Anti-1-Amino-3-\textsuperscript{18}F-Fluorocyclobutane-1-Carboxylic Acid: Physiologic Uptake Patterns, Incidental Findings, and Variants That May Simulate Disease

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Anti-1-amino-3-\textsuperscript{18}F-fluorocyclobutane-1-carboxylic acid (\textsuperscript{18}F-FACBC) is a synthetic amino acid analog PET radiotracer undergoing clinical trials for the evaluation of prostate and other cancers. We aimed to describe common physiologic uptake patterns, incidental findings, and variants in patients who had undergone \textsuperscript{18}F-FACBC PET.

**Methods:** Sixteen clinical trials involving 611 \textsuperscript{18}F-FACBC studies from 6 centers, which included dosimetry studies on 12 healthy volunteers, were reviewed. Qualitative observations of common physiologic patterns, incidental uptake, and variants that could simulate disease were recorded and compared with similar observations in studies of the healthy volunteers. Quantitative analysis of select data and review of prior published reports and observations were also made.

**Results:** The liver and pancreas demonstrated the most intense uptake. Moderate salivary and pituitary uptake and variable mild to moderate bowel activity were commonly visualized. Moderate bone marrow and mild muscle activity were present on early images, with marrow activity decreasing and muscle activity increasing with time. Brain and lungs demonstrated activity less than blood pool. Though \textsuperscript{18}F-FACBC exhibited little renal excretion or bladder uptake during the clinically useful early imaging time window, mild to moderate activity might accumulate in the bladder and interfere with evaluation of adjacent prostate bed and seminal vesicles in 5\%–10\% of patients. Uptake might also occur from benign processes such as infection, inflammation, prostatic hyperplasia, and metabolically active benign bone lesions such as osteoid osteoma.

**Conclusion:** Common physiologic uptake patterns were similar to those noted in healthy volunteers. The activity in organs followed the presence of amino acid transport and metabolism described with other amino acid–based PET radiotracers. As with other PET radiotracers such as \textsuperscript{18}F-FDG, focal nonphysiologic uptake may represent incidental malignancy. Uptake due to benign etiologies distinct from physiologic background also occurred and could lead to misinterpretations if the reader is unaware of them.

Key Words: \textsuperscript{18}F-FACBC; physiologic uptake; positron emission tomography

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Amino acids are involved in a variety of biologic processes including protein synthesis, and amino acid transport is upregulated in many neoplasms (1–4). Consequentially, radiolabeled amino acids, both natural and synthetic, have been used for oncologic molecular imaging.

Anti-1-amino-3-\textsuperscript{18}F-fluorocyclobutane-1-carboxylic acid (\textsuperscript{18}F-FACBC) is an investigational synthetic nonmetabolized amino acid analog PET radiotracer (5–14). Transport is primarily mediated by sodium-dependent amino acid transporters, specifically system ASC, with contribution by sodium-independent system L (15,16). Though this PET radiotracer has been most actively studied in patients with prostate carcinoma, other trials have been completed or are under way, including those for cerebral gliomas and breast, lung, and head and neck cancers, among others.

For well-established radiotracers such as \textsuperscript{18}F-FDG, normal uptake and variants have been reported (17–19). However for \textsuperscript{18}F-FACBC, biodistribution and radiation dosimetry have been obtained only in small sets of healthy volunteers (9,20,21). At our institutions, we have also obtained \textsuperscript{18}F-FACBC scans in clinical trials involving prostate cancer and other neoplasms. The purpose of this study was to report our collective experience with \textsuperscript{18}F-FACBC imaging in patients enrolled in clinical trials, correlating uptake patterns to those of healthy volunteers in the description of common physiologic uptake, incidental findings, and variants that may simulate disease.

**MATERIALS AND METHODS**

**Study Protocols and Demographics**

The \textsuperscript{18}F-FACBC studies of 598 subjects, including 12 healthy volunteers (23 women and 575 men; 611 total scans; 13 patients with repeated studies), spanning from October 16, 1996, to February 10,
Table 1 lists the protocols under which the patients received the $^{18}$F-FACBC scan. Imaging was acquired for all studies, commencing approximately 1–5 min after radiotracer injection. All study protocols were approved by the local Institutional Review Board or Committee on Ethics or equivalent in accordance with the principles of the Declaration of Helsinki and with national regulations. Written informed consent was obtained from all enrolled subjects.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Activity (MBq)</th>
<th>Extent of scan</th>
<th>Technique</th>
<th>Mean age (y)</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emory initial pilot</td>
<td>18</td>
<td>292.3 (99.9)</td>
<td>Skull vertex to thighs</td>
<td>60-min dynamic brain (followed by whole-body imaging)</td>
<td>53.8 (9.3)</td>
<td>Male, 12; female, 6</td>
</tr>
<tr>
<td>Emory dosimetry</td>
<td>6</td>
<td>366.6 (51.0)</td>
<td>Skull vertex to thighs</td>
<td>6 sets of serial static scans for 120 min</td>
<td>48 (15.0)</td>
<td>Male, 3; female, 3</td>
</tr>
<tr>
<td>Emory prostate pilot</td>
<td>15</td>
<td>372.6 (22.9)</td>
<td>Abdomen/pelvis</td>
<td>65-min dynamic pelvis (followed by abdomen/pelvis)</td>
<td>62.0 (8.8)</td>
<td>Male, 15</td>
</tr>
<tr>
<td>Emory renal pilot</td>
<td>6</td>
<td>388.5 (14.1)</td>
<td>Abdomen</td>
<td>120-min dynamic renal-level abdomen</td>
<td>67.3 (15.1)</td>
<td>Male, 5; female, 1</td>
</tr>
<tr>
<td>Emory lung pilot</td>
<td>10</td>
<td>313.5 (76.7)</td>
<td>Chest</td>
<td>45-min dynamic lesion-level chest</td>
<td>66.4 (12.8)</td>
<td>Male, 3; female, 7</td>
</tr>
<tr>
<td>Emory recurrent prostate cancer outcomes</td>
<td>128 scans in 115 patients</td>
<td>358.9 (51.8)</td>
<td>Abdomen/pelvis</td>
<td>60-min sequential multiphase abdomen/pelvis</td>
<td>67.3 (7.6)</td>
<td>Male, 128</td>
</tr>
<tr>
<td>Emory primary prostate cancer</td>
<td>11</td>
<td>347.8 (81.4)</td>
<td>Pelvis</td>
<td>60-min dynamic pelvis</td>
<td>60.8 (6.3)</td>
<td>Male, 11</td>
</tr>
<tr>
<td>Emory breast pilot</td>
<td>3</td>
<td>360.0 (14.1)</td>
<td>Chest</td>
<td>45-min dynamic breast level</td>
<td>60 (8.9)</td>
<td>Female, 3</td>
</tr>
<tr>
<td>Emory parathyroid</td>
<td>3</td>
<td>351.5 (34.0)</td>
<td>Neck</td>
<td>60-min sequential multiphase neck/upper chest</td>
<td>60.3 (6.4)</td>
<td>Male, 1; female, 2</td>
</tr>
<tr>
<td>Emory recurrent prostate cancer outcomes</td>
<td>13</td>
<td>367.0 (15.5)</td>
<td>Abdomen/pelvis</td>
<td>30-min sequential multiphase abdomen/pelvis</td>
<td>61.5 (9.2)</td>
<td>Male, 13</td>
</tr>
<tr>
<td>Emory PET and MR recurrent prostate cancer</td>
<td>6</td>
<td>373.7 (9.4)</td>
<td>Abdomen/pelvis</td>
<td>30-min sequential multiphase abdomen/pelvis</td>
<td>69 (5.1)</td>
<td>Male, 6</td>
</tr>
<tr>
<td>Bologna recurrent prostate cancer</td>
<td>61</td>
<td>379 (12.1)</td>
<td>Skull vertex to thighs</td>
<td>Single static scan starting at thighs</td>
<td>67.8 (6.5)</td>
<td>Male, 61</td>
</tr>
<tr>
<td>Kitasato phase one dosimetry</td>
<td>6</td>
<td>195.0 (10.3)</td>
<td>Skull vertex to thighs</td>
<td>11 series of whole-body PET scans during 3 sessions of 0–90, 150–170, and 220–240 min</td>
<td>24 (3.0)</td>
<td>Male, 6</td>
</tr>
<tr>
<td>Uppsala phase one primary prostate cancer</td>
<td>6</td>
<td>418 (10.0)</td>
<td>Pelvis</td>
<td>90 (optional 120)-min dynamic pelvis</td>
<td>67 (5.0)</td>
<td>Male, 6</td>
</tr>
<tr>
<td>NIH primary prostate cancer</td>
<td>21</td>
<td>351.5 (9.0)</td>
<td>Pelvis/lower abdomen dynamic, whole-body static at end</td>
<td>30-min dynamic pelvis, then 10-min dynamic lower abdomen (followed by static whole body)</td>
<td>62 (6.5)</td>
<td>Male, 21</td>
</tr>
<tr>
<td>Oslo University Hospital prostate and other cancers</td>
<td>298</td>
<td>296 (56.0)</td>
<td>Skull vertex to thighs</td>
<td>Single static scan starting at thighs</td>
<td>66.0 (6.4)</td>
<td>Male, 297; female, 1</td>
</tr>
</tbody>
</table>

Data in parentheses are SDs.
18F-FACBC Synthesis

18F-FACBC was synthesized at an institutional or central radiopharmacy through previously reported automated radiosynthesis methods or via a cassette produced by GE Healthcare into a synthesis module (FastLab) (22).

Details of 18F-FACBC Scans

Details of most of the clinical study protocols and acquisition parameters have been previously reported (5–14, 23). PET/CT was performed on a Discovery DLS, DST, STE, or MV690 (GE Healthcare); a TruePoint Biograph 6 or Biograph mCT 40 (Siemens Medical Solutions); or a Gemini TF scanner (Philips Healthcare), except for the scans of 18 patients acquired on a PET-only Siemens ECAT 921. PET and CT acquisition parameters were specific to the PET device and protocol and ranged from dynamic acquisition in list mode to 2- to 4-min static time frames using either 2- or 3-dimensional mode and filtered backprojection or iterative reconstruction. All patients fasted for 4 h or longer before the study.

Image Analysis

Images were reviewed on MIMvista (MIMSoftware), Xeleris (GE Healthcare), Syngo Multimodality Volumetric Analysis (Siemens Medical Solutions), or PMOD 3.1 (PMOD Technologies) workstations. Studies were examined qualitatively, though supplemented with quantitative data from prior and ongoing analyses, such as bladder activity data collected for Table 2 and published dosimetry data (9, 20, 21). For descriptive purposes in this paper, mild uptake is defined as equal to or greater than blood pool but less than marrow, moderate as equal to or greater than marrow but less than liver, and intense as equal to or greater than liver. Absent uptake or uptake less than blood pool is described as such. Reference mean standardized uptake values (SUV\text{mean}) for blood pool, marrow, and liver at varying time points from a subanalysis of a 128-study cohort are provided in Table 2.

RESULTS

Physiologic Uptake Patterns

Cerebrum, Head, and Neck. Brain parenchyma demonstrated uptake less than blood pool, though brain conspicuity slightly increased with time. Moderate pituitary uptake, which decreased with time, was present in more than 90% of patients. The scalp was seen as a separate structure covering the skull. Salivary glands and lymphoid tissue of Waldeyer’s ring had moderate symmetric uptake, also decreasing with time. Thyroid tissue had mild activity. [Fig. 1] Figure 1A is an example of a whole-body early acquisition from a 18F-FACBC scan for recurrent prostate cancer, and Figure 1B is a dedicated acquisition of the head and neck region.

Chest. After initial blood pool diminished, mild to moderate uptake in the myocardium became evident and increased in a manner similar to muscle. Lung parenchyma demonstrated absent uptake or uptake less than blood pool. Breast parenchyma had mild 18F-FACBC uptake but absent uptake or less than blood pool with increasing fatty change. Some degree of mild to moderate diffuse esophageal uptake was seen in more than 50% of patients (Fig. 2). Though the relationship of this activity to reflux disease has not been formally studied, the pattern was similar to that seen with inflammatory reflux with 18F-FDG PET, more frequently involving the distal esophagus and gastroesophageal junction.

Abdomen and Pelvis. The liver and pancreas were most intense on 18F-FACBC (Fig. 2). Pancreatic activity was greater than that of liver initially, but by 15 min pancreatic uptake diminished to or TABLE 2

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Bladder SUV\text{mean}</th>
<th>Blood-pool (aorta) SUV\text{mean}</th>
<th>Marrow (L3) SUV\text{mean}</th>
<th>Liver SUV\text{mean}</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (n = 128)</td>
<td>0.82 (0.84)</td>
<td>1.54 (0.38)</td>
<td>2.70 (0.60)</td>
<td>6.98 (1.47)</td>
</tr>
<tr>
<td>17 (n = 127)*</td>
<td>3.97 (5.03)</td>
<td>1.27 (0.36)</td>
<td>2.26 (0.52)</td>
<td>6.82 (1.44)</td>
</tr>
<tr>
<td>29 (n = 125)*</td>
<td>4.08 (4.6)</td>
<td>1.14 (0.30)</td>
<td>1.91 (0.46)</td>
<td>6.30 (1.47)</td>
</tr>
</tbody>
</table>

*Acquisition halted prematurely in 1 and 3 studies by 17 and 30 min, respectively. Data in parentheses are SDs.

18F-FACBC scan for recurrent prostate cancer, and Figure 1B is a dedicated acquisition of the head and neck region.

FIGURE 1. (A) Early-time-point 18F-FACBC maximum-intensity-anterior projection (MIP) demonstrates intense liver and pancreatic uptake, cerebral and lung uptake less than blood pool, and absent urinary excretion. Greater muscle uptake is noted in upper body because scanning proceeded caudal to cranial, and muscle uptake increased with time. (B) MIP from different patient in dedicated head and neck study demonstrates moderate uptake in salivary glands, lymphoid tissue of Waldeyer’s ring, and pituitary activity (arrow).
expected locations of red marrow (Fig. 2). Heterogeneous bone uptake, which decreased over time and appeared to correlate with and frequently somewhat heterogeneous or patchy 18F-FACBC pausal uterus or ovaries could be offered.

in a linear configuration. Because of limited experience with pelvic cancer. The urethral region demonstrated mild 18F-FACBC uptake. More intense excreted activity might be present in the proximal collecting system. The adrenals also had mild uptake, though this requires further validation because most studies have been in patients with prostate cancer. The urethral region demonstrated mild 18F-FACBC uptake in a linear configuration. Because of limited experience with pelvic imaging in women, no descriptions of normal pre- or postmenopausal uterus or ovaries could be offered.

Bladder activity was typically absent or less than blood pool on early images but might be mild to moderate in 10%–15% of patients. In our experience, 18F-FACBC excretion and resultant focal bladder activity may interfere with the evaluation of adjacent prostate bed and seminal vesicles in 5%–10% of early images in some patient cohorts and may be related to diuretic load from intravenous contrast given as part of a CT protocol. Mild diffuse uptake in the bladder wall has also been observed on early sequences. Table 2 contains data from a subanalysis of 128 studies describing bladder activity.

The prostate had mild uptake, though this requires further validation because most studies have been in patients with prostate cancer. The urethral region demonstrated mild 18F-FACBC uptake in a linear configuration. Because of limited experience with pelvic imaging in women, no descriptions of normal pre- or postmenopausal uterus or ovaries could be offered.

Musculoskeletal System. The marrow demonstrated moderate and frequently somewhat heterogeneous or patchy 18F-FACBC uptake, which decreased over time and appeared to correlate with expected locations of red marrow (Fig. 2). Heterogeneous bone marrow activity might present a more complex background for the evaluation of bone marrow metastases. Skeletal muscle also had mild uptake initially, which increased with time and surpassed that of marrow at approximately 30–60 min after radiotracer injection (Fig. 1A).

Incidental Findings and Variants

On the basis of published and unpublished data, 18F-FACBC has demonstrated elevated uptake in carcinomas of the prostate, breast, and lung, as well as colon neoplasia, squamous cell carcinoma of the scalp, follicular lymphoma, multiple myeloma, and primary and metastatic tumors in the brain (Fig. 3) (5,7,11,14,24).

Simple renal dysfunctions do not have 18F-FACBC uptake, in our experience (Fig. 4A). Although papillary cell carcinoma had elevated uptake, clear cell carcinoma had uptake similar to parenchyma (14). As with 18F-FDG, any degree of 18F-FACBC uptake in a renal mass might represent malignant etiology (Fig. 4B). Benign hepatic cysts and hemangiomas are photopenic, compared with the liver (Fig. 4A).

Postprostatectomy uptake in the urethra might be challenging to differentiate from disease in the prostate bed, but sagittal images aid interpretation (Fig. 5A). Nonmalignant uptake in the prostate [Fig. 4] might be seen with benign prostatic hyperplasia and acute and chronic inflammation (Figs. 5B and 5C), including after radiation (12,23).

Focal increased uptake in a pituitary adenoma, a meningioma, an osteoid osteoma, and an adrenal gland adenoma has been seen (Fig. 6; written communication from coauthor Trond V. Bogsrud, 2014). 18F-FACBC uptake was also observed with both acute and chronic inflammation and infection, including mild to moderate uptake in apparently benign hilar, axillary, and inguinal lymph nodes, which diminished from early to more delayed sequences. Moderate to intense uptake was noted in inflammatory skin lesions, inguinal nodes due to ringworm infection, and musculoskeletal inflammation (Fig. 6; personal observation of first author David M. Schuster, 2008). Mild focal uptake in degenerative facet disease might be seen but not to the same degree as with 18F-FDG.

DISCUSSION

18F-FACBC is a nonnatural alicyclic amino acid analog PET radiotracer that has in vivo properties similar to its parent compound, 18F-FDG.
Amino acids and amino acid transporters are ubiquitous in the body, and it would seem logical that much 18F-FACBC physiologic activity may be explained with this knowledge (2,4,26,29). For example, the pancreas and liver are centers of amino acid metabolism or synthesis of plasma proteins (4,9,30). Increased uptake with certain amino acid radiotracers in the salivary glands, lymphoid tissue, and pituitary seems to be a normal variant (2,30). Muscle is also involved with amino acid metabolism and transport (31). The kidneys contain amino acid transporters such as those used for 18F-FACBC (32). 18F-FACBC bladder activity, when present, is mostly derived from the parent 18F-FACBC compound having escaped reabsorption and not metabolites (33). If interfering bladder activity is apparent, re-imaging prone or after bladder emptying may be of help.

As a synthetic amino acid radiotracer, the physiologic pattern of 18F-FACBC distribution in background structures is similar to that of other amino acid PET radiotracers including 11C-methionine and l-3-18F-α-methyltyrosine (2,30,34,35). Yet some important differences exist. Unlike 11C-methionine, 18F-FACBC is a nonnatural synthetic amino acid radiotracer that is neither metabolized nor used for protein synthesis (28). Compared with 11C-methionine, 18F-FACBC demonstrates more rapid pancreatic clearance but comparatively little renal and bladder activity (9). Methionine transport is governed primarily by sodium-independent system L transporters, whereas 18F-FACBC is transported primarily by sodium-dependent system ASC, with lesser contribution by system L (15,16,30). 18F-FACBC has greater liver uptake and less bladder activity than does l-3-18F-α-methyltyrosine, another nonnatural amino acid radiotracer (35). These differences are likely secondary to the presence and density of specific amino acid transporters and other factors such as biologic and electrolyte properties of the ligand, modes of physiologic excretion, and interplay with other nutrient transporters and microenvironments.

Amino acid transport is upregulated in a variety of tumors. Unexpected uptake beyond that ascribed to physiologic activity, especially if focal, intense, and accompanied by an anatomic abnormality on CT, should be further investigated. Though amino acid imaging is believed to be less prone to inflammatory uptake, amino acid transport also occurs in benign inflammation. Uptake of amino acid radiotracers not specific to malignancy has been described, and as demonstrated in this paper, 18F-FACBC is no exception (2,36). We have recently shown that although 18F-FACBC uptake ratios of tumor cells to activated macrophages and granulocytes are higher than those for 18F-FDG, the uptake ratios of tumor cells to activated T or B cells might cause uptake in 18F-FACBC imaging (16).

In the differentiation of benign from malignant uptake in recurrent prostate cancer, Schuster used the prospective criteria of abnormal focal visual and quantitative uptake greater than that of background
marrow at L3 persisting from early to delayed imaging using multiphase abdominopelvic acquisitions (6,13). More recently, other groups have reported success with single-time-point whole-body imaging starting from the pelvis 3–5 min after 18F-FACBC injection (10). Analysis from multiple trials and ongoing consensus development will help standardize scan protocols and interpretative criteria.

The limitations of this investigation include our relatively narrow experience with 18F-FACBC, compared with more commonly used radiotracers such as 18F-FDG. Because most imaging to date has been of men, there are less data for women. Also, there is less experience with certain body regions, such as the head and neck. In addition, most patients studied had cancer, and it is possible that global physiologic patterns involving 18F-FACBC are thus altered. Yet, it is reassuring that our observed common physiologic activity pattern, which included highest intensity in the pancreas and liver. Moderate uptake was noted in salivary, lymphoid, and pituitary tissue, whereas variable mild to moderate activity was present in the bowel. The brain had uptake less than the blood pool. Mild to moderate uptake was present in the kidneys, with absent bladder activity or less than blood pool in early images, though more intense accumulation of excreted activity might occur in a small number of patients. Lack of significant parenchymal uptake in the brain and relatively minimal renal excretion might be advantageous for cerebral and pelvic imaging, respectively. Intense liver and pancreatic uptake would limit disease detection in those organs. Because of efflux of tracer from the tumor, early imaging at less than 30 min was most useful for disease detection. Incidental benign and malignant uptake might occur and should be further evaluated with clinical correlation or other imaging.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. Support was provided by the National Institutes of Health (5R01CA129356 and P50 CA 128301); Society of Nuclear Medicine and Molecular Imaging Research and Education Foundation; Nihon Medi-Physics Co., Ltd.; GE Healthcare; Blue Earth Diagnostics Limited; Glenn Family Breast Center Award, Winship Cancer Institute of Emory University; Georgia Cancer Coalition; and Programma di Ricerca Regione (Emilia Romagna)—Università 2010–2012, Bando Giovani Ricericatori. Emory University and Dr. Mark Goodman are eligible to receive royalties for 18F-FACBC. Dr. Schuster participates in sponsored research involving 18F-FACBC and other radiotracers. No other potential conflict of interest relevant to this article was reported.

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REFERENCES
