Clinical and Technical Considerations for Imaging Colorectal Cancers with Technetium-99m-Labeled AntiCEA Fab′ Fragment

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Objective: Colorectal cancer is the third most common cancer, after lung and breast cancers. Approximately 133,500 Americans develop colorectal cancer annually and approximately 54,900 die of the disease. As many as 600,000 individuals in the US are under care after surgery for colorectal cancer (*1*).

After reading this article, the nuclear medicine technologist will be able to: (a) describe the role of Arcitumomab in evaluating and managing patients with recurrent colorectal carcinoma metastasizing to the liver; (b) discuss the clinical use of CEA-Scan® (Immunomedics, Inc., Morris Plains, NJ) and its overall imaging performance characteristics and sensitivity related to specific anatomical sites compared to conventional diagnostic modalities; (c) describe radiopharmaceutical preparation and quality control; (d) identify the pertinent patient history before starting the test; and (e) explain the imaging procedure, processing and display of data to optimize study interpretation.

Key Words: technetium-99m Arcitumomab; technetium-99m-labeled CEA-Scan®; tumor-specific radiolabeled antibody imaging; colorectal cancer

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Work with antibodies progressed rapidly and took a giant step forward with the discovery by Kohler and Milstern of the hybridoma technology in 1974, which enabled the large-scale production of monoclonal antibodies to predefined antigens (*2*). Only 20 y have elapsed since the first successful clinical demonstration of targeting and imaging cancers with ^{131}I-labeled antibodies against a carcinoembryonic antigen, as reported by Goldenberg et al. in 1978 (*3*). The refinement in antibody generation and production also was paralleled by advances in chelator chemistry which enabled isotopes other than ^{131}I or ^{125}I , such as ^{111}In or ^{99m}Tc, to be used to label monoclonal antibodies without affecting the antibody's affinity to antigens nor altering the chemical structure of the antibody in ways that would render the radiolabeled compound ineffective for tumor targeting (*4*).

All these efforts by investigators, working individually and independently from each other, culminated in the generation of and approval by the FDA of several cancer diagnostic radioimmunoconjugates starting with OncoScint CR/OV (Cytogen Corp., Princeton, NJ) for colorectal and ovarian cancers, Verluma (NeoRx Corp., Seattle, WA) for staging small-cell lung cancers, Prostascint (Cytogen Corp.) for prostate cancers, and most recently CEA-Scan® (Immunomedics, Inc., Morris Plains, NJ) antiCEA Fab′ or Arcitumomab for recurrent colorectal carcinoma.

ANTICEA Fab′ FRAGMENT

Articumomab is a ^{99m}Tc-labeled Fab′ fragment of IMMU-4, an antiCEA antibody of the immunoglobulin G1 (IgG1) class, specific for the 200,000-dalton carcinoembryonic antigen (CEA). It is an antigen arising from the entodermally derived epithelium of the digestive system. It is expressed by the majority of colorectal cancers and by up to 75% of all adenocarcinomas.

Being a fragment, it has a rapid disappearance from the blood pool, which usually achieves high tumor-to-background ratio that improves early imaging, especially in the liver. There is low complexation with CEA in the blood and less than 1% HAMA response (*5*).

The CEA-Scan (IMMU-4 ^{99m}Tc Fab′ antibody fragment) was approved by the FDA in 1995 for imaging ''in conjunction with standard diagnostic evaluations, for detection of the presence, location and extent of recurrent and/or metastatic colorectal carcinoma involving the liver, extrahepatic abdomen and pelvis in patients with a histologically confirmed diagnosis of colorectal carcinoma.'' This indication was based on retrospective analysis of a Phase-III multicenter trial (*6*). Highlights of these results will be discussed.

Compared to OncoScint CR/OV, which was approved for a more general indication (evaluation of patients with primary, recurrent or occult colorectal carcinoma), Arcitumomab is best used to evaluate the extent of disease in a patient with colorectal cancer and with at least 1 site of presumed cancer revealed by another method. The ultimate goal is to determine whether the patient's cancer is resectable or not. This is a particularly

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difficult and often confounding situation that leads, in many instances, to patients being subjected to unnecessary surgery.

COLORECTAL CANCER

Approximately 150,000 new cases of colorectal cancer are diagnosed annually in the US. Data from the National Cancer Data Base of the Commission on Cancer have shown an increase in the number of proximal (ascending colon) bowel tumors. There is also an increase in the number of early-stage cancers being detected, due primarily to hospital screening and general public awareness. Almost half of the patients diagnosed can be cured by surgery alone. The use of chemotherapy and radiotherapy with surgery is reserved for more advanced stages of the disease.

Although almost 95% of patients with Stage I disease will be alive 5 y after the primary tumor is removed, survival for patients whose tumors have invaded the bowel wall and those with lymph node metastases varies from 10% to 60% (*7*). The main cause of death in these patients is disease recurrence and/or metastases.

The preponderance of these recurrences, 60% of which will be in the liver and 40% will be locoregional, will develop within the first 2 y after complete resection of the primary tumor. While there is no strong evidence to suggest cure after resection of local or regional recurrences, resection of apparently isolated liver metastases offers the best chance of survival. Five-year disease-free survival rates of approximately 20%–30% may be obtained in a carefully selected group of patients (*8–10*).

Despite careful preoperative screening and selection, additional hepatic or extrahepatic nodal metastases are identified in 35% of patients during exploratory surgery, negating the proposed liver resection (*11*). Failures after liver resection for metastasis are divided between re-recurrence in the liver and, less frequently, extrahepatic metastasis.

MULTIMODALITY APPROACH

Careful work-up of these patients with state-of-the-art imaging modalities, such as CT, MRI and intraoperative ultrasonography, is routinely performed to distinguish patients who are candidates for curative resection (i.e., no evidence of cancer outside the liver) and those with extrahepatic disease in whom surgery may be inappropriate due to extensive disease. Using this multimodality approach has greatly enhanced the detection of intrahepatic lesions as well as assessing the size and exact location of these lesions. Immunoscintigraphy with Arcitumomab has been found to be helpful in identifying locoregional and pelvic recurrences, lymph node metastases and small-volume peritoneal surface disease.

After the Phase III studies were completed, an independent assessment of the role of CEA-Scan in the presurgical evaluation of patients for possible curative resection was conducted. Results of CT scans, CEA-Scans, surgical and histopathological findings in 208 patients who had surgery were analyzed to determine how accurate they were in distinguishing between resectable and nonresectable patients (*6*).

Criteria for resectability, such as the number of liver lesions (≦ 4 lesions) and the absence of extrahepatic disease, were derived from published literature. By definition resectable referred to lesions whose removal by surgery can be reasonably expected to result in long-term favorable outcome or cure. The results of imaging by modality as compared with surgery (histopathologically confirmed) in 208 evaluable patients is listed in Table 1.

This table indicates that CEA-Scan alone is more likely to be correct than CT alone in predicting resectability or nonresectability. The combination of both CT and CEA Scans, especially when concordant, significantly enhances the ability to predict resectability. A patient whose CT and CEA-Scans both are interpreted as nonresectable should not be subjected to a costly and futile exploratory surgery.

Another group of patients likely to benefit from CEA-Scan evaluations are those with occult recurrent disease. This subset of patients, which accounts for up to 30% of patients with a recurrence, typically presents with an insidious (seldom abrupt) rise in their serum CEA (tumor marker) and the patients usually are asymptomatic. Detecting a rise in serum CEA level triggers a cascade of diagnostic tests, often ending with surgical exploration. Routine blood tests with liver function tests to rule out liver metastases, chest radiograph, colonoscopy, and liver and pelvic CT scans are ordered traditionally to try to identify the source of the CEA elevation. They usually are negative or equivocal, however, due primarily to the inability to diagnose recurrence outside the bowel lumen (colonoscopy), nor detect metastatic disease in normal-sized abdominal lymph nodes (CT scans). The limited accuracy of CT scans in differentiating recurrences from postoperative or postradiation changes is well documented (*12,13*). Immunoscintigraphy with a variety of monoclonal antibodies, including ^{111}In-labeled antiTAG-72 MOAB B72.3, ^{111}In antiCEA MOAB ZCE 025, or C110 have been consistently superior and more accurate than CT scans in identifying the source of disease in a large percentage of patients, with accuracies ranging from 70%–90% (*14–17*). In a previous article, we have demonstrated the cost effectiveness of immunoscintigraphy with ^{111}In B72.3 in patients with occult

TABLE 1
Modality Accuracy at Predicting Curative Resection

	Percent correct		
	CT alone	CEA-Scan alone	CT and CEA-Scan combined
Surgical outcome			
Resectable (n = 85)	47%	68%	72%
Nonresectable (n = 72)	23%	42%	51%
Negative (absence of cancer) (n = 46)	85%	75%	70%
Totals (N = 208)	47%	60%	63%

TABLE 2
Technetium-99m CEA-Scan® Preparation

Step 1	Allow container of Arcitumomab to come to room temperature and maintain sterile aseptic technique throughout.
Step 2	Obtain 25–30 mCi ^{99m}Tc in sodium chloride injection, USP, at a concentration of 30 mCi/ml.
Step 3	Inject 25–30 mCi ^{99m}Tc in 1 ml into a shielded, vented vial of Arcitumomab to resuspend the contents.
Step 4	Gently swirl the vial for approximately 30 sec to mix. Allow the labeling reaction to proceed for at least 5 min. To facilitate easy removal, you may add 1 ml sodium chloride. Remove the entire contents of the vial and assay in dose calibrator.
Step 5	Determine radiochemical purity. Ensure percentage level of free technetium is less than 10%. Before administration, visually inspect product for particulate matter and discoloration. If either are present, the product should be discarded and the manufacturer notified.
	Note: The product can be stored at room temperature and should be used within 4 h of reconstitution.

disease, as compared with the traditional procedures (colonoscopy, CT scans of liver, abdomen and pelvis, and ultrasonography) (*18*).

In 88 patients with presumed recurrent disease based on CEA serum level elevations and negative conventional evaluation, Arcitumomab, plus conventional diagnostic modalities, was more accurate (61%) than conventional diagnostic modalities alone (33%) in identifying recurrent disease. In addition, CEA-Scan was the only correct modality to identify surgically confirmed disease in 36 patients, all of whom were negative by CT scans (*19,20*). Because of this limited number of patients, and the potential for false-positive interpretations, new lesions, first detected by CEA-Scan and negative on CT scans should be evaluated further, bearing in mind that new tumors detected by CEA-Scan are significantly more likely to be true-positive than false-positive.

The data demonstrate that CEA-Scan has an excellent benefit-to-risk profile for determining resectability (combined with standard diagnostic modalities) as well as the presence and location of tumor sites.

CEA-Scan is safe and virtually nonimmunogenic, which would allow multiple repeated administrations to:

1. Follow up patients who are at a high risk of recurrence after initial curative resection of their primary tumor;
2. Continuously monitor patients with a rising CEA level and whose conventional diagnostic tests remain negative or equivocal.

Since CEA-Scan results have the potential to affect patient management, the nuclear medicine technologist's role in obtaining a technically high-quality study cannot be underestimated. Proper camera setup and recommended acquisition and processing parameters must be adhered to rigorously. Each nuclear medicine department is encouraged to develop their own filtering and processing parameters, particularly for SPECT. A thorough understanding of the pharmacokinetics of CEA-Scan, and potential causes of false-positive and false-negative results would minimize greatly the risks of performing an incomplete or suboptimal study. In the next section we will discuss these technical parameters and offer guidance for acquiring and processing CEA-Scan images.

ARCITUMOMAB PREPARATION AND QUALITY CONTROL

A single-use dose of 1.25-mg lyophilized Arcitumomab (Immunomedics, Inc., Morris Plains, NJ) should be stored at 2°-8°C (do not freeze). The Arcitumomab should be allowed to come to room temperature before radiolabeling. The Arcitumomab contains no preservatives, therefore, it is essential that the user adhere to strict aseptic procedures during the preparation and withdrawal of CEA-Scan, which can be injected 5 min after reconstitution and should be used within 4 h after reconstitution. The reconstituted radiopharmaceutical can be stored at room temperature. Preparing CEA-Scan is straightforward, as outlined in Table 2. Radiochemical purity is determined by thin-layer chromatography, using a method similar to that of other technetium-labeled compounds using acetone as a solvent (Table 3).

TABLE 3
Technetium-99m CEA-Scan® Quality Control Procedure

1. Fill chromatography developing chamber to a depth of 1 cm with acetone.
2. Dilute a 10-μl sample of the radiolabeled antibody with 1.5 ml saline.
3. Perform thin-layer chromatography on silica gel ITLC strip 1 × 9 cm. Pencil mark line at 1 cm from bottom (origin) and 1 cm from top. Spot a small amount of the sample at the origin mark, allow spot to dry and place into developing chamber.
4. Allow the solvent to migrate up the strip to 1 cm from the top of strip. Remove strip, cut in half and place each half into a glass tube.
5. Count each tube in a gamma scintillation counter or dose calibrator.
6. Calculate the percent free technetium, as follows, to ensure that the level of free technetium meets specifications of less than 10%:

$$\%\ \text{free technetium} = \frac{\text{Activity in top half of strip}}{\text{Total activity}} \times 100$$

PATIENT PREPARATION AND DOSE ADMINISTRATION

Begin by obtaining a detailed patient history. Include primary tumor location, type of surgery performed and date, and the location of the colostomy site if present. CT, MRI, and ultrasound reports and, preferably, the films should be available to the physician for review. CEA levels and liver function tests are also important. All of this supportive data will aid the interpreting physician, particularly since most often abnormal uptake seen on CEA-Scan images can appear as subtle uptake (only slightly more intense than blood-pool activity).

Make sure the patient is well hydrated before administering the radiopharmaceutical. It is best to have the patient drink plenty of fluids the day before injection and stop taking additional fluids a few hours before injection. This will help reduce image artifacts around the bladder and reduces the concentration of radiopharmaceutical in the kidneys. Catheterization may be necessary before imaging if the patient has a medical condition that interferes with spontaneous bladder emptying.

Establishing definite venous access is essential. This may be best achieved by using a butterfly infusion set with a saline flush. Slowly inject the entire amount of ^{99m}Tc-CEA-Scan into the patient and flush the line well with saline.

IMAGING METHODOLOGY

Imaging can be started 2–5 h postinjection, however, imaging closer to 5 h postinjection allows more clearance of blood-pool activity and increases the target-to-background ratio (*11*). Normal biodistribution of CEA-Scan (Fig. 1) shows uptake in the heart, lungs and major vessels, such as the aorta. If there is ever any question of abnormal uptake in the chest, additional imaging at 18–24 h will ensure blood-pool clearance in this specific area. In the abdomen, the liver, spleen, kidneys, major vessels and bowel will be visualized. In the pelvis, major vessels, bowel and bladder will be seen. The kidney and bladder are usually the organs with the greatest uptake at this time, since these organs extract and excrete the labeled antibody fragment. Understanding these patterns of biodistribution clearly gives SPECT imaging a valuable role in being able to separate the kidneys from the liver and the bladder from the rest of the pelvic area.

The bladder can be a problem if it is not emptied. A full bladder will mask nearby lesions, particularly in patients with a history of rectal cancer. SPECT imaging will help to delineate a lesion close to the bladder (Figs. 2 and 3).Make sure the patient can void completely before imaging this area and, in the case where a patient is unable to void, catheterization may be necessary.

Colostomy sites, usually in the left lower quadrant, may appear as intense as the blood pool but other times may appear as a faint, hazy uptake (Fig. 4). Always have patients change their colostomy bags before imaging. Taking an extra abdominal planar view marking the colostomy site is advisable.

Planar imaging should be performed using a high-resolution collimator beginning at 4–5 h postinjection. Spot views should include the anterior and posterior head, thorax, abdomen and pelvis for 10 min per view using a 256 $\times$ 256 matrix. Whole-body imaging should be done at a scan speed of 8–10 cm/min from the head to the mid thigh with a 256 $\times$ 1024 matrix (Table 4).

Delayed planar imaging (18–24 h) may be needed to resolve the question of bowel uptake or equivocal lesion with a low uptake seen on earlier images. Uptake persisting at 18–24 h usually is indicative of tumor. It is not recommended to perform 18–24-h delayed images of the abdomen routinely since additional bowel uptake can confuse the interpreting physician. In fact, in clinical trials delayed imaging tended to increase the rate of false-positive findings (*10*).

SPECT imaging is the single most important component in

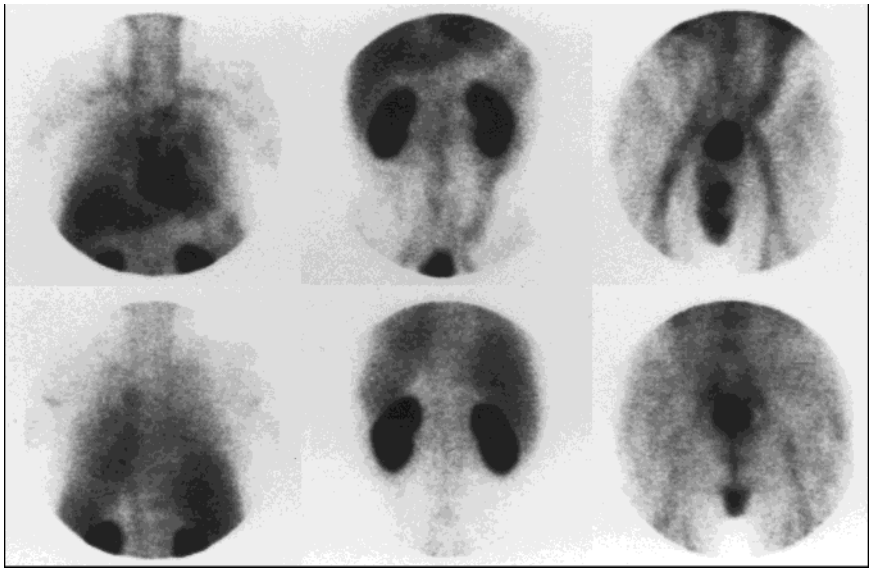

FIGURE 1. Normal biodistribution of ^{99m}Tc-CEA-Scan® at 4 h postinjection. Top row shows anterior planar images of the chest, abdomen and pelvis. Bottom row shows posterior planar images of the chest, abdomen and pelvis.

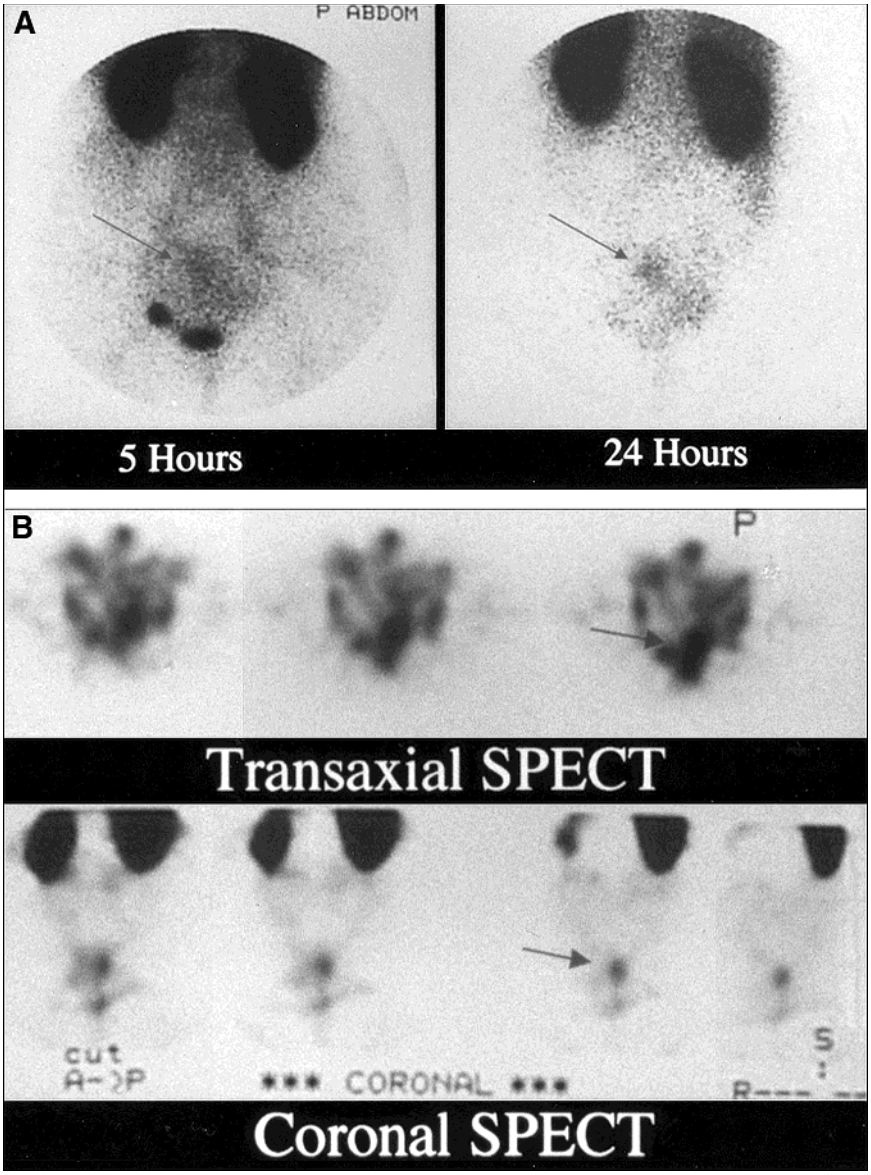

FIGURE 2. (A) Planar anterior pelvis at 5 h and 24 h postinjection. Arrows point to the lesion that was located close to the bladder. (B) SPECT images acquired at 4–5 h helped clearly delineate this lesion.

maximizing lesion detection. Two separate SPECT scans need to be performed, 1 of the abdomen and 1 of the pelvis. Instruct the patient to empty his/her bladder and begin with the pelvic SPECT. Position the patient so that the area just below the kidneys to the groin is included. For SPECT of the abdomen, the liver should be positioned in the center of field of view. Dual- and triple-headed camera systems can increase the number of stops, thereby increasing image contrast and enhancement of smaller areas of uptake near vessels and the bladder and kidneys.

PROCESSING AND DISPLAYING IMAGES

Optimum filtering is essential when processing CEA-Scan images. Customizing filtering methods for your camera system and allowing for interpatient variability will need to be considered. Using a preview filter option, you can view several reconstructions with the same or different filters. By using different filters and cutoff frequencies you will be able to choose the best reconstruction parameters for your department. Using a Butterworth or low-pass filter may work well with a cutoff frequency between 0.26 and 0.45 and an order between 6 and 10. However, these parameters may not be ideal for your particular system. Optimum filtering will show the liver with a well-defined edge. It will look homogeneous with a texture and not glassy smooth. Major vessels will be well defined. Over-filtered images (high cutoff frequency) will cause streaking. Under-filtered images (low cutoff frequency) will be too smooth and subtle differences will blend into the background.

Using a linear gray scale, display images at 2 intensities. Increasing the intensity will bring out subtle disease and lymph node metastases. Lowering the intensity will disclose liver lesions and lesions near the kidneys and/or the bladder.

Other computer tools, such as CINE and three-dimensional

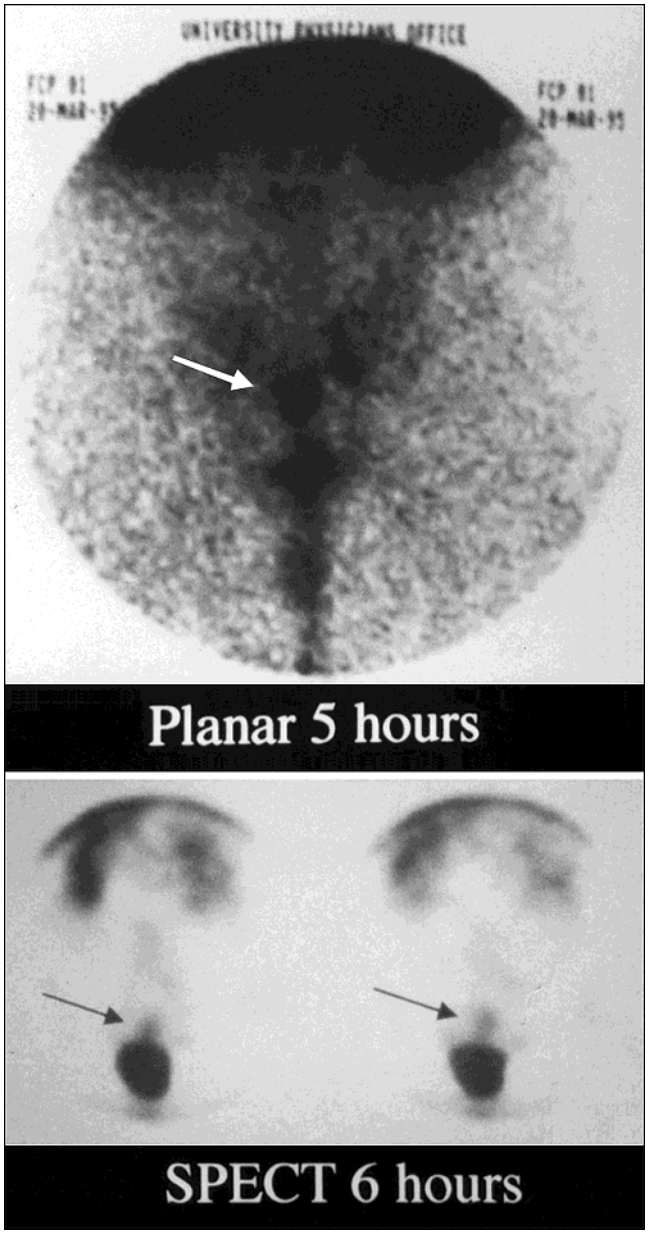

FIGURE 3. (Top) A focus of increased antibody localization appearing in the rectal sigmoid area. SPECT imaging at 6 h (bottom) separated this lesion from the bladder despite the intense activity seen in the bladder.

TABLE 4
Acquisition Parameters for CEA-Scan® Imaging

	Planar	SPECT
Collimator	High resolution	High resolution
Photopeak	140 KeV	140 KeV
Window	20% symmetric	20% symmetric
Matrix		64 × 64 minimum
Spot view	256 × 256, word mode	
Whole body	256 × 1024, 8–10 cm/min	
Time per view	10 min	30–40 sec/stop, 360° orbit

rendering options, are useful, especially for the interpreting physician. You can capitalize on this three-dimensional rendering approach to notice suspicious areas in the liver, bowel or bladder (Fig. 5). You can optimize your search by examining various slices in 1 plane and varying the intensity. Triangulate all suspicious findings by comparing in the transaxial, sagittal and coronal planes. Using this triangulation technique will help demonstrate disease that is hard to see on film or planar images alone. When putting images onto film, make images large enough (35–50 mm wide) and no more than 16 images on an 8 × 10 sheet of film.

SUMMARY

CEA-Scan imaging provides useful clinical information that can affect patient management. Proper techniques for patient imaging and data processing are crucial for generating high-quality and diagnostically useful scans. Familiarizing physicians with normal and abnormal patterns and recognizing the known reasons for artifact generation and how to avoid them are equally important.

Colorectal cancers are just one of the few CEA-secreting cancers that can be targeted with Arcitumomab. Other tumors, which have been shown to localize Arcitumomab, include breast and nonsmall-cell lung cancers. The potential contribution of CEA-Scan to patient management in these 2 cancers is being investigated currently.

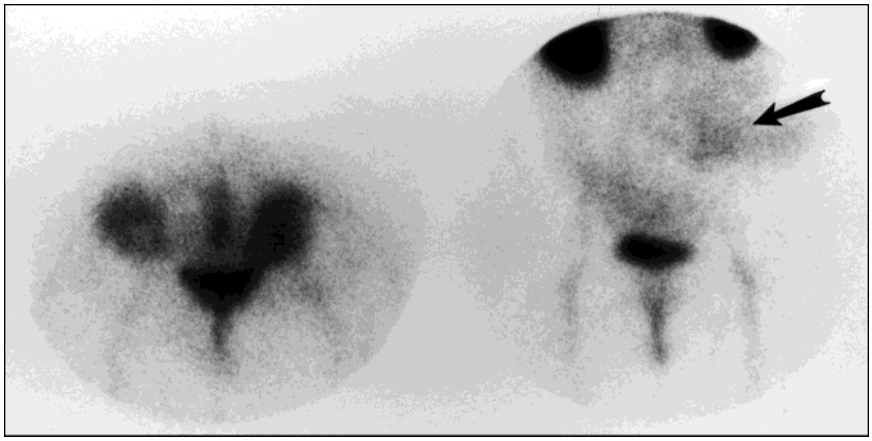

FIGURE 4. The left (tail on the detector) planar imaged showed increased localization in the presacral region, which was suggestive of a local tumor recurrence in the rectal/sigmoid area. The anterior pelvis (right, arrow) planar image shows subtle uptake in the left iliac area, which represented nonspecific activity in a colostomy bag.

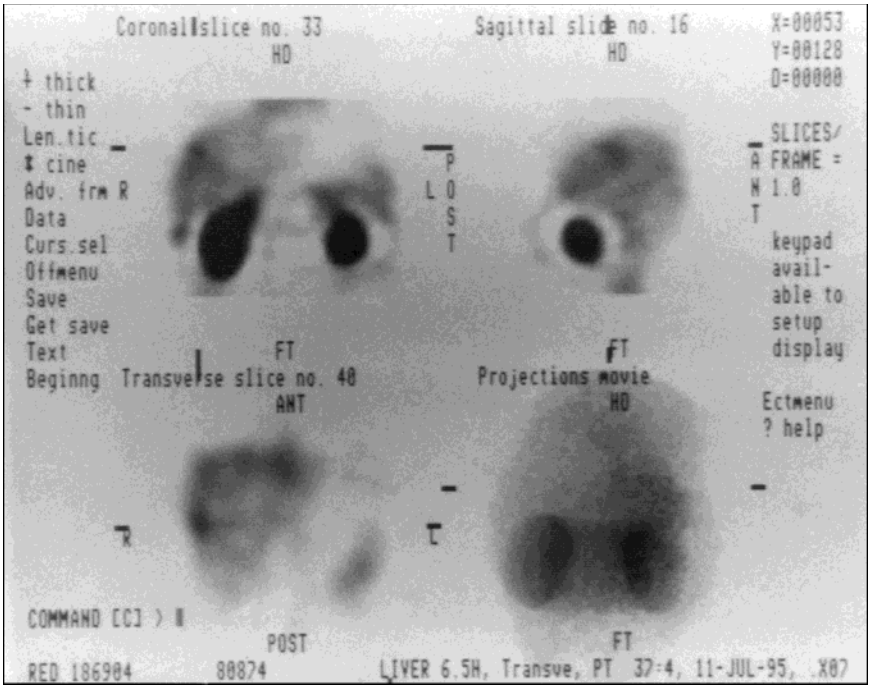

FIGURE 5. CINE and three-dimensional rendering were used on this patient to identify a lesion (increased CEA-Scan® uptake compared with normal liver tissue) in the right lobe of the liver. A second lesion was identified in the medial aspect of the left lobe. Triangulation of suspicious areas helped provide spatial orientation in the transaxil, saggital and coronal planes.

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