  | 0.762 (0.6778–0.8460)   |
| Subcohort (n = 47)        |                |                        |
| PSAV > 1.32†              | 8.7 (1.91–39.25)   | 0.747 (0.6042–0.8888)   |

*ng/mL.
†ng/mL per year.
which risks over shooting the radiotherapy salvage threshold of PSA of 2.0 ng/mL. Moreover, in the reality of evaluating patients on referral, calculating PSA velocity and doubling times from a series of PSA values obtained from disparate laboratory methodologies is tenuous at best. Our data suggest that by using only the most recent PSA value to determine the timing of the scan, $^{11}$C-acetate PET/CTAC imaging can detect early prostate cancer recurrence with reasonable sensitivity and specificity.

A negative effect of antiandrogen therapy on acetate or choline PET sensitivity has widely been suspected. Giovacchini et al. did confirm a negative correlation on univariate logistic regression. However, the current study was unable to confirm this statistically, as the positivity of an $^{11}$C-acetate scan was still determined by PSA value, regardless of the patient’s hormone status. Krause et al. were also unable to establish a negative correlation between antiandrogen therapy and PET sensitivity. This is an area that needs further investigation.

Other patients’ characteristics, such as age, stage, and Gleason score, failed to demonstrate predictive value for the $^{11}$C-acetate PET/CTAC imaging in our analysis. There were not sufficient data to determine the usefulness of PSA doubling time.

Our study has several limitations. To our knowledge, there are no previous large-scale $^{11}$C-acetate PET/CTAC studies of recurrent prostate cancer in American men. However, whereas our study population was uniquely American, only one of our patients was African American. Therefore, extrapolating our findings to an African American population, which is known to be at higher risk for prostate cancer occurrence and mortality, may not be justified. In addition, treatment regimens were not standardized between patients. Some patients had multiple types of therapies before the study and still met our inclusion criteria. It is plausible that patients who have failed one treatment may be more likely to develop recurrence and may have higher rates of PET positivity. This study also included a large group of nonsurgical patients, whereas some of the previous $^{11}$C-choline and $^{18}$F-choline studies included only patients who had postprostatectomy. Nevertheless, our cohort most likely reflects typical clinical practice, where patients are referred for scanning with biochemical recurrence after differing treatment regimens.

Moreover, it is important to note that in this study and those like it, a positive scan does not definitively indicate a site of recurrence. Although these studies seek to elucidate the best timing for $^{11}$C-acetate PET imaging, the putative positive areas of the scan could be false positives. In the world literature to date, there is a paucity of prospective trials of adequate size that have used tissue confirmation.

CONCLUSIONS

Our retrospective analysis of the first 250 $^{11}$C-acetate PET/CTAC scans we performed for recurrent prostate cancer found that scans performed after the patient had achieved a PSA value greater than 1.24 ng/mL had the highest likelihood of producing positive findings. Whereas our study also showed that a PSAV greater than 1.32 was also associated with a greater probability of positive findings, and multiple European studies have shown the value of a PSADT of less than 6 months, we feel there may be unique advantages in a threshold model that is based on a single PSA value. Nevertheless, this study and those like it suffer from the lack of a large number of biopsy-confirmed results. A large prospective biopsy-proven trial of $^{11}$C-acetate, $^{11}$C-choline, and/or $^{18}$F-choline is needed to confirm these findings.
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