

Dual-Isotope Protocol for Indium-111 Capromab Pendetide Monoclonal Antibody Imaging

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Objective: A dual-isotope imaging protocol using ^{99m}Tc -labeled red blood cells with ^{111}In capromab pendetide monoclonal antibody imaging for detecting and localizing nodal metastasis in prostate cancer is described.

Methods: This protocol involves a single SPECT acquisition that is less time consuming and more comfortable for the patient than the currently recommended method, which requires two separate SPECT acquisitions performed on different days.

Results: Forty patients were studied with the dual-isotope protocol. Preliminary data suggest increased accuracy compared with the single-isotope technique.

Conclusion: The dual-isotope technique assures the precise image registration needed for accurate comparison of blood pool and pelvic lymph node activity that is required for confident and accurate image interpretation.

Key Words: prostate cancer; ProstaScint®; indium-111 capromab pendetide; tumor imaging

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Prostate cancer is the most common cancer in men in the U.S. and is second only to lung cancer as the most common cause of cancer-related deaths in men (1). Accurate clinical staging or restaging when recurrence is suspected is necessary for choosing the most appropriate therapy. Approximately 40%–60% of patients with prostate cancer have lymphatic or extraprostatic disease at the time of the initial presentation and 70% develop it during the course of their disease (2,3). Undetected and untreated disease within the lymph nodes is a major contributor to the development of bone metastasis in 75% of these patients within 5 yr of initial treatment (3).

Currently CT and MR, which are the conventional imaging modalities used for staging, detect only 30%–70% of nodal metastases (3). Nuclear medicine imaging with ^{111}In capromab pendetide (ProstaScint®, Cytogen Corp., Princeton, NJ), a monoclonal antibody (MAb) directed at prostate-specific

membrane antigen (PSMA), is another tool available to provide information about disease extent. Reported sensitivity and specificity during clinical trials were 62% and 72%, respectively (4). The dual-isotope, single-imaging session technique described in this paper provides the precise image registration that is essential for accurate interpretation of these scans, and which will probably be associated with greater diagnostic accuracy (Khan SH and Holder LE, *personal communication*, 1998).

MATERIALS AND METHODS

Since February 1997, 43 patients have been studied in our department for prostate cancer metastases. The first three patients were imaged using the manufacturer's recommended imaging protocol which required two separate SPECT scans performed on two separate days. The first SPECT scan of the abdomen and pelvis was performed approximately 30 min post antibody injection to obtain blood-pool images for outlining the vascular anatomy of these regions. The second SPECT scan was performed 3–5 days postinjection for antibody localization in lymph nodes that are located close to the blood vessels. At this time a total-body axial scan also was acquired.

After realizing the difficulties associated with the conventional protocol (see the Discussion), the last 40 patients were imaged using the dual-isotope simultaneous imaging technique. In a single imaging session, ^{99m}Tc -labeled RBCs and ^{111}In capromab pendetide (ProstaScint®) SPECT images were simultaneously acquired according to the protocol described in detail below. This effectively reduced the SPECT acquisition time by half and assured reliable, precise image registration. Imaging was performed on Day 4 after antibody injection. A planar whole-body ^{111}In antibody scan was obtained first, during which time in vitro labeling of the patient's RBCs with ^{99m}Tc using an UltraTag® kit (Mallinckrodt, St. Louis, MO) (5) was accomplished. At the completion of the whole-body scan, the ^{99m}Tc -labeled RBCs were injected and dual-isotope SPECT imaging was performed.

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TABLE 1
Imaging Parameters

| Scan type | Matrix | Speed/acquisition time | Scan length/ no. of stops | Energy peak | Window |
|-------------------------------|------------|------------------------|------------------------------|---|--|
| Whole-body scan | 512 × 2048 | 6 cm/min | ~150 cm | 173,247 keV | 20% |
| SPECT* (Noncircular orbit) | 64 × 64 | 40 sec/stop | 32/head | Isotope A 173 keV 247 keV Isotope B 140 keV | 10% (164–182) [†] 20% (222–272) 20% (126–154) |

*SPECT acquisition is acquired using dual-isotope, simultaneous imaging. In Image A counts are acquired from ¹¹¹In ProstaScint®. In Image B counts are acquired from ^{99m}Tc RBCs.

[†]Reduce the window width to prevent crossover of 140-keV and 173-keV counts.

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Radiopharmaceuticals and Preparation. This protocol requires these radiopharmaceuticals in these amounts: 5.0 mCi ¹¹¹In ProstaScint® (carpromab pentetide) and 5–8.0 mCi ^{99m}Tc RBCs (UltraTag® kit). ProstaScint® is supplied in single-dose vials containing 0.5 mg capromab pentetide. The vial, which is stored at 2°–8°C, is brought to room temperature. Six to seven millicuries of buffered ¹¹¹In chloride are added to the vial and mixed using aseptic technique. The vial is incubated at room temperature for 30 min, and then 1.9 ml sodium acetate are added. The contents are filtered using a 0.22- μ m Millex® (Millipore, Bedford, MA) GV sterile filter. A radiochemical purity of 90% or greater by instant thin-layer chromatography (ITLC) is required (6).

Scheduling Considerations. The following scheduling considerations should be made:

1. The patient should not be hypersensitive to any product of murine origin or to ¹¹¹In-chloride.
2. Advise the patient that this is a 2-day procedure with history and injection on one day and imaging 4 days later.
3. Record the specific clinical indication for imaging, for example presurgical staging or rising serum tumor marker after therapy.
4. Obtain a detailed patient history that should include information about any prior prostate therapy, which may include radical prostatectomy, radiation therapy (to pelvis or prostate), cryosurgery and/or any hormonal therapy.
5. Obtain the current and lowest tumor marker values (PSA and PAP).
6. Record the clinical and/or pathological staging (Gleason sum score).
7. Note and obtain any correlative imaging, such as CT, MRI and/or ultrasound.

Indium-111 ProstaScint® Injection. Five millicuries ¹¹¹In ProstaScint® are injected intravenously using either a butterfly infusion set or an angiocath connected to a three-way stopcock with a 30-cc saline flush. The injection should be made slowly over 5 min with patient observation for signs of adverse reactions. Epinephrine and the emergency cart should be available

per department protocol. The radiopharmaceutical should be injected within 8 hr of compounding.

Bowel Preparation and Patient Hydration. A laxative is given to cleanse the bowel area so interpretation is not compromised. Give the patient two bottles of magnesium citrate (10 fl oz) with instructions to drink one on Day 2 and one on Day 3, with imaging to begin on Day 4. After the injection and before imaging encourage the patient to drink fluids to hydrate the patient and to reduce the radiation burden, since ¹¹¹In ProstaScint® is excreted through both the kidneys and bowel.

Imaging on Day 4 Postinjection.

Red blood cell labeling and injection. When the patient arrives in the department on Day 4, have the patient void, place an angiocath or butterfly infusion catheter, and withdraw 3 cc of blood for red cell labeling. The intravenous line is kept open with heparin flush. The red cell labeling is performed using an UltraTag® kit, with careful adherence to the manufacturer's procedure. For labeling, use 5–8 mCi ^{99m}Tc-pertechnetate. While the blood is being labeled, the planar ¹¹¹In antibody whole-body images are acquired. After whole-body imaging, the patient voids again, the labeled red blood cells are injected, the angiocath is removed, and the patient is positioned for SPECT imaging. Voiding before both the whole-body and SPECT acquisitions ensures that the patient will be able to complete the scans, and it minimizes bladder activity in the pelvis.

Imaging parameters. Our facility uses the following parameters for imaging. Our camera is a DST-XL (SMV America, Twinsburg, Ohio) with a 500 × 400-mm field of view, dual-head system (using the largest field of view camera available). A medium-energy, parallel-hole collimator is used. See Table 1 for our acquisition parameters.

Patient positioning. For the whole-body axial image, position the patient supine as for any planar, whole-body scan, making sure the patient is lying flat and symmetrically. Remove any metal such as snaps, zippers or belt buckles from pockets or clothing. Make sure the patient is comfortable and understands how important it is that they not move during the acquisition. Scan from the head and neck to the midfemur area.

For the SPECT scan, if possible, rotate detector heads so that the SPECT acquisition will use the long axis of the detectors. The SPECT acquisition field of view (FOV) should include the entire pelvis from the penile blood pool caudally,

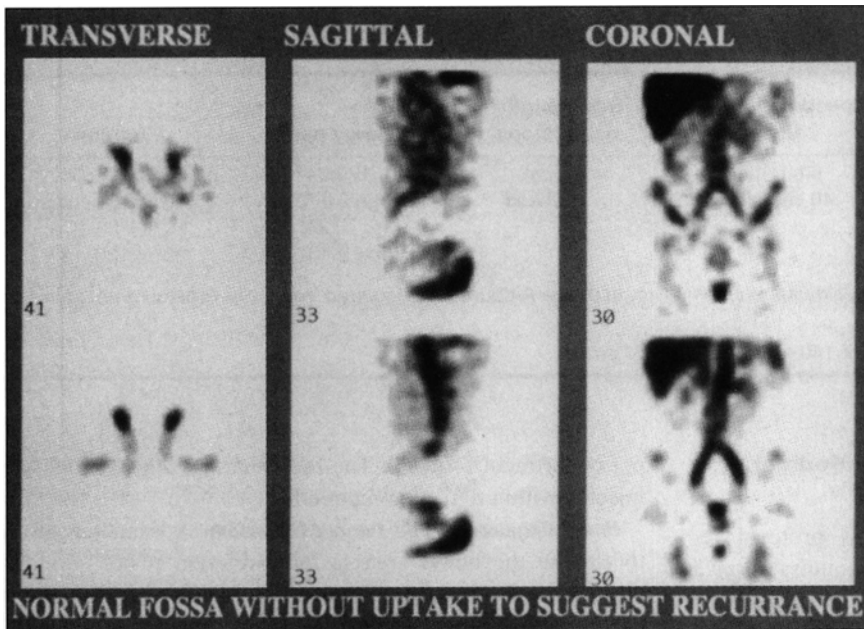


FIGURE 1. Selected multiplanar images from a normal dual-isotope study. Top row is ^{111}In ProstaScint® images. Bottom row is $^{99\text{m}}\text{Tc}$ RBC images. Transverse slices demonstrate slight asymmetry in external iliac vessel activity on both ProstaScint® and RBC images with right iliac activity more prominent than left. On coronal slices the iliac crest marrow on the ProstaScint scan, seen well in this patient, and the common iliac veins joining to form the inferior vena cava are good anatomic landmarks. The prostate fossa region, defined in relation to the urinary bladder on the sagittal images, does not have any abnormal uptake.

with as much of the abdomen and chest as possible cranially. Visualize the penile blood pool on the screen and then position the edge of the camera slightly below this level. If the patient is unable to void, and on the planar scan there was significant urine activity, consider either delaying the SPECT acquisition until after the patient is able to void or catheterize the patient and empty the bladder. The patient should be lying flat and the pelvis not rotated or twisted.

Processing and Reconstruction. No processing is required for the whole-body image. The display may be manipulated as needed.

After the SPECT acquisition, visually check the cine raw data for completeness, artifacts and signs of any patient motion. Generate and evaluate a sinogram. Slight patient motion can be motion corrected but any gross movement warrants a repeat acquisition. Reconstruct the entire field of view ac-

quired, at 1-pixel thick, with a Butterworth 6.24 filter for both the ^{111}In ProstaScint® and the $^{99\text{m}}\text{Tc}$ RBC images. A smoother filter can be used as needed.

Image Display and Analysis. The two processed datasets, which are precisely aligned, are displayed in a comparison format similar to the familiar stress redistribution displays for myocardial perfusion imaging. Window and leveling, contrast enhancement or background subtraction is done separately on individual datasets before merged viewing. When reviewing the images, the interpreting physician routinely uses the $^{99\text{m}}\text{Tc}$ RBC blood-pool images to define vascular structures, particularly those in the area of the pelvic lymph nodes. The blood-pool images are compared slice by slice with the antibody images, which often have bone marrow uptake which also can be used for anatomic orientation. Figure 1 is an example of a

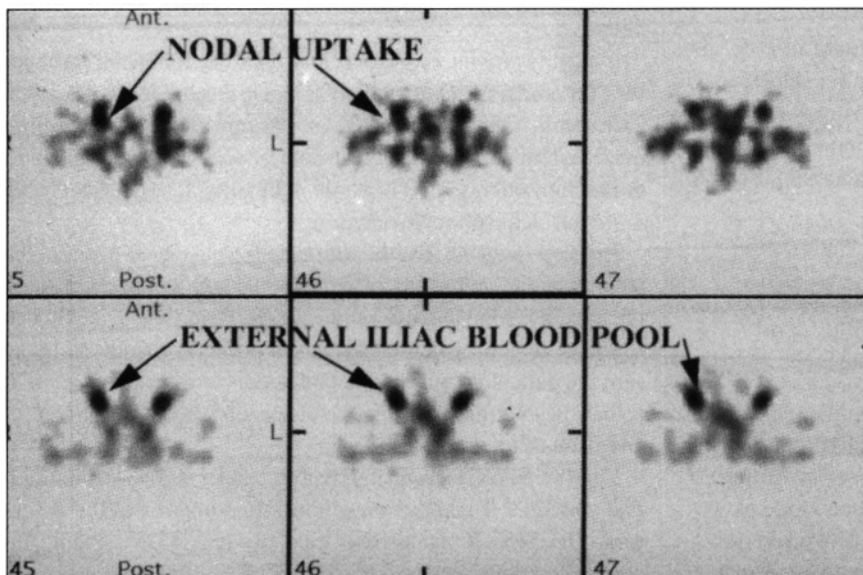


FIGURE 2. Selected transaxial images from an abnormal dual-isotope study. Top row is ^{111}In ProstaScint® images. Bottom row is $^{99\text{m}}\text{Tc}$ RBC images. Abnormal right external nodal uptake (arrow) is evident by comparing the larger size and orientation of tracer uptake in the external iliac vein/node region on the ProstaScint® image with the activity on the absolutely registered blood-pool image below.

normal scan. Figure 2, which is abnormal, demonstrates the value of the blood-pool scan.

DISCUSSION

The manufacturer's recommended imaging protocol, which was used during clinical trials before FDA approval of this tracer, required only a single radiotracer injection followed by both 30-min and then 3- to 5-day postinjection SPECT acquisitions. Two SPECT imaging sessions were required since tracer uptake observed in the area of the lymph nodes must be differentiated from tracer retained in the blood vessels which are anatomically adjacent to the lymph nodes. Absolute reproducible patient positioning for the two SPECT acquisitions and special image processing efforts aimed at attaining comparable slice data were critical, and were not possible in practice. Furthermore, if an extra large field-of-view gamma camera was not available to include the lowermost pelvis and the upper abdomen on a single study, in larger patients a total of four acquisitions, two on each day, were often needed, further compounding the problems with this technique. A recent article by Williams et al. (7) nicely describes this protocol.

The protocol suggested here does require RBC labeling and the administration of an additional radiotracer. This results in an additional 0.075- to 0.125-rem (5) whole-body patient radiation dose, which is well within diagnostic acceptability. There are no additional computer processing or image display requirements. This additional risk is, in our experience, more than offset by the clinically useful information provided. The blood-pool image is of a much higher quality because of the marked increase in available photons from the technetium label. Absolute registration allows subtle foci of abnormal labeled antibody accumulation to be regularly identified and differentiated from retained tracer in the blood pool of adjacent vessels. With separate acquisitions these were incorrectly attributed to variations in patient positioning. The technologist staff saves time because repeat acquisitions, as a result of discordant patient positioning between sessions, have been eliminated. Physician staff time has been saved because difficulties in alignment of the study slices are eliminated.

CONCLUSION

The dual-isotope protocol described in this paper is easy to perform for the technologist, minimizes patient study time and discomfort associated with being imaged, and is enthusiastically accepted by the interpreting and referring physicians. It provides reliable, high-resolution information about vascular anatomy with absolute anatomic registration with labeled antibody accumulation both in normal marrow and in lymph nodes. Preliminary data suggest increased accuracy compared with the single-isotope technique (Khan SH and Holder LE, *personal communication*, 1998).

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