

## Original Article

# Combined SPECT and multidetector CT for prostate cancer evaluations

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**Abstract:** <sup>111</sup>In-capromab pentetide is an imaging probe for noninvasive detection of prostate cancer dissemination, and can be difficult to interpret because of low photon statistics resulting in noisy images with limited anatomical precision. We examined if a 16-slice multidetector computed tomography (MDCT) combined with single photon emission computed tomography (SPECT) could increase the impact on the clinical management and improve confidence in SPECT image interpretations in comparison to a relatively low-mA (limited resolution) CT. 17 scans were reviewed from a SPECT combined with low-mA CT scanner; 21 scans were reviewed from a SPECT combined with 16-slice MDCT scanner. Reports of the clinical interpretations from the imaging studies, additional examinations performed by referring physicians as a follow-up to the imaging results, and long-term clinical and laboratory follow-ups were used to define confidence of the SPECT/CT readings and impact of the readings on the patient management. The impact was defined as: the occurrence of the <sup>111</sup>In-capromab pentetide interpretation resulted in additional imaging studies or biopsies. MDCT improved the quality and confidence in the characterization of small lymph nodes with or without uptake of <sup>111</sup>In-capromab pentetide. The increased confidence with MDCT in SPECT/CT readings was evident in all cases reviewed in this study, and the impact on the clinical management was higher (8 out of 21) using SPECT/MDCT than the impact using SPECT combined with low-mA CT (2 out of 17). The dual-modality SPECT/CT provides a quantifiable benefit when MDCT is used instead of low-mA CT, particularly for prostate cancer evaluations using <sup>111</sup>In-capromab pentetide.

**Keywords:** Prostate cancer, capromab pentetide, SPECT/CT, MDCT, prostate specific membrane antigen (PSMA)

## Introduction

Oncologic imaging with SPECT combined with CT (SPECT/CT) is promising because many SPECT tracers used in oncologic evaluations can benefit from the anatomic localization provided by CT [1-4]. Among SPECT oncologic applications, <sup>111</sup>In-capromab pentetide scans are considered difficult to interpret primarily because of the tracer's nonspecific uptake patterns [5-7]. Capromab pentetide targets the intracellular epitope of prostate specific membrane antigen (PSMA). Due to the high background PSMA expression in normal tissues and the tracer's somewhat suboptimal targeting efficiency, reliably mapping the anatomic distri-

bution of <sup>111</sup>In-capromab pentetide with high resolution CT is likely to improve the diagnostic utility of the method. <sup>111</sup>In-capromab pentetide was developed exclusively for the SPECT technology, and there is no comparable radiotracer developed for the PET technology yet.

The development of SPECT/CT [8-10] has stimulated research with radiotracers like <sup>111</sup>In-capromab pentetide for oncologic evaluations [1, 11-16]. What has not been evaluated is the benefit of having a high-quality multidetector CT when it is combined with SPECT. Hence, the direct comparison between two totally different approaches of SPECT/CT scanner development, namely SPECT with low-mA (thus, limited resolu-

tion) CT (e.g., GE Healthcare's Infinia Hawkeye 4) versus SPECT with standard diagnostic multidetector CT (e.g., Siemens Healthcare's Symbia T16 or Philips Healthcare's Precedence 16) is the focus of this work.

For the comparison, a quantifiable metric is essential. At our institution, we have two SPECT/CT scanners that have been utilized for the  $^{111}\text{In}$ -capromab pendetide studies, with one a low-mA CT combined with SPECT (GE Infinia Hawkeye 4) and the other standard diagnostic CT (16 slice MDCT with a diagnostic x-ray tube) scanner combined with SPECT (Philips Precedence). In the past years, we performed  $^{111}\text{In}$ -capromab pendetide SPECT/CT scans using both scanners. One benefit of the 16-slice MDCT is time saved from the CT acquisition compared to the slower CT of the low-mA scanner.

In this report, we illustrate the capability of the 16-slice MDCT (hereinafter, we refer this CT simply as MDCT) in the SPECT evaluations of  $^{111}\text{In}$ -capromab pendetide, and how the MDCT addition potentially makes a quantifiable impact on the disease management. A comparison study of standalone SPECT versus dual-modality SPECT/CT as well as a comparison between simple analytic reconstruction algorithms (e.g., filtered backprojection) and more sophisticated iterative reconstruction methods involving corrections of obvious physical perturbations such as photon attenuation have already been extensively reported in literature including our own previous investigations [1, 11, 17-19]. Thus, these comparisons are not part of the present manuscript.

## Materials and methods

### *Patient recruitment and data collection*

Patients data were retrieved following an institutional review board (IRB) approved protocol. Although the imaging study itself is an FDA-approved procedure that does not need additional approval from IRB, the data collection and other test results including descriptive pathologic evaluations require an IRB approval for patient recruitment. The imaging protocols were consistent regardless of the choice of the scanner. Patients were administered with 185-222 MBq of  $^{111}\text{In}$ -capromab pendetide followed by postinjection SPECT/CT scans at 96 hours. In

our  $^{111}\text{In}$ -capromab pendetide SPECT/CT scans included in this report, we have not performed simultaneous blood pool imaging because the coregistered CT from either MDCT or low-mA CT provided the anatomical reference. A total of 38 patients (21 MDCT-SPECT: 17 low-mA CT-SPECT) are included in the study. The patient demographics including prescan prostate specific antigen (PSA) levels (ng/ml) and Gleason scores are tabulated in **Table 1**. The assessment for lymph node uptake of  $^{111}\text{In}$ -capromab pendetide by SPECT/CT studies is also listed in the same table. Since the volume of  $^{111}\text{In}$ -capromab pendetide scans has been small at our institution, the patient studies included in this report were performed over the years from 2000 to 2009.

**Table 1.** Demographics of patients and relevant information for  $^{111}\text{In}$ -capromab pendetide SPECT/CT studies, including prescan Gleason scores. The lymph node uptake assessment by SPECT/CT studies is listed, and the cases that need clarifications are explained in the footnotes.

	SPECT/ MDCT	SPECT/(low- mA)CT
Pre-scan Gleason score	3+3 (5) 3+4 (7) 4+3 (5) 5+4 (2) 5+5 (1) N/A (0)	3+4 (2) 4+3 (2) 6 (2) 7 (2) 8 (2) 9 (1) N/A (6) <sup>a</sup>
Pre-scan PSA (ng/ml)	0-5 (4) 5-10 (6) 10-15 (5) 15-20 (2) 20 (4)	0-5 (9) 5-10 (3) 10-20 (2) 20 (3) N/A (1) <sup>b</sup>
LN assessment <sup>c</sup>	LN positive (9) <sup>d</sup> LN negative (12) <sup>f</sup>	LN positive (3) <sup>e</sup> LN negative (15) <sup>g</sup>
Total	21	17

<sup>a</sup>Gleason score was not archived when the data were reviewed. Single digit scores are combined Gleason grades. <sup>b</sup>Prescan PSA was not archived when the data were reviewed. <sup>c</sup>Only suspicious lymph node uptake is considered for this assessment. <sup>d</sup>One case was pathologically confirmed false positive. The others did not have other definitive confirmation. <sup>e</sup>No definitive pathologic confirmation was made. <sup>f</sup>One case was pathologically confirmed false negative. Two were pathologically confirmed true negatives. <sup>g</sup>One case was LN (obturator) positive by magnetic resonance studies.

### *SPECT/CT systems and SPECT reconstruction algorithm parameters*

Our studies were performed using the SPECT/CT scanner with a 16-slice MDCT (Precedence 16, Philips Healthcare, Andover, MA) installed at the San Francisco Veterans Affairs Medical Center (SFVAMC), and the two SPECT/CT scanners with a low-mA CT (Infinia Hawkeye 4 and Millennium VG, GE Healthcare, Chalfont St. Giles, UK) installed at the China Basin Outpatient Imaging Center and the Moffitt-Long Hospital of the University of California, San Francisco (UCSF). The Millennium VG SPECT/CT scanner was decommissioned in 2004, and all low-mA CT/SPECT studies were done with the Infinia Hawkeye 4. The 16-slice MDCT/SPECT studies that are included in this report were mostly performed between 2008 and 2009.

All SPECT reconstructions were iterative ordered-subsets expectation maximization (OS-EM) algorithm with photon attenuation correction based on CT transmission scan, provided by each manufacturer. The reconstruction parameters recommended by the vendor of  $^{111}\text{In}$ -capromab pentetide (EUSA Pharma, Oxford, UK) for each scanner were implemented for all patient studies. The SPECT projections were acquired with  $128 \times 128$  matrix at 120-128 angles and 55-60 s per stop. The variables were only due to the use of different scanners; however within the studies using a single scanner, the acquisition parameters were maintained consistently. The reconstructed images were post-filtered using Hanning filter.

### *CT acquisition and registration*

For corresponding SPECT field of view, abdominal-pelvic CT was acquired for all patient studies. No iodinated contrast agent was used. For the 16-slice MDCT, 140 kVp tube voltage and 30-150 mA modulated tube current were used. The data were acquired using a  $512 \times 512$  matrix and a 2.5 mm slice thickness. For low-mA CT, 140 kVp tube voltage and 2.5 mA tube current were used. The data were acquired using a  $256 \times 256$  matrix and a 10 mm slice thickness. The reconstruction algorithm was not modified specifically for these studies. Conventional filtered backprojection (FBP) provided by manufacturers was used for reconstruction of CT data. Registration of CT reconstructed images over SPECT images was based on preset trans-

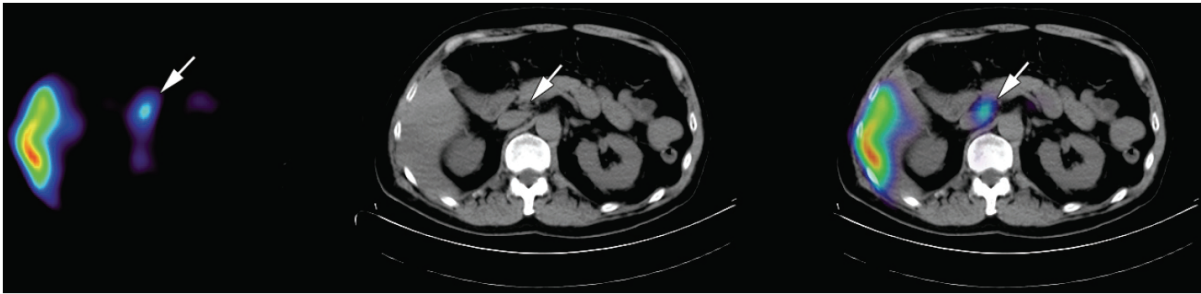
formation matrix, and the registered CT was rescaled to patient-specific attenuation map, as an input to iterative SPECT reconstruction with corrections for photon attenuation. The accuracy of registration between SPECT and CT was visually inspected for each study for attenuation correction and generation of CT data for correlative anatomical reference of SPECT uptake patterns.

### *Clinical follow-up*

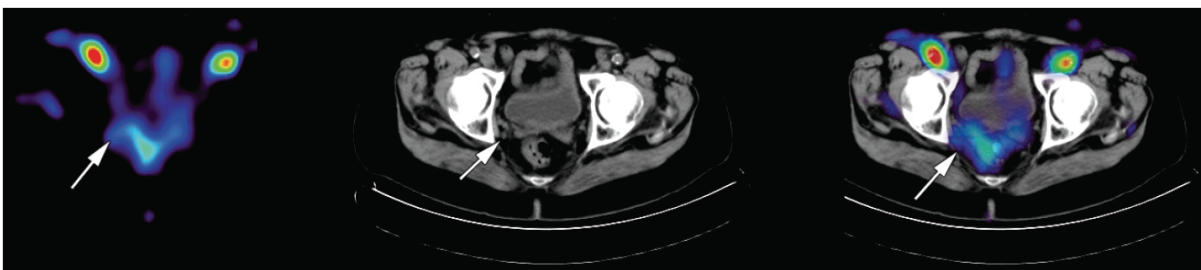
Clinical outcomes were examined after the imaging studies in order to investigate the effect of the difference in CT resolutions (limited resolution versus standard high resolution) on SPECT/CT evaluations of  $^{111}\text{In}$ -capromab pentetide. The clinical follow-up period was in the range from 3 to 107 months with an average of 51 months. The indications for the SPECT/CT studies, and the outcomes of the SPECT/CT readings were the main data points used to assess the quantifiable metrics of added effects of each CT scans to  $^{111}\text{In}$ -capromab pentetide SPECT/CT scans. These clinical follow-ups included: clinical examinations by referring physicians (mostly urologists), biopsy results, pathologic analyses in cases of prostatectomy, external beam radiotherapy, brachytherapy, and PSA monitoring.

### *Quantifiable metrics*

From the clinical follow-ups, we developed a criterion to quantify the benefit of adding CT to the SPECT interpretation. The criterion we used was whether the interpretation from SPECT/CT made an impact on the clinical management of prostate cancer. The impact was defined as the occurrence of the  $^{111}\text{In}$ -capromab pentetide interpretation that resulted in additional correlative imaging studies and biopsies, which initiated reassessment of the treatment strategies. The confidence of the interpretation results was also followed for each SPECT/CT readings with a scale from 1-3, with 1 being the lowest confidence and 3 being the highest confidence. The confidence in readings was strictly limited to the anatomic precision of the radiotracer uptake. The readings were initially performed by nuclear medicine residents (D.C. and N.N.) and confirmed by attending nuclear medicine physicians (C.M.A. and R.H.), and the impact and confidence level scales were tabulated by one attending nuclear medicine physician (C.M.A.)



**Figure 1.** SPECT/MDCT case of showing a 1.5 × 0.7 cm peripancreatic lymph node with correlative <sup>111</sup>In-capromab pentetide uptake. Images of SPECT alone (left); CT alone: (middle); SPECT-CT fusion (right). Arrows indicate where the lymph node uptake was identified.



**Figure 2.** Another SPECT/MDCT case of showing a right external iliac lymph node with correlative <sup>111</sup>In-capromab pentetide uptake. Images of SPECT alone (left); CT alone: (middle); SPECT-CT fusion (right). Arrows indicate where the lymph node uptake was identified.

based on the imaging reports generated from the readings.

## Results

### *Unique capability of high quality MDCT in SPECT interpretations*

We report two representative cases in **Figures 1** and **2** where the MDCT showed anatomical visualizations of lymph nodes that were not enlarged, but correlated with suspicious SPECT uptakes. Small lymph nodes approximately less than 10 mm in diameter were never identified in the cases that were reviewed for this manuscript using a low-mA CT combined with SPECT. In **Figure 2**, the suspicious uptake of <sup>111</sup>In-capromab pentetide in the small right external iliac lymph node may not look so clear because of the limited spatial resolution of SPECT. In comparison to **Figures 1** and **2**, representative images from SPECT combined with low-mA CT (**Figure 3**) show suspicious lymph node uptake of <sup>111</sup>In-capromab pentetide at the level of pelvis, showing asymmetric focal activity in the right external iliac region. However, because of

the limited resolution of CT, a lymph node was difficult to be clearly identified. In this case, a differential diagnosis is normal blood pool activity in external iliac vessels.

### *Confidence level changes*

Regardless of the indications for the SPECT/CT studies of <sup>111</sup>In-capromab pentetide, our result of comparing the scales of confidence in reading the scans from SPECT combined with the low-mA CT versus SPECT/MDCT is shown in **Table 2**. The scale we used was a whole number in the range from 1 to 3 with 3 being the highest confidence. These scales were calibrated as a comparative scale with adjustments after reviewing all cases presented in this manuscript from both SPECT/CT scanners. **Table 2** indicates a pattern of preference of using MDCT in correlating SPECT uptake patterns with anatomical reference (e.g., **Figures 1** and **2**), with an overwhelming confident readings using the SPECT/MDCT scanner. Our confidence level assessment was semiquantitative without the power to derive statistical significance. However, we note that there is no overlap in the con-

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**Figure 3.** Example of SPECT/(low-mA)CT case of showing a suspicious  $^{111}\text{In}$ -capromab pentetide uptake at the level of the pelvis in the right external iliac region. Low-mA CT with the limited resolution could not differentiate lymph node from blood pool in this example. Images of SPECT alone (left); CT alone: (middle); SPECT-CT fusion (right). Arrows indicate where the lymph node uptake was suspected.

**Table 2.** Confidence of image interpretations with added benefits of CT to localize SPECT uptake patterns. Confidence was on a scale between 1 and 3 while 1 being the lowest confidence and 3 being the highest confidence.

Confidence	1 (low)	2	3 (high)	subtotal
SPECT/(low-mA)CT	3	14		17
SPECT/MDCT			21	21

confidence level differences between the two types of SPECT/CT scanners, showing clear advantages of using SPECT/MDCT over SPECT/(low-mA)CT for the confident assessment of  $^{111}\text{In}$ -capromab pentetide.

### *Impact on clinical management*

In **Table 3**, we tabulated the numbers of SPECT/CT studies using these two SPECT/CT scanners to determine whether the scan results made an impact on the clinical management. A binary scale was used because our definition of the impact described in the Methods section simplified how the impact was assessed. Out of 17 scans reviewed for the case of SPECT/(low-mA)CT, only 2 cases made clinical impact when both indications of the scans and outcomes of the scans were compared. One of these 2 cases, additional biopsy was performed, which turned out to be negative. The other case had influence on the external beam radiation treatment planning.

On the other hand, 8 out of 21 scans resulted in clear clinical impacts on the patient managements when the SPECT/MDCT was utilized for the  $^{111}\text{In}$ -capromab pentetide studies. In 7 of these 8 cases, additional ultrasound, diagnostic CT, or  $^{18}\text{F}$ -fluorodeoxyglucose positron emission

**Table 3.** Impact of  $^{111}\text{In}$ -capromab pentetide SPECT/CT readings on the clinical management of prostate cancer. The impact was defined as the occurrence of the  $^{111}\text{In}$ -capromab pentetide interpretations that resulted in additional correlative studies such as extra imaging procedures and biopsies.

Impact	yes	no	percentage
SPECT/(low-mA)CT	2	15	11.8 %
SPECT/MDCT	8	13	38.1 %

tomography (FDG-PET/CT) studies were obtained to correlate with the positive/negative assessment of  $^{111}\text{In}$ -capromab pentetide. The other one case was a patient with very high PSA and negative imaging study for metastases. The patient had a biopsy of the prostate bed that confirmed prostatitis and no cancer recurrence. Follow up PSA numbers decreased.

### **Discussion**

Although we presented only a limited set of studies in this report, the importance of our findings could be significant considering the degree of difficulty in the interpretations of  $^{111}\text{In}$ -capromab pentetide studies. The limited data-

sets were mostly due to the limited volume of  $^{111}\text{In}$ -capromab pendetide studies at our institution; however, all the studies performed using either of SPECT/CT techniques (with low-mA CT or MDCT) were valuable to make this comparison study possible. Even for experienced readers (C.M.A. and R.H.), the clarity of anatomical localization power that MDCT provided added benefits in the identification of suspected SPECT uptake patterns. It also helped increase the confidence of the readings significantly in a relative scale when the readings were compared with the SPECT/CT studies using SPECT combined with low-mA CT. The confidence we defined in this manuscript, when the images were presented for interpretation, could be somewhat biased because the quality of CT images from MDCT was, by any means, superior to that from low-mA CT.

The limited spatial resolution of SPECT, typically over 10 mm full-width at half maximum (FWHM), sometimes presents challenges of interpreting  $^{111}\text{In}$ -capromab pendetide studies, even with the help of MDCT, as shown in **Figure 2**. In addition, the inherent problem of the radiopharmaceutical,  $^{111}\text{In}$ -capromab pendetide, which binds to intracellular domain of PSMA, for its limited sensitivity should not be overlooked even when the MDCT is used for SPECT/CT. This is a biological property of the radiopharmaceutical, not the technological issue of the imaging procedure. For some of emerging radiotracers for prostate cancer imaging under development such as  $^{123}\text{I}$ -MIP-1072 [20], the sensitivity and specificity of the radiotracer will potentially be improved. However, even in that case, the technical capability of SPECT spatial resolution will be still a limiting factor, and an appropriate anatomical reference of lymph node from MDCT will be important for suspected lymph node uptake of  $^{111}\text{In}$ -capromab pendetide SPECT.

The number of the slices in MDCT might not be an important factor in oncologic studies of SPECT/CT. However, the higher slice number (16 and higher) apparently provides faster scans, which could result in reduced physical and physiologic motion artifacts [21, 22], which sometimes requires manual registration of the two images.

Another aspect of SPECT combined with MDCT is radiation dose. The MDCT with standard diagnostic x-ray tube delivers more radiation dose (e.g., 9.1 mSv for abdominal-pelvic CT using

Philips Brilliance 16-slice CT that is used for Precedence 16 SPECT/CT, shown in [23]) to patients in comparison to the dose delivered by a low-mA CT (e.g., 1.5 mSv for abdominal-pelvic CT using Hawkeye CT used for Infinia Hawkeye SPECT/CT, shown in [24]) in some SPECT/CT scanners. A better anatomic map of disease distribution with MDCT in patients with prostate cancer likely outweighs the added radiation risk of MDCT compared to low-mA CT. This is particularly true for prostate cancer patients who have or will have radiation therapy. In those patients, the added radiation risk of MDCT is negligible.

### Conclusion

Although we have performed SPECT/CT studies of  $^{111}\text{In}$ -capromab pendetide over the last decade, and accumulated expertise in reading these difficult studies, it is only recently that we were able to assess and quantify the differences between two significantly different SPECT/CT approaches, one SPECT combined with low-mA (limited resolution) CT and the other SPECT combined with high-quality standard diagnostic multidetector CT. This study is the first to quantify the differences between these two SPECT/CT approaches, and shows the quantifiable benefit of using MDCT in SPECT/CT evaluations of prostate cancer in terms of confidence in readings and impact on the clinical management.

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