

# Detection of Recurrent Prostate Carcinoma with *anti*-1-Amino-3-<sup>18</sup>F-Fluorocyclobutane-1-Carboxylic Acid PET/CT and <sup>111</sup>In–Capromab Pendetide SPECT/CT<sup>1</sup>

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## Purpose:

To compare the diagnostic performance of the synthetic amino acid analog radiotracer *anti*-1-amino-3-fluorine 18-fluorocyclobutane-1-carboxylic acid (*anti*-3-<sup>18</sup>F-FACBC) with that of indium 111 (<sup>111</sup>In)–capromab pendetide in the detection of recurrent prostate carcinoma.

## Materials and Methods:

This prospective study was approved by the institutional review board and complied with HIPAA guidelines. Written informed consent was obtained. Fifty patients (mean age, 68.3 years ± 8.1 [standard deviation]; age range, 50–90 years) were included in the study on the basis of the following criteria: (a) Recurrence of prostate carcinoma was suspected after definitive therapy for localized disease, (b) bone scans were negative, and (c) *anti*-3-<sup>18</sup>F-FACBC positron emission tomography (PET)/computed tomography (CT) and <sup>111</sup>In–capromab pendetide single photon emission computed tomography (SPECT)/CT were performed within 6 weeks of each other. Studies were evaluated by two experienced interpreters for abnormal uptake suspicious for recurrent disease in the prostate bed and extraprostatic locations. The reference standard was a combination of tissue correlation, imaging, laboratory, and clinical data. Diagnostic performance measures were calculated and tests of the statistical significance of differences determined by using the McNemar  $\chi^2$  test as well as approximate tests based on the difference between two proportions.

## Results:

For disease detection in the prostate bed, *anti*-3-<sup>18</sup>F-FACBC had a sensitivity of 89% (32 of 36 patients; 95% confidence interval [CI]: 74%, 97%), specificity of 67% (eight of 12 patients; 95% CI: 35%, 90%), and accuracy of 83% (40 of 48 patients; 95% CI: 70%, 93%). <sup>111</sup>In–capromab pendetide had a sensitivity of 69% (25 of 36 patients; 95% CI: 52%, 84%), specificity of 58% (seven of 12 patients; 95% CI: 28%, 85%), and accuracy of 67% (32 of 48 patients; 95% CI: 52%, 80%). In the detection of extraprostatic recurrence, *anti*-3-<sup>18</sup>F-FACBC had a sensitivity of 100% (10 of 10 patients; 95% CI: 69%, 100%), specificity of 100% (seven of seven patients; 95% CI: 59%, 100%), and accuracy of 100% (17 of 17 patients; 95% CI: 80%, 100%). <sup>111</sup>In–capromab pendetide had a sensitivity of 10% (one of 10 patients; 95% CI: 0%, 45%), specificity of 100% (seven of seven patients; 95% CI: 59%, 100%), and accuracy of 47% (eight of 17 patients; 95% CI: 23%, 72%).

## Conclusion:

*anti*-3-<sup>18</sup>F-FACBC PET/CT was more sensitive than <sup>111</sup>In–capromab pendetide SPECT/CT in the detection of recurrent prostate carcinoma and is highly accurate in the differentiation of prostatic from extraprostatic disease.

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**P**rostate carcinoma is the second leading cause of death in men in the United States, with 32050 estimated deaths in 2010 (1). The presence of an elevated prostate-specific antigen (PSA) level after definitive therapy for prostate cancer is suggestive of recurrence. Although approximately 30% of patients will experience recurrence of elevated PSA levels, those with biochemical failure may not manifest clinical disease (2–4).

Recurrence can occur within the prostate bed, in extraprostatic locations, or both. The restaging of patients with stage D0 disease (biochemical recurrence after definitive therapy) is crucial because the differentiation of prostatic bed from extraprostatic recurrence is vital for tailoring subsequent therapy, especially the use of salvage techniques. This differentiation cannot be made with PSA values alone, although a faster PSA doubling time may be indicative of a higher risk for distant disease (5,6).

Typically, restaging is performed with a combination of ultrasonography (US)-guided transrectal biopsy, bone scanning, computed tomography (CT), and magnetic resonance (MR) imaging (7–11). Molecular imaging with indium 111 (<sup>111</sup>In)-capromab pentetide (ProstaScint; EUSA Pharma, Langhorne, Pa)

is also used to restage recurrent prostate cancer (9,11–14). However, accurate determination of the extent and location of recurrent disease with existing imaging techniques has proved challenging (14,15).

*anti*-1-amino-3-fluorine 18-fluorocyclobutane-1-carboxylic acid (*anti*-3-<sup>18</sup>F-FACBC) is a synthetic amino acid analog that has demonstrated promise in a pilot study for the staging and restaging of prostate carcinoma (16). The uptake of *anti*-3-<sup>18</sup>F-FACBC is likely mediated through one amino acid transport protein or a combination of amino acid transport proteins, and the radiotracer is not metabolized (17,18). Normal biodistribution of *anti*-3-<sup>18</sup>F-FACBC includes relatively intense uptake in the liver and pancreas and little renal excretion or brain uptake compared with <sup>18</sup>F fluorodeoxyglucose (FDG) (19). In this study, we set out to compare the diagnostic performance of the synthetic amino acid analog radiotracer *anti*-3-<sup>18</sup>F-FACBC with that of <sup>111</sup>In-capromab pentetide in the detection of recurrent prostate carcinoma.

### Materials and Methods

One author (M.M.G.) and Emory University are eligible to receive royalties from the radiotracer being studied. The other authors had control of the data that might be a conflict for the author with a potential conflict of interest.

### Preparation of *anti*-3-<sup>18</sup>F-FACBC

The preparation of *anti*-3-<sup>18</sup>F-FACBC has been previously reported (20). The decay-corrected radiochemical yield of the desired product was 24%, and its radiochemical purity was 99% 80 minutes after the end of bombardment. The mass of amino acids, predominantly *anti*-1-amino-3-hydroxycyclobutane-1-carboxylic acid, in the production batch was approximately 1.5 mg or 9.0 μmol, and the specific activity was 580–820

MBq/μmol based on *anti*-1-amino-3-hydroxycyclobutane-1-carboxylic acid at the end of synthesis.

### Patient Selection

This prospective study was approved by the institutional review board and complied with Health Insurance Portability and Accountability Act guidelines. Written informed consent was obtained. Studies were performed between December 12, 2007, and June 17, 2010. All patients were evaluated at Emory Health Care. No adverse events were reported. Patients were included in this study if the following criteria were met: (a) Patients were originally diagnosed with localized (stage T1c, T2, or T3) prostate carcinoma and had undergone definitive therapy for localized disease; (b) recurrent prostate carcinoma was suspected on the basis of previous American Society for Radiology and Oncology (ASTRO) criteria of three consecutive increases in PSA level, the more recent ASTRO-Phoenix criteria of an increase in PSA level of at least 2.0 ng/mL above the nadir level after radiation therapy or cryotherapy, and/or an absolute PSA level of 0.3 mg/mL or

### Advances in Knowledge

- Amino acid transport as characterized with *anti*-1-amino-3-fluorine 18-fluorocyclobutane-1-carboxylic acid (*anti*-3-<sup>18</sup>F-FACBC) PET/CT enabled detection of local recurrence with a sensitivity of 89% (95% confidence interval [CI]: 74%, 97%); conventional imaging with <sup>111</sup>In-capromab pentetide SPECT/CT had a sensitivity of 69% (95% CI: 52%, 84%).
- *anti*-3-<sup>18</sup>F-FACBC PET/CT helped detect extraprostatic recurrent disease with a sensitivity of 100% (95% CI: 69%, 100%); <sup>111</sup>In-capromab pentetide SPECT/CT had a sensitivity of 10% (95% CI: 0%, 45%).

### Implication for Patient Care

- *anti*-3-<sup>18</sup>F-FACBC PET/CT can be used to accurately restage prostate cancer.

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### Abbreviations:

*anti*-3-<sup>18</sup>F-FACBC = *anti*-1-amino-3-fluorine 18-fluorocyclobutane-1-carboxylic acid  
 CI = confidence interval  
 FDG = fluorine 18 fluorodeoxyglucose  
 PSA = prostate-specific antigen

### Author contributions:

Guarantor of integrity of entire study, D.M.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, D.M.S., P.J.R.; clinical studies, D.M.S., B.S.B., P.T.N., R.K.H., P.J.R., M.M.L., J.A.N., W.Y.; statistical analysis, D.M.S., P.J.R., J.A.N., F.D.B.; and manuscript editing, D.M.S., P.T.N., P.J.R., J.A.N., F.D.B., M.M.G.

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Potential conflicts of interest are listed at the end of this article.

greater after prostatectomy; (c) bone scans were negative for metastatic disease; and (d)  $^{111}\text{In}$ -capromab pendetide and *anti*-3- $^{18}\text{F}$ -FACBC studies were performed within 6 weeks of each other.

#### ***anti*-3- $^{18}\text{F}$ -FACBC Imaging Protocol**

Scanning was conducted by using a positron emission tomography (PET)/CT unit (Discovery DLS; GE Medical Systems, Milwaukee, Wis), and scans were interpreted on a workstation with use of software (MIMvista 4.2; MIMvista, Cleveland, Ohio). All patients fasted for 4–6 hours before undergoing scanning with *anti*-3- $^{18}\text{F}$ -FACBC.

After patients underwent CT of the abdomen and pelvis (80–120 mA, 120 kVp) with oral contrast material and without intravenous contrast material, *anti*-3- $^{18}\text{F}$ -FACBC (199.8–484.7 MBq) was injected intravenously over 2 minutes. After a 3-minute delay for blood pool clearance, PET was performed with three contiguous acquisitions (4 minutes per frame) starting from the pelvis below the prostate and extending superiorly to include the abdomen above the kidneys. This process was repeated twice. Thus, 5–16-minute (early), 17–28-minute (delayed 1), and 29–40-minute (delayed 2) acquisitions were performed. Images above the diaphragm were not acquired.

#### **$^{111}\text{In}$ -Capromab Pendetide Imaging Protocol**

Whole-body planar and abdominopelvic SPECT/CT examinations were performed 4 days after injection of 185-MBq  $^{111}\text{In}$ -capromab pendetide. Patients underwent imaging without fasting by using a protocol similar to that used by Sodde and co-workers (21). Imaging was performed with one of two single photon emission computed tomography (SPECT)/CT systems (VG/Hawkeye [GE Healthcare, Waukesha, Wis] or Symbia T6 [Siemens, Hoffman Estates, Ill]) equipped with medium-energy all-purpose parallel-hole collimation with two photopeak settings of 171 and 245 keV. Whole-body planar images were acquired with a  $1024 \times 256$  matrix from head to midthigh; this was followed by CT without oral or

intravenous contrast material at 2.5 mA and 140 kVp (VG/Hawkeye) or 120 mA and 130 kVp (Symbia T6). SPECT was performed with a  $128 \times 128$  matrix with no zoom and with either 120 60-second projections (VG/Hawkeye) or 60 100-second projections (Symbia T6); images were reconstructed with and without attenuation correction by using iterative reconstruction with appropriate postreconstruction filtering. Images were then viewed on a workstation (Xeleris, GE Medical Systems). One patient underwent  $^{111}\text{In}$ -capromab pendetide SPECT at another facility, and his images were fused with separately acquired CT scans by using software.

#### **Image Analysis**

One nuclear radiologist with 14 years of experience (D.M.S.) and one nuclear medicine physician with 25 years of experience (R.K.H.) assessed both the *anti*-3- $^{18}\text{F}$ -FACBC and  $^{111}\text{In}$ -capromab pendetide studies. The investigators had access to the patient's history but not to the results of recent imaging studies. The *anti*-3- $^{18}\text{F}$ -FACBC scans were interpreted individually by each reader, with disagreements to be resolved by consensus; however, there were no discrepancies.  $^{111}\text{In}$ -capromab pendetide scans were interpreted in a separate combined session by both readers; this reading session was performed at least 2 weeks later to minimize recall bias.

For *anti*-3- $^{18}\text{F}$ -FACBC scans, uptake in the focus was compared with that in background structures and classified as mild (higher than that of blood pool but less than that of marrow), moderate (higher than or equal to that of marrow but less than that of liver), or intense (equal to or higher than that of liver). Quantitative criteria (maximum standardized uptake value in the lesion/mean standardized uptake value in background) were used to aid the visual analysis. The maximum and mean standardized uptake values were recorded for each focus of abnormal uptake as well as for background structures including liver, marrow at L3, aorta, and bladder. An edge-seeking conformational volume of interest tool (PET Edge, MIMvista) was typically used. For prostate beds as

well as extraprostatic sites (eg, lymph nodes and bone), abnormal moderate or intense focal uptake that was higher than that of background marrow and that persisted from early to delayed imaging was considered prospectively positive.

Well-established criteria were used to evaluate the  $^{111}\text{In}$ -capromab pendetide scans. Uptake was considered to be abnormal when there was activity or asymmetries of increased uptake compared to background expected biodistribution in normal adjacent organs or structures (22–24).

#### **Reference Standard**

The prostate bed in patients with either positive or negative imaging studies was typically investigated with transrectal US and biopsy as clinically appropriate. For patients who had previously undergone prostatectomy, biopsy was not performed if negative imaging studies were obtained at the surgical site and transrectal US did not show abnormal tissue in which to target.

Patients with abnormal foci in extraprostatic tissue at imaging were further investigated by using a combination of percutaneous imaging-guided needle biopsy, laparoscopic techniques, and open lymph node dissection. Because it is unusual for prostate carcinoma to metastasize to inguinal nodes, it was agreed that the inguinal regions would be evaluated with physical examination and percutaneous biopsy performed only if findings were suspicious for carcinoma.

A ground truth panel composed of a nuclear radiologist (D.M.S.), two urologists (P.T.N. and V.A.M., with 32 and 8 years of experience, respectively), and a radiation oncologist (P.J.R., with 5 years of experience) met at a regular conference and communicated via e-mail. Truth was ascertained by means of the criteria outlined below. If there were initial differences of opinion, further discussion ensued until a consensus was achieved.

The presence of disease in the prostate bed was confirmed by means of biopsy, with truth overridden only with use of clinical data. For example, a substantial reduction in PSA level after prostatic bed salvage therapy without

a subsequent substantial increase in PSA level in 6 months would establish not only the presence of presumed prostatic bed disease but also the absence of extraprostatic disease. Extraprostatic nodal involvement per patient was confirmed by means of pathologic proof alone. Skeletal involvement was confirmed with either biopsy or a typical appearance on MR images (25). The absence of extraprostatic disease was confirmed with either a substantial reduction in PSA level after prostatic bed therapy without a substantial increase in 6 months as mentioned earlier and/or stable appearance on CT or MR images for more than 1 year without evidence of nodal or bone involvement. Because some patients had definitive follow-up results for prostate bed but not extraprostatic disease, and vice versa, the number of patients in each subanalysis differed.

### Statistical Analyses

The statistical analyses provided measures of diagnostic performance (eg, sensitivity, specificity, negative predictive value, and positive predictive value) along with the associated confidence intervals (CIs). We determined the statistical significance of differences in sensitivity, specificity, and overall accuracy between *anti*-3-<sup>18</sup>F-FACBC and <sup>111</sup>In-capromab pentetide by using the McNemar  $\chi^2$  test to adjust for correlations in the accuracy measures. The significance of differences for other diagnostic performance measures (positive and negative predictive values) was assessed by using approximate tests based on the difference between two proportions. Statistical significance was determined by using a type I error rate of  $\alpha = 0.05$  for overall comparisons. Statistical analyses were performed by using MatLab software (version 7.10; MathWorks, Natick, Mass) and the R statistical package (R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org>).

### Results

#### Demographics

Fifty patients met the inclusion criteria. The mean patient age ( $\pm$ standard de-

viation) was 68.3 years  $\pm$  8.1 (range, 50–90 years), and the mean PSA level was 6.62 ng/mL  $\pm$  7.63 (range, 0.11–44.74 ng/mL). PSA values were obtained within 16.8 days  $\pm$  37.4 of *anti*-3-<sup>18</sup>F-FACBC scanning. <sup>111</sup>In-capromab pentetide studies were performed within 15.7 days  $\pm$  10.9 (range, 2–37 days) of *anti*-3-<sup>18</sup>F-FACBC scanning. Thirteen patients originally underwent radical prostatectomy, and 37 patients were treated with cryotherapy, high-frequency ultrasound, external beam radiation therapy, and/or brachytherapy. Forty-eight patients had definitive follow-up results for the prostate bed and 17 had definitive follow-up results for extraprostatic disease. Table E1 (online) lists individual patient data and results of imaging and follow-up.

#### Diagnostic Performance: Prostatic Bed

The diagnostic performance of *anti*-3-<sup>18</sup>F-FACBC in the prostate bed was better than that of <sup>111</sup>In-capromab pentetide, with sensitivities of 89% (32 of 36 patients; 95% CI: 74%, 97%) and 69% (25 of 36 patients; 95% CI: 52%, 84%), respectively ( $P = .035$ ). Figure 1 and Table 1 summarize data and reference standards applied for the prostatic bed. Table 2 includes a summary of diagnostic performances.

Four patients had false-positive findings in the prostate bed with *anti*-3-<sup>18</sup>F-FACBC; these patients also had false-positive findings with <sup>111</sup>In-capromab pentetide. Three of these four patients originally underwent a nonradical prostatectomy treatment, and one patient underwent radical prostatectomy. Inflammation was not present in any biopsy sample. Benign glands and stroma were reported in two of the four patients, treatment-related changes were reported in one patient, and benign gland and stroma with fibromuscular tissue and a single lymphoid aggregate were reported in one patient. Four patients had false-negative findings with *anti*-3-<sup>18</sup>F-FACBC; three of these patients also had false-negative findings with <sup>111</sup>In-capromab pentetide. Two of the four patients had undergone radical prostatectomy and two had undergone a nonradical prostatectomy

treatment. Figure 2 shows an example of a patient with true-positive findings in the prostate bed with *anti*-3-<sup>18</sup>F-FACBC and false-negative findings with <sup>111</sup>In-capromab-pentetide after radical prostatectomy. Figure E1 (online) is an example of true-positive uptake in the prostate bed with both modalities.

#### Diagnostic Performance: Extraprostatic Disease

The diagnostic performance of *anti*-3-<sup>18</sup>F-FACBC in the detection of extraprostatic disease was better than that of <sup>111</sup>In-capromab pentetide, with sensitivities of 100% (10 of 10 patients; 95% CI: 69%, 100%) and 10% (one of 10 patients; 95% CI: 0%, 45%), respectively ( $P = .003$ ). Figure 3 and Table 3 summarize data and reference standards applied for extraprostatic disease. Table 2 includes a summary of diagnostic performances.

Extraprostatic recurrence was limited to lymph nodes in eight patients and to bone in one patient. One patient had both nodal and bone involvement. Figure 4 illustrates the detection of extraprostatic disease in a 5-mm node with *anti*-3-<sup>18</sup>F-FACBC PET/CT in a patient with a PSA level of 1.1 ng/mL. Figure 5 illustrates detection of a skeletal metastasis in a patient with a PSA level of 2.97 ng/mL. Both are examples of true-positive findings with *anti*-3-<sup>18</sup>F-FACBC and false-negative findings with <sup>111</sup>In-capromab pentetide. Figures E2 and E3 (online) are more examples of the localization of extraprostatic disease with both modalities.

### Discussion

We set out to determine the diagnostic performance of *anti*-3-<sup>18</sup>F-FACBC PET/CT in the detection of recurrent prostate carcinoma and to compare it with that of <sup>111</sup>In-capromab pentetide SPECT/CT. We demonstrated that *anti*-3-<sup>18</sup>F-FACBC PET/CT enabled the detection of more recurrent disease than did <sup>111</sup>In-capromab pentetide SPECT/CT.

Our findings are important because approximately one-third of patients will have biochemical evidence of recurrence and the therapeutic approach



**Table 1**

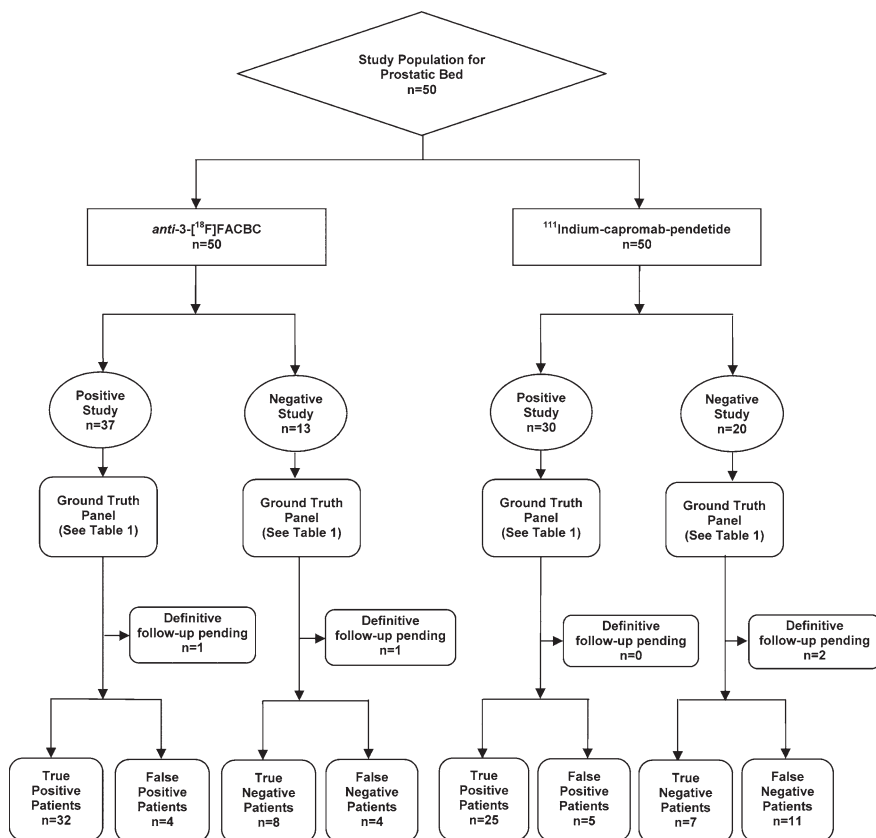
**Reference Standards Applied to Prostate Bed Analysis**

Reference Standard	<i>anti</i> -3- <sup>18</sup> F-FACBC		<sup>111</sup> In-Capromab Pentetide	
	Positive (n = 37)	Negative (n = 13)	Positive (n = 30)	Negative (n = 20)
Biopsy				
Positive	32	2	24	10
Negative	4	8	5	7
PSA nadir level (positive)*	0	2	1	1
Definitive follow-up pending	1	1	0	2

Note.—Data are numbers of patients.

\* Local disease was proved with PSA nadir level after local therapy only.

**Figure 1**



**Figure 1:** Flow diagram of study patients and results obtained for disease in the prostatic bed with <sup>111</sup>In-capromab pentetide and *anti*-3-<sup>18</sup>F-FACBC.

depends not only on confirming recurrence but, most important, determining whether recurrence is confined to the prostate bed or located at extraprostatic sites (2). The suspected location of distant disease may be evaluated with a combination of bone scanning, CT, and MR

imaging. Each of these techniques has its limitations (9–11). A noninvasive method for guiding pathologic confirmation on a whole-body basis is important (14).

<sup>111</sup>In-capromab pentetide is a radiolabeled murine monoclonal antibody that binds to prostate-specific

membrane antigen (26). Its sensitivity and specificity in the detection of recurrent prostate carcinoma was originally reported to be 62% and 72%, respectively (9). Yet, diagnostic performance in the subsequent literature varied widely, with sensitivities of 17%–92% and specificities of 47%–86%—likely reflecting differences in intraobserver variability and study population and design (9,11–14, 27,28). Fusion with CT or MR images has been reported to improve accuracy (24,26,29). In our study, the sensitivity of <sup>111</sup>In-capromab pentetide was 69% for detecting disease in the prostate bed and 10% for detecting disease in extraprostatic sites.

Seltzer and co-workers (13) also compared <sup>111</sup>In-capromab pentetide images to biopsy-sampled nodes and reported that findings from <sup>111</sup>In-capromab pentetide imaging were true positive in only one of six patients. The lower sensitivity of <sup>111</sup>In-capromab pentetide is likely explained by several factors. The antibody in <sup>111</sup>In-capromab pentetide helps detect the intracellular epitope of prostate-specific membrane antigen, which is problematic when the radiotracer is not internalized (23). In addition, the use of *anti*-3-<sup>18</sup>F-FACBC with PET results in images with higher spatial resolution than those obtained with SPECT, possibly contributing to the differences in detection between the two radiotracers in our study. Newly reported advanced SPECT reconstruction methods with <sup>111</sup>In-capromab pentetide may improve accuracy (30,31).

CT is considered of low yield in the detection of recurrent local disease, with one study (32) reporting positive results in only 36% of cases, reflecting the difficulty in distinguishing recurrence from scar. Dynamic contrast material-enhanced MR imaging is used more frequently for the detection of local recurrence, with sensitivities of 70%–95% and specificities of 73%–100% depending on the type of previous therapy (33–36). Routine MR imaging and CT are limited in the detection of nodal involvement, with typical sensitivities in the lower range of 25%–78% and specificities of 66%–100% (26,37–41). MR imaging with superparamagnetic particles may

Table 2

Diagnostic Performance of *anti*-3-<sup>18</sup>F-FACBC and <sup>111</sup>In-Capromab Pentetide

Parameter*	Prostate Bed			Extraprostatic Sites		
	<i>anti</i> -3- <sup>18</sup> F-FACBC	<sup>111</sup> In-Capromab Pentetide	<i>P</i> Value	<i>anti</i> -3- <sup>18</sup> F-FACBC	<sup>111</sup> In-Capromab Pentetide	<i>P</i> Value†
Sensitivity	89% (32/36)	69% (25/36)	.035‡	100% (10/10)	10% (1/10)	.003‡
Specificity	67% (8/12)	58% (7/12)	.317	100% (7/7)	100% (7/7)	NA
NPV	67% (8/12)	39% (7/18)	.068	100% (7/7)	44% (7/16)	.006‡
PPV	89% (32/36)	83% (25/30)	.256	100% (10/10)	100% (1/1)	NA
Accuracy	83% (40/48)	67% (32/48)	.083	100% (17/17)	47% (8/17)	.003‡

Note.—Data in parentheses are numbers of patients.

\* NPV = negative predictive value, PPV = positive predictive value.

† NA = not applicable (sample size was too small).

‡ Statistically significant ( $P \leq .05$ ).

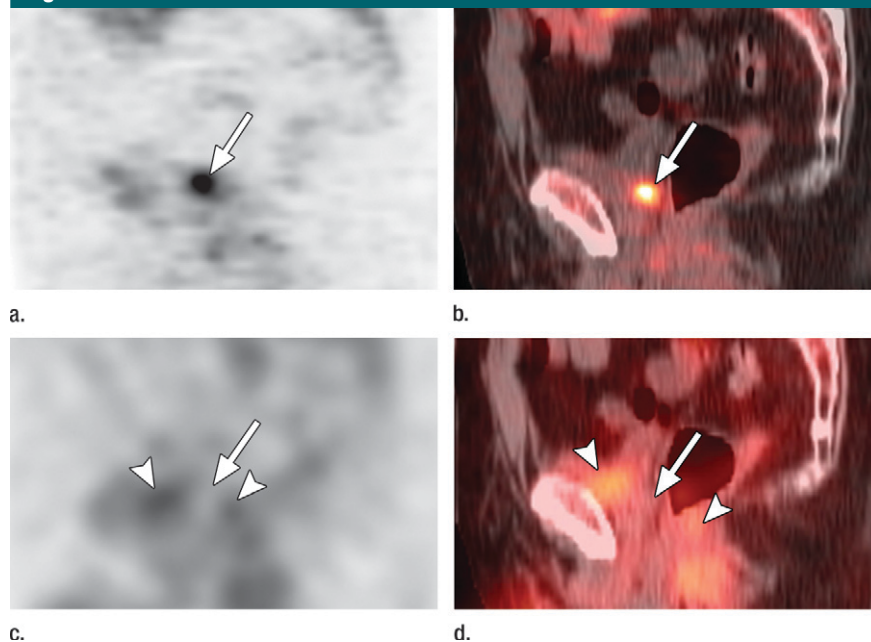
be more promising for lymph node assessment, with a reported per-patient sensitivity of 80%–100% and specificity of 73%–95.7% (40–42).

FDG PET has little utility for normally slow-growing prostate carcinoma, with detection rates in the range of 31%–66% (43,44); better diagnostic performance was obtained for more aggressive disease (43). Interpretation of FDG PET scans of the pelvis is also hampered by renal excretion of FDG. PET/CT and iterative reconstruction techniques may result in improved accuracy.

Other PET and SPECT radiotracers are undergoing investigation (39,45–48). The most well studied of these radiotracers are carbon 11 (<sup>11</sup>C)-choline and <sup>18</sup>F-choline, with published sensitivities of 36%–100% and specificities of 12.5%–100% (33,48–50). <sup>11</sup>C-acetate has also been investigated, with sensitivities reported to be 75%–83% (48). <sup>11</sup>C-methionine is an amino acid radiotracer that, in limited studies, demonstrated a sensitivity of 72% in the detection of metastatic prostate cancer (44) and an overall detection rate of 46.7% for primary carcinoma (51).

In this study, *anti*-3-<sup>18</sup>F-FACBC PET/CT demonstrated 89% sensitivity and 67% specificity in the detection of local recurrence in the prostate bed and 100% sensitivity and specificity in the detection of extraprostatic disease; these findings compare favorably to those with the above-mentioned techniques. Comparison on the basis of

Figure 2



**Figure 2:** Images in a patient who had undergone radical prostatectomy (PSA level, 16.9 ng/mL). (a) Sagittal PET and (b) fused PET/CT scans obtained with *anti*-3-<sup>18</sup>F-FACBC. (c) SPECT and (d) fused SPECT/CT scans obtained with <sup>111</sup>In-capromab pentetide. Images were fused to same CT scan. Intense uptake between bladder base and rectum on scans obtained with *anti*-3-<sup>18</sup>F-FACBC (arrow in a and b) corresponded to biopsy-proved recurrence. No uptake is seen in same region on images obtained with <sup>111</sup>In-capromab pentetide (arrow in c and d). This is an example of a true-positive finding with *anti*-3-<sup>18</sup>F-FACBC and a false-negative finding with <sup>111</sup>In-capromab pentetide. Note bladder and rectal activity on <sup>111</sup>In-capromab pentetide images (arrowheads in c and d).

published studies alone, however, is problematic owing to differences in patient populations, study methodology, and reference standards used to establish truth. For example, diagnostic performance may be dependent on PSA

level and scan method (eg, PET alone vs PET/CT).

We chose to make this comparison to conventional imaging with <sup>111</sup>In-capromab pentetide because that is the current standard of care in our institution

**Table 3**

**Reference Standards Applied to the Analysis of Extraprostatic Disease**

Reference Standard	Findings with <i>anti-3-<sup>18</sup>F-FACBC</i>			Findings with <sup>111</sup> In–Capromab Pendetide		
	Positive (n = 12)	Negative (n = 37)	Indeterminate (n = 1)	Positive (n = 4)	Negative (n = 45)	Indeterminate (n = 1)
Biopsy (positive)	9	0	0	1	8	0
PSA nadir level (negative)*	0	4	0	0	4	0
Bone/MR imaging (positive)†	1	0	0	0	1	0
Follow-up CT (negative)‡	0	3	0	0	3	0
Definitive follow-up pending	2	30	1	3	29	1

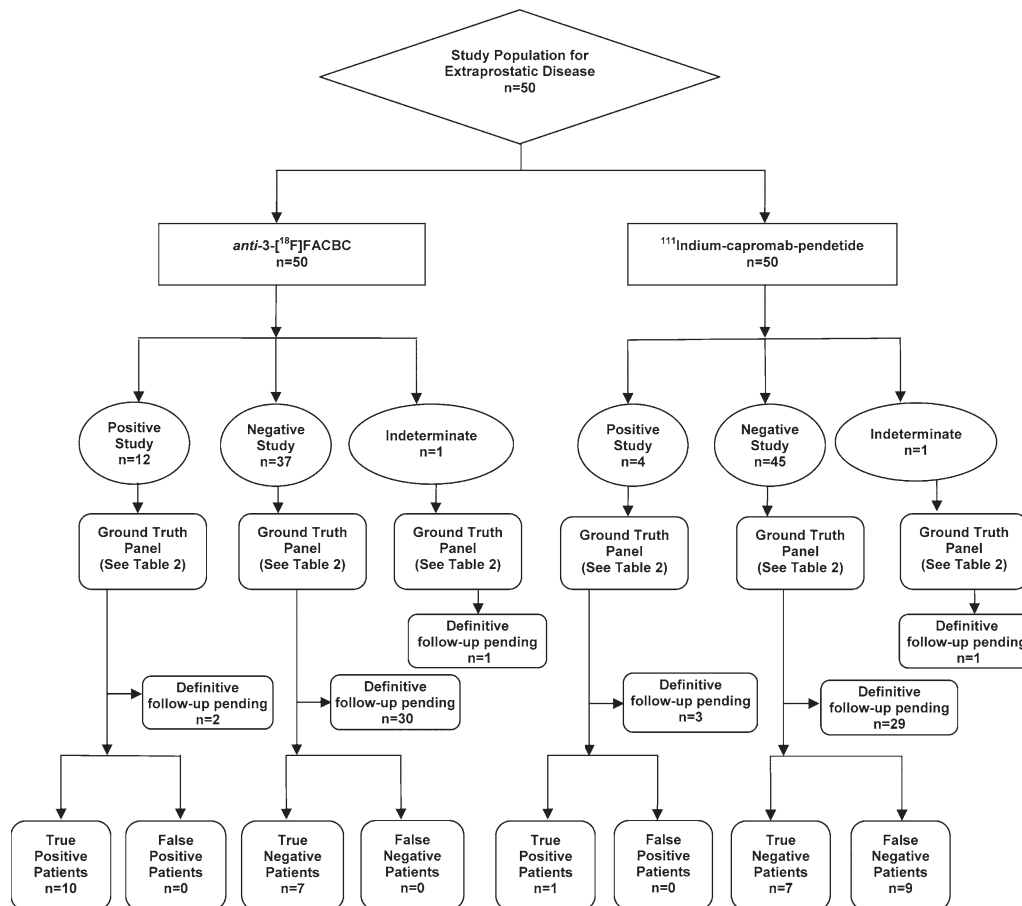
Note.—Data are numbers of patients.

\* Proved with PSA nadir level after local therapy only.

† Characteristic imaging features of a skeletal lesion were seen at MR imaging.

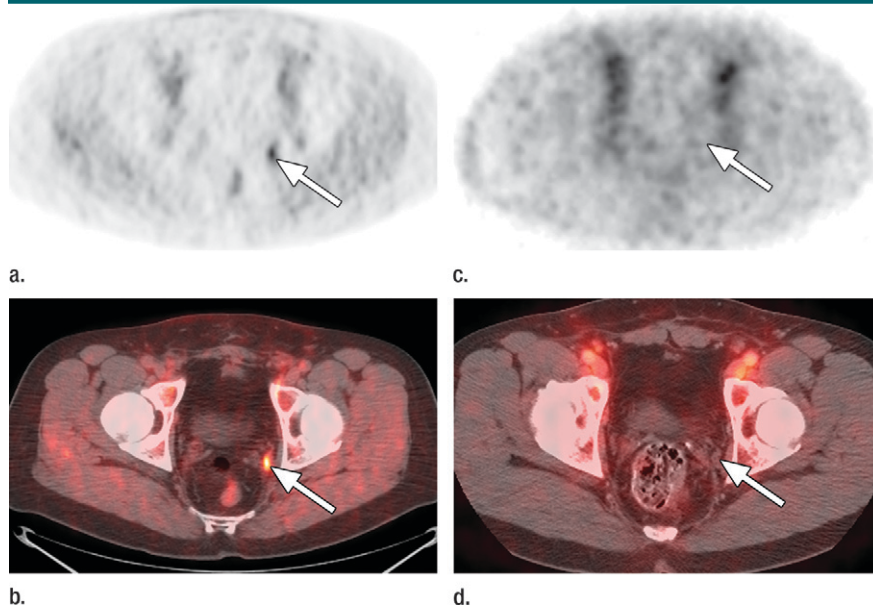
‡ The CT appearance of the abdomen and/or pelvis was stable for more than 1 year.

**Figure 3**



**Figure 3:** Flow diagram of study patients and results obtained for extraprostatic disease with <sup>111</sup>In–capromab pendetide and *anti-3-<sup>18</sup>F-FACBC*.

Figure 4



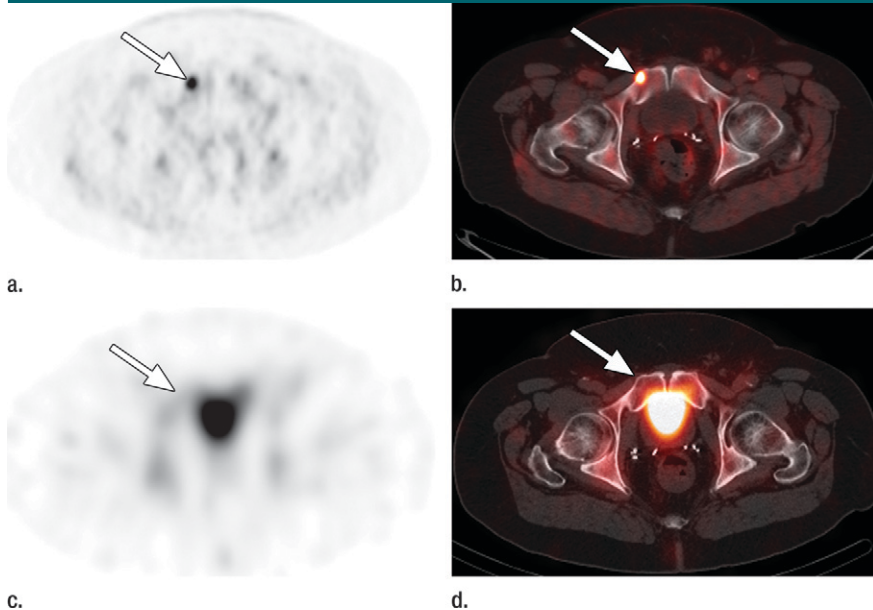
**Figure 4:** Images in a patient who had undergone radical prostatectomy (PSA level, 1.1 ng/mL). (a) Transverse PET and (b) fused PET/CT scans obtained with  $anti\text{-}3\text{-}^{18}\text{F}\text{-FACBC}$ . (c) SPECT and (d) fused SPECT/CT scans obtained with  $^{111}\text{In}\text{-capromab pentetide}$ . Intense uptake on images obtained with  $anti\text{-}3\text{-}^{18}\text{F}\text{-FACBC}$  (arrow in a and b) corresponded to a 5-mm recurrence in the left obturator lymph node, which was proved at biopsy. There is no uptake in same region on images obtained with  $^{111}\text{In}\text{-capromab pentetide}$  (arrow in c and d). This is an example of a true-positive finding with  $anti\text{-}3\text{-}^{18}\text{F}\text{-FACBC}$  and a false-negative finding with  $^{111}\text{In}\text{-capromab pentetide}$ .

environment, should be carried out before clinical recommendations can be made.

One limitation of a clinical study involving prostate carcinoma is the dilemma in establishing truth for absence of disease. PSA level in isolation is not an adequate end point and must be correlated in clinical context. Even an increase in PSA level after prostatectomy does not necessarily equate with clinical failure (2,4). Yet, prostate biopsies—especially those performed after therapy—are subject to sampling error and may underestimate true-positive disease (7,8, 33,52,53). Most of our patients underwent nonradical prostatectomy procedures in which an increase in PSA level may be due to prostatitis or benign hypertrophy. A patient is more likely to receive salvage radiation therapy after radical prostatectomy with increasing PSA level and negative biopsy than after a nonradical prostatectomy technique in which biopsy proof is usually required at lower PSA levels before undergoing salvage surgery or cryotherapy.

There is no ideal method with which to establish truth in all circumstances, as reflected in the acceptable practice variations in the restaging of patients with prostate carcinoma (2). We chose to default to biopsy findings, which were overridden only with data obtained during the patient's subsequent clinical and therapeutic course. If there was insufficient proof of the presence or absence of disease, the outcome was then considered indeterminate awaiting further follow-up. Thus, each patient was independently

Figure 5



**Figure 5:** Images in a patient who had undergone radical prostatectomy (PSA level, 2.97 ng/mL). (a) Transverse PET and (b) fused PET/CT scans obtained with  $anti\text{-}3\text{-}^{18}\text{F}\text{-FACBC}$ . (c) SPECT and (d) fused SPECT/CT scans obtained with  $^{111}\text{In}\text{-capromab pentetide}$ . Intense uptake on images obtained with  $anti\text{-}3\text{-}^{18}\text{F}\text{-FACBC}$  (arrow in a and b) corresponded to a subtle lytic bone lesion in the right pubic ramus, which was proved as recurrence at biopsy. There is no uptake in same region on images obtained with  $^{111}\text{In}\text{-capromab pentetide}$  (arrow in c and d). This is an example of a true-positive finding with  $anti\text{-}3\text{-}^{18}\text{F}\text{-FACBC}$  and a false-negative finding with  $^{111}\text{In}\text{-capromab pentetide}$ .

and many others. Direct comparisons of  $anti\text{-}3\text{-}^{18}\text{F}\text{-FACBC}$  PET/CT to other promising imaging techniques such as

choline PET/CT and/or advanced MR imaging, ideally with use of the patient as his or her own control in a multicenter



assessed by our multidisciplinary team in his unique circumstance, more closely mirroring clinical practice. In fact, it may take longer than the 1–2-year follow-up in this study for clinical disease to manifest (54,55). All patients are part of an ongoing clinical trial and will be followed up for a longer period of time.

Another potential limitation of this study is the fact that *anti*-3-<sup>18</sup>F-FACBC imaging was not carried out above the diaphragm. However, prostate skip metastases are rare, and there was no indication of such disease at either clinical examination or <sup>111</sup>In-capromab pentetide imaging. Investigation of false-positive and false-negative findings in the prostate bed as well as diagnostic performance at different PSA levels will be the subject of future analysis.

In conclusion, *anti*-3-<sup>18</sup>F-FACBC PET/CT is more sensitive than <sup>111</sup>In-capromab pentetide SPECT/CT in the detection of recurrent prostate carcinoma in the prostatic bed and in extraprostatic sites.

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