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Early Imaging Improves the Performance of C11-Acetate PET/CT for Recurrent Prostate Adenocarcinoma

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ABSTRACT

Purpose: We evaluated the performance of C11-Acetate positron emission tomography/computed tomography (PET/CT) in recurrent prostate cancer patients with early and late imaging.

Patients and Methods: Forty-one patients with recurrent prostate adenocarcinoma as evidenced by a rising prostate-specific antigen (PSA) after prior definitive treatment where imaged with C11-Acetate PET/CT. Patients with prior initial prostatectomy and prior radiation were similar in number. Early post-tracer injection PET/CT imaging was performed (3 to 7 minutes, mean 4.25), with subsequent later pelvic/lower abdominal imaging (21 to 31 minutes, mean 26.6). Target lesions where identified visually and with quantitative measurements of maximal standardized uptake valve (SUV) and lesion-to-background (L/B) ratios obtained for each lesion. Analysis was performed to determine statistical significance.

Results: Twenty-eight patients had evaluable lesions in the pelvis, which could be compared across the imaging time points. Sixty lesions were detected with 12 in the prostate, 33 in lymph nodes, 7 in the peri-prostate soft tissues or seminal vesicles (SV), and 8 in the bone. Lesions involving the lymph nodes, peri-prostate soft tissues, and bone were all more visually conspicuous on the early imaging as compared to the later imaging, and demonstrated statistically significant higher maximal SUVs and L/B ratios ($P < 0.001$). Lesions in the intact prostate and seminal vesicles on the early images also demonstrated significantly higher maximal SUVs ($P < 0.001$), but the L/B ratios were similar or slightly higher on the later images with the difference not found to be statistically significant.

Conclusion: C11-Acetate positron emission tomography/computed tomography with early imaging post injection provides improved lesion detection both in terms of maximal SUV and lesion-to-background ratios for lesions involving nodes, peri-prostate soft tissues, and bone. Lesions in the prostate and seminal vesicles showed equal visual conspicuity and lesion-to-background ratios across early and later imaging. Early imaging appears optimal in the evaluation of recurrent prostate adenocarcinoma. In a larger application (300 patients) of early imaging in this patient population, C11-Acetate PET/CT demonstrates a consistently high detection rate.

KEYWORDS: C11-Acetate positron, PET/CT

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INTRODUCTION

Prostate cancer is the second most common cancer in American men with the American Cancer Society 2011 estimating about 240,890 new cases of prostate cancer diagnosed and 33,720 deaths from prostate cancer. About 1 man in 6 will be diagnosed with prostate cancer during his lifetime, and death from prostate cancer in American men lags only behind lung cancer.

Regardless of the type of primary treatment, a significant proportion of patients will experience relapse of prostate adenocarcinoma, occurring approximately 35% after radical prostatectomy [1,2] and up to 40% after external beam radiotherapy [3-5]. In these patients, evidence of residual or recurrent disease is heralded by detectable or increasing serum prostate-specific antigen (PSA) [6-11], with many of these patients demonstrating no or minimal evidence of disease on standard imaging studies such as magnetic resonance imaging (MRI), CT, ultrasound, and technetium bone scans—also referred to as "biochemical relapse." Subsequent treatment decisions rely critically on distinguishing between loco-regional relapse in the prostate bed and adjacent soft tissues, loco-regional relapse in lymph nodes, and distant metastases. Imaging with F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is successful in most malignant diseases, but is not useful for prostate adenocarcinoma, primarily because prostate adenocarcinoma does not routinely exhibit a glycolytic phenotype [12,13]. Additionally, FDG tracer excretion through the kidneys into the bladder significantly obscures evaluation of the prostate bed.

Over the past few years, novel PET tracers have been introduced to assist with the evaluation of prostate adenocarcinoma. In addition to C11-choline and F18-choline, C11-Acetate (AC) appears to be highly promising. Various groups have tested the potential of AC PET imaging in prostate adenocarcinoma [14-20], providing encouraging results. Limitations in several of the previous studies, however, have been a lack of standardization of the imaging technique, primarily in terms of time to commence imaging post injection. Additionally, the majority of prior studies have been performed with PET only or separately co-registered morphologic and metabolic imaging techniques. It has been established that combined hybrid PET/CT imaging provides improved diagnostic accuracy and impact on clinical patient management [21]. Thus, we evaluated the performance of AC PET/CT at our institution in men with biochemically recurrent prostate cancer after definitive treatment, with an integrated PET/CT imaging system and multiple time-point imaging.

PATIENTS AND METHODS

Our institutional review board approved the study for all patients undergoing C11-Acetate PET/CT imaging at our institution. Forty-one male patients (ages 54 to 85, mean 71) with histologically proven prostate adenocarcinoma and biochemical recurrence (BCR) were imaged. Biochemical recurrence was defined as PSA 0.2 ng/mL or greater for a patient who underwent prior prostatectomy, nadir plus 2 ng/mL or a sequential increase in PSA for patients treated with radiation or cryotherapy, or a sequential increase in PSA for the patients treated with primary androgen deprivation therapy (ADT). The PSA range for these patients was 0.5 to 60.2 ng/mL (mean 8.6 ng/mL). Gleason scores (Gs) ranged from 5 to 9 (Gs5 N = 2; Gs6 N = 8; Gs7 N = 19; Gs8 N = 8; Gs9 N = 4). Prior primary therapy consisted of prostatectomy (N = 7), external beam radiation therapy (N = 18), external beam plus brachytherapy (N = 4), prostatectomy with subsequent salvage radiation therapy (N = 11), and ADT (N = 1).

C11-Acetate was produced by reacting methylmagnesium bromide with [11C]CO2. In brief, [C-11]CO2 gas was produced from the cyclotron (PETtrace series 800, General Electric) after a 45-minute, 60 micro-Amp target irradiation producing approximately 4 Curies of [C-11]CO2. [11C]CO(2) gas from the target was directed to the synthesis unit containing a column of methylmagnesium bromide in diethyl ether used for carbonation of the gas. The intermediate was then hydrolyzed under heat and unreacted [C-11]CO2 removed from the mixture, passed through C18 resin to remove ionic and organic compounds, and collected into a batch vial through a membrane filter. Our typical yield of C11-Acetate is 1.4 Curies with a total synthesis time of 10 minutes.

C11-Acetate PET/CT imaging was performed on an integrated PET/CT scanner (Siemans Biograph 6 TruePoint; Malvern, Pennsylvania, United States). Patients were positioned on the camera and then 740-1480 MBq C11-Acetate (half-life 20.4 minutes) was administered as a bolus intravenous injection. A CT topogram was obtained from the vertex through the pelvis. On the basis of the topogram, the tube current for the CT scan was adjusted utilizing a Care doseTM application to minimize exposure. The tube voltage was 130 kVp. Reconstructed images were 3 mm thick slices. After the CT scan, emission images beginning at the pelvis and proceeding cranially were obtained (3 to 7 minutes post injection, mean 4.25). After completion of the initial imaging sequence, delayed imaging (21 to 31 minutes post injection, mean 26.6) was performed of the pelvis and lower abdomen. PET imaging acquisition parameters were weight-based for bed stop and filter settings with an average of 2.25 minutes per bed stop with 6 to 8 bed positions. Images were reconstructed with iterative reconstruction (2 iterations, 8 subsets, matrix 168, Gaussian filter). The administration of C11-Acetate was well tolerated by all patients and no adverse events were encountered.

Detected lesions were defined as moderate to intense focal

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areas of increased AC metabolic activity over background in the prostate, prostatic bed, nodes, and bone. Maximal standardized uptake values (SUVmax) were determined for each lesion with a spherical region of interest (ROI), with SUV representing the calculated ratio of tissue radioactivity concentration c (e.g., MBq/kg) at time point t and injected dosage (e.g., in MBq) at the time of injection, and then divided by body weight (e.g., in kg).

SUV = c(t)/injected activity(t)/body weight

Early and late imaging sequences for each study were anatomically fused on a PET/CT workstation (MIMFusion V5.6.2, MIMSoftware; Cleveland, Ohio, United States), allowing for precise measurement of the same location/lesion on each comparison imaging study. Background values were also obtained in the prostate, muscle, blood pool, bone, and urinary bladder. Lesion-to-background ratios where determined for each lesion, with background selected on the basis of the type of lesion. For lesions in the intact prostate, a contralateral area in the prostate was selected for the background. For lesions in the post prostatectomy bed or for lymph nodes, the lower abdominal aortic blood pool was selected. For bony lesions, background was selected in the intramedullary space of the L5 vertebral body. Data analysis was performed utilizing statistical software (SigmaXL, SigmaXL Inc.; Toronto, Ontario, Canada) and consisted of comparison of the difference in maximal SUV values utilizing a 2-tailed paired *t* test. Lesion-to-background ratios were also determined for each lesion and compared across early and late imaging studies utilizing the paired *t* test.

RESULTS

Of the 41 patients imaged, 28 patients were found to have evaluable lesions in the pelvis and lower abdomen, which could be compared across the different time-point sequences. A total of 60 lesions were detected in these patients (12 in the prostate, 33 in lymph nodes, 7 in the peri-prostate soft tissues or seminal vesicles, and 8 in the bone).

All of the evaluable lesions where visually detectable on both the early and late imaging sequences. In lesions involving lymph nodes, peri-prostate soft tissues, and bone, nearly all lesions appeared visually more prominent on the early images as compared to the late images. The maximal SUV values were also demonstrated to be higher on the earlier imaging sequence compared to later imaging, with a mean difference of 1.09 and maximum difference of 6.02. Data comparison across the imaging studies demonstrated the difference in SUV values to be statistically significant ($P < 0.001$). Lesion-to-background ratios (L/B) in the AC-positive lymph nodes, peri-prostate regions, and in bone were also found to be statistically higher on early imaging compared to delayed imaging ($P < 0.001$).

In lesions involving the prostate or seminal vesicles, AC accumulation in many cases appeared visually similar between the different imaging time points. The maximum SUV in these lesions was statistically higher on the early imaging, but ratios of lesion-to-background where similar or slightly higher on the later imaging in a few lesions. A difference in the L/B ratios for these lesions was not found to be statically significant (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5).

Figure 1. 60 y/o, Gleason 7, treated with brachytherapy and EBRT 5 years previously. Rising PSA at the time of AC PET/CT imaging was 14.4 ng/mL. The left image shows a sub-centimeter focally metabolic lymph node in the proximal right common iliac region on early imaging (SUVmax 4.51, L/B 2.36). The right image shows the same finding in the lymph node on the later imaging but with this appearing much less conspicuous (SUVmax 3.44, L/B 1.67).

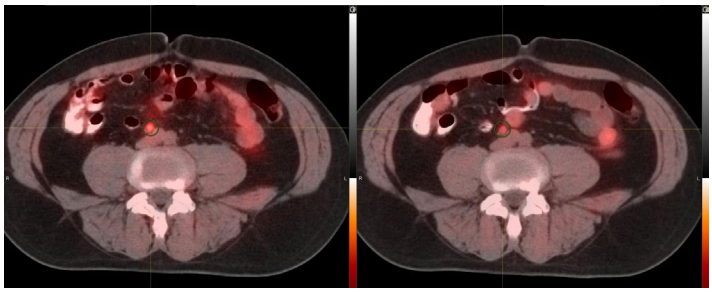


Figure 2. 59 y/o, Gleason 9 (4+5), treated with prostatectomy and subsequent salvage radiation therapy to the bed for rising PSA 1 year later. Rising PSA 1 1/2 years later, and at the time of AC PET/CT imaging, was 0.7 ng/mL. The left image shows a sub-centimeter focally metabolic lymph node in the left external iliac region on early imaging (SUVmax 3.22, L/B 2.73). The right image shows the same finding in the lymph node on the later imaging but with this appearing less conspicuous (SUVmax 2.36, L/B 1.92).

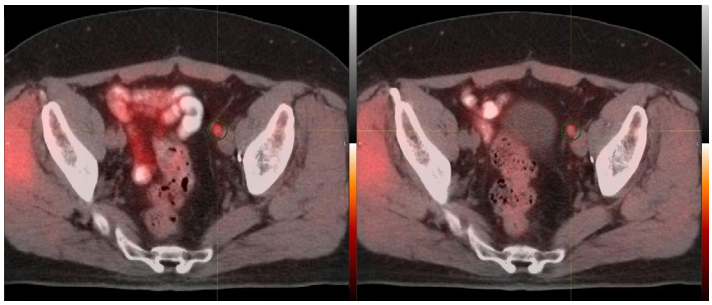


Figure 3. 71 y/o, Gleason 7, treated with prostatectomy 15 years previously. Rising PSA at the time of AC PET/CT imaging was 0.87 ng/mL. Multiple nodal and bony lesions were positive in this patient. Only 1 example node is shown. The left image shows a sub-centimeter focally metabolic lymph node in the left proximal common iliac region on early imaging (SUVmax 2.43, L/B 1.94). The right image shows the same finding in the lymph node on the later imaging but with this appearing less conspicuous (SUVmax 1.77, L/B 1.7).

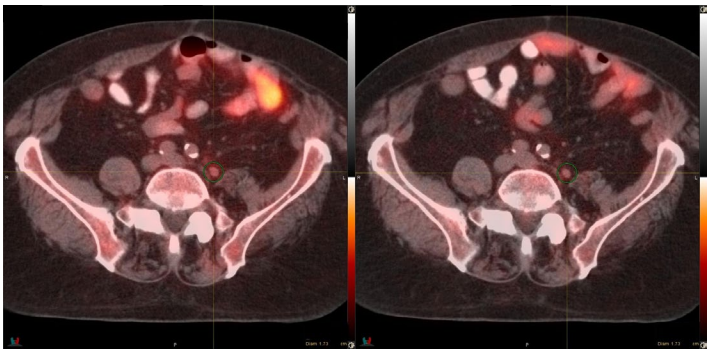


Figure 4. 75 y/o, Gleason 7, treated with brachytherapy and EBRT 11 years previously. Rising PSA at the time of AC imaging was 11.15 ng/mL. The left image shows a focal bone metastasis in the right ilium with early imaging (SUVmax 9.06, L/B 3.28). The right image shows the same finding in the bone but is much less conspicuous on later imaging (SUVmax 5.08, L/B 2.43).

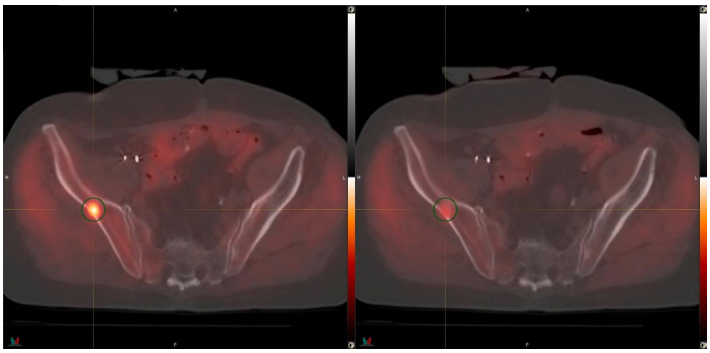


Figure 5. 70 y/o, Gleason 7, treated with EBRT 4 years previously. PSA nadir was 0.43 ng/mL. Rising PSA at the time of AC imaging was 3.9 ng/mL. The left image shows focal recurrent disease in the right aspect of the prostate gland with early imaging (SUVmax 6.14). The right image shows the same finding in the prostate gland on the later imaging (SUVmax 5.15). The L/B ratio was 2.74 for the early and 3.0 for the later imaging, respectively.

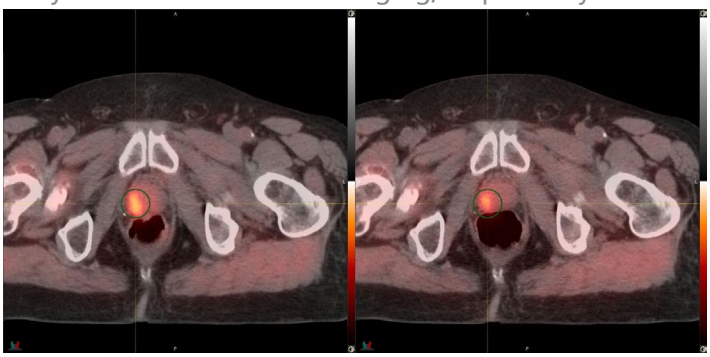
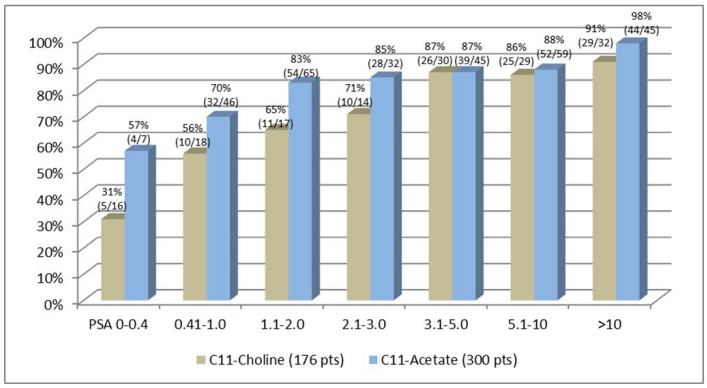


Figure 6. Detection rate of C11-Acetate PET/CT imaging across various PSA levels in 300 patients,[33] compared to C11-Choline PET/CT in 176 patients.[32]



DISCUSSION

The reported sensitivity for detection of recurrent or metastatic prostate cancer with C11-Acetate PET has varied widely in publications to date (55 to 100%) and is difficult to compare due to variations in camera technology, PSA levels, and timing [15,17,18,22-28]. A study by Vees et al. [23] showed only a 55% detection rate, but PSA was < 0.8 in all patients, and PET-only technology was used. In a study by Yu et al. [27], sensitivity was 100%, but all patients had documented bone lesions by technetium bone scans and much higher PSAs, ranging from 6.3 to 2,012 ng/mL. An early study by Frickle [18] showed a good detection rate, but the mean PSA (50ng/mL) was also higher than most other studies, which may have influenced performance. Most prior studies with shorter delay to imaging have additionally used "PET only" technology, which may also have contributed to lower detection rates [21]. With the PET-

Table 1. C11-Acetate PET imaging performance in BCR/metastatic prostate cancer. Prior studies have varied in terms of technology (PET versus integrated PET/CT), PSA levels, and timing for imaging post injection. Studies with earlier time to imaging generally show improved detection rates compared to later imaging.

Author	Year	Camera	N	Delay	PSA ng/mL	Detection Rate
Kotzerke[17]	2002	PET	31	5 min	0.1 - 150.6 (mean 10.4) < 2.0	83% 63%
Frickle[18]	2003	PET	25	2 min	0.3 - 400 (mean 50)	83%
Oyama[15]	2003	PET	46	10 - 20 min	0.3 - 47.5 (mean 5.2)	59%
Sandblom[22]	2006	PET	20	10 min	Median 2.0	75%
Vees[23]	2006	PET	11	2min	< 0.8	55%
Wachter[24]	2006	PET	50	15 min	0.5 - 24.9	64%
Albrecht[25]	2007	PET	17 (RT) 15 (RP)	2 min	2.6 - 30.2 0.08 - 4.8	82% 60%
Dusing[26]	2010	PET/CT	20	5 - 10 min	Unknown	85%
Yu[27]	2011	PET	8	2 min	6.3 - 2,012	100%
Haseebuddin[28]	2013	PET/CT	107	10 - 15 min	1.4-225.4	68%
Almeida[33]	2013	PET/CT	300	3 min	0.2 - 98 (mean 6.9)	84%

only studies, longer imaging acquisition times where generally necessary compared to modern PET/CT. Additionally, the detection of smaller lesions may have been less compared to higher-resolution, modern PET/CT. A recent meta analysis by Mohsen et al. [29] demonstrated a pooled sensitivity of 64% and specificity of 93%. In that analysis, included studies were generally small and highly heterogeneous. In 14 literature references evaluated in the meta analysis, 3 small studies were extreme outliers with very low detection rates (21 to 38%). Pooled sensitivity of the remaining 11 studies was significantly higher at 75% and likely more representative of the overall performance of prior studies. Our review of several publications where the timing of imaging could be ascertained demonstrates a trend of lower detection rates with longer delay from injection to imaging. See Table 1.

The differences in the early-to-late imaging findings in our study are not fully understood, as the kinetic molding work by Schiepers et al. [30] suggests pooling or trapping of AC for intracellular processes (for example, incorporation into mitochondria for energy metabolism, in the cytosol for enhanced lipid synthesis, and for building blocks for membranes, amino acids, and steroids). Time-activity curves from that study suggest rapid clearance from the blood pool with an early peak of AC uptake in prostate cancer cells, but then with a plateau after 5 to 10 minutes. In the meta analysis by Mohsen et al. [29], the authors indicated that time to imaging did not appear to influence sensitivity; however, their analysis did not distinguish between detection of local recurrence from detection of regional nodal and distant metastatic disease. Our data suggests, at least in sites of regional or distant metastatic disease, that a degree of AC washout or oxidation via the tricarboxylic acid cycle to CO2 and H2O may play a part after a 20-minute post-tracer injection. In conjunction with the rapid decay of C11 due to its short half-life, this may contribute to the lower levels of measured lesion tracer activity and L/B ratios in the later time-point imaging sequences.

Use of C11 choline PET imaging in patients with BCR prostate cancer has recently been approval by the U.S. Food and Drug Administration (FDA) for "in house" use at the Mayo Clinic. This has generated intense interest in the biomedical molecular imaging community. The primary experience with C11 choline in prostate cancer has been in Europe. Briefly, C11 choline has been found to be relatively insensitive in patients with BCR after surgery, with PSA values less than 2 ng/mL. In a study by Giovacchini et al. [31], C11 choline had a 5% detection rate for PSA levels of < 1 ng/mL, 15% for PSA levels of 1 to 2 ng/mL, and 28% for PSA levels of > 2 ng/mL. Data published on 176 patients by the Mayo Clinic, which formed a portion of the basis for FDA approval, demonstrated better imaging characteristics in the less than 2 ng/mL PSA range compared to the European data, but still performed poorly overall [32].

Based on our findings in this multiple time-point imaging study, early AC PET/CT imaging (3 minutes post injection) has been applied in an ongoing larger evaluation of performance characteristic in patients with biochemically recurrent prostate cancer [33]. Results in 300 patients (PSA 0.2 to 98 ng/mL, mean 6.9) thus far enrolled demonstrated an overall detection rate

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of 84%, which was in concordance with other AC PET studies performed with shorter delay to imaging. When compared to performance data for C11 choline, AC demonstrates a superior overall detection rate (84% for AC versus 74% for choline). Additionally, AC performed better at nearly all levels of PSA. See Figure 6. In the PSA greater than 2ng/mL range, AC shows a 90% detection rate compared to 86% for choline. In the lower PSA range (0.4 to 2.0ng/mL), AC has a much higher overall detection rate of 77% compared with 60% for choline. Possible explanations for the higher performance of AC compared to choline may be the difference in imaging technique and patient characteristics, but also urinary tracer excretion may have contributed. Choline demonstrates some urinary excretion, while AC does not have significant urinary excretion. On AC studies, better evaluation and detection of lesions was likely afforded in the prostate bed, peri-prostate soft tissues, and lymph nodes along the ureters. Our study of AC PET/CT continues with more detailed analysis and publication pending. Further analysis of the impact of PSA kinetics and patient follow-up will be of significant importance to add to the understanding of the performance characteristic of AC PET/CT.

In conclusion, in patients with biochemically recurrent prostate cancer, early post injection C11 acetate PET/CT imaging utilizing modern hybrid PET/CT systems appears to demonstrate higher lesion tracer activity and higher lesion-to-background ratios compared to later imaging. This was found to be the case in the evaluation for nodal, peri-prostate, and bony metastasis, likely leading to the detection of small lesions that may otherwise have gone undetected on late imaging. Lesions in the prostate and seminal vesicles were detected, with higher tracer activity on earlier imaging but without statistically different early-to-late lesion-to-background ratios. Our findings are further confirmed by implementation of early imaging in a large series of patients (300), with generally superior detection rates of recurrent or metastatic prostate cancer when compared to studies performed with longer post-injection imaging times. The detection rate of AC PET/CT also appears to be generally superior to C11 choline PET/CT, particularly in the low PSA ranges (0.4 to 2.0ng/mL).

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