

Indium-111 Satumomab Pendetide: The First FDA-Approved Monoclonal Antibody for Tumor Imaging

Paul J. Bohdiewicz

Nuclear Medicine Department, William Beaumont Hospital, Royal Oak, Michigan

Objective: Colon cancer is the second most common cause of cancer mortality. Ovarian cancer is the most common gynecologic malignancy cause of death in women.

A labeled monoclonal antibody attaches to a tumor-associated antigen and allows these tumor masses to be imaged or treated, depending on the radionuclide used. Indium-111 satumomab pendetide was the first labeled monoclonal antibody to be approved by the Food and Drug Administration (FDA) for tumor imaging. It is reactive with most colorectal and ovarian cancers, as well as other cancers.

After reading this article, the technologist will understand the FDA approval process, phase trial results, safety and adverse reactions, human antimurine antibody response, indications, imaging protocol, and strengths and weaknesses of imaging with satumomab pendetide. Representative cases are presented.

Key Words: indium-111 satumomab pendetide; indium-111 OncoScint® CR-OV; monoclonal antibody; radionuclide tumor imaging

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Cancer of the colon is the fourth most common cancer in the U.S., after lung, breast and prostate cancers. It is the second most common cause of cancer mortality after lung cancer. The incidence of colon cancer is approximately the same for both men and women, although rectal cancer is more common among men. The DCC (deleted in colon carcinoma) gene and the MCC (mutated in colon carcinoma) gene are two tumor-associated genes that have been identified. In addition, mutations in p53, k-ras and APC (familial adenomatous polyposis gene) are important in the development of colorectal cancer. The incidence of colon cancer varies at least tenfold throughout the world, with the highest incidence rates occurring in North America and northern Europe and the lowest incidence in Asia and Africa (1).

Ovarian cancer, which is the most common gynecologic malignancy cause of death in female patients, accounts for about 4% of cancers and 5% of cancer deaths in women. The highest incidence rates occur in Scandinavian countries. The cause of the disease is poorly understood (1). Ovarian cancer is usually asymptomatic until it has metastasized, and thus patients present with advanced disease in more than 70% of cases (2). There are an estimated 26,700 new cases of ovarian cancer per year in the U.S., and approximately 14,800 women will die of ovarian cancer. One woman in 100 will die of this disease (3).

ANTIBODIES, MONOCLONAL ANTIBODIES, IMMUNOSCINTIGRAPHY AND B72.3

Until the 1970s little was known about antigens (Ags) and antibodies (Abs). It was uncertain what would happen if milligram quantities of murine IgG were infused into a human being. Since in vivo immune complex formation was known to cause life-threatening disease, investigators felt that the administration of a mouse protein into a human being would constitute a considerable risk. In mammals there are five classes of Abs (chemically these molecules are glycoproteins) varying in size from the smallest, IgG, which weighs approximately 150,000 daltons up to the very large IgM molecule which has an estimated weight of over 900,000 daltons. Antibody similarities between different species of mammals are greater than the differences. In a schematic diagram the IgG molecule usually is represented in the shape of the letter "Y." However, this configuration only occurs when the Ab interacts with an Ag. In its resting state the IgG molecule, like many proteins, is globular in appearance. The IgG molecule consists of two light chains and two heavy chains linked together by disulfide bridges. The stem of the "Y" is the Fc portion which weighs approximately 50,000 daltons (approximately one-third of the molecule), and it contains nearly all the carbohydrate moieties of the entire molecule. The Fc portion is more or less constant in structure, unlike the rest of the Ab molecule. The other end of the molecule consists of two Fab portions which are the immunoreactive regions of the molecule. There are

For correspondence or reprints contact: Paul J. Bohdiewicz, MD, Nuclear Medicine Department, William Beaumont Hospital, 3601 West 13 Mile Rd., Royal Oak, MI 48073-6769.

variable regions at the ends of all heavy and light chains, and these are the regions that react with the Ag (4).

In 1975 Kohler and Milstein described their method of production of monoclonal antibodies (Mabs), which won them a Nobel prize in 1987. Antibodies are produced by the immune system after being exposed to a foreign substance, an Ag. The Abs are secreted by plasma cells which are derived from B lymphocytes. A complex antigenic determinant will result in several immunoglobulins that differ from each other in their affinity for Ag binding surfaces. These are known as polyclonal Abs. Mabs are derived by generating a specific immunoglobulin-producing cell line after the mouse is immunized with the specific Ag that stimulates the B lymphocytes to produce the antibody. According to the method of Kohler and Milstein, the B lymphocytes are harvested from the mouse and incubated with immortalized myeloma cells in the presence of polyethylene glycol. The resultant hybridoma cells are capable of living in culture for a long period of time and are capable of producing a large amount of Ab. The cell lines can be screened using immunoassays to identify the specific cell line or clone that produces the specific Mab that has the most desirable features. The most important feature is the affinity of the Ab for the Ag. The hybridoma cells can be grown in the peritoneal cavity of a mouse or in tissue culture (4,5).

The principle of radioimmunosciintigraphy (RIS) and radioimmunotherapy (RIT) is as follows. A Mab is incubated with a bifunctional chelating agent to produce a Mab conjugate. This Mab conjugate is incubated with an appropriate radionuclide to produce a radiolabeled Mab. The latter is injected into an animal or a patient where it seeks out tumor cells and attaches to them. Because of this the tumor mass can be imaged or treated, depending on the radionuclide used.

Typical isotopes used for RIS include ^{111}In , $^{99\text{m}}\text{Tc}$, ^{131}I and ^{123}I . Each has its own advantages and disadvantages. Indium-111 has a half-life of approximately 3 days, emits gamma photons and is best suited for whole Abs because imaging over many days can be performed, which corresponds to the kinetics of whole Abs. Its disadvantage is its uptake in the liver. Technetium-99m has a half-life of 6 hr, is inexpensive and has a relatively low radiation dose per millicurie, allowing for more isotope to be used and resulting in an excellent counting rate. Technetium-99m is best tagged to Mab fragments because of its shorter half-life. This works well because of the faster kinetics of Mab fragments when compared to whole Mabs. Its disadvantage is the relatively complex chemistry involved, and the fact that significant renal and bladder activity result. Iodine-123 and ^{131}I are both easily labeled to proteins, however, both are known to dehalogenate. Iodine-123 is expensive and ^{131}I has both a high radiation dose and a suboptimal gamma camera imaging energy of 364 keV.

It is always desirable to use a gamma emitter for Ab imaging that might predict the kinetics and distribution of the Ab which will later be labeled with a therapeutic isotope. Examples of imaging/therapy counterparts include $^{123}\text{I}/^{131}\text{I}$, $^{99\text{m}}\text{Tc}/^{186}\text{Re}$ and $^{111}\text{In}/^{90}\text{Y}$ (4).

When an isotope is attached to a Mab or fragment, it must be done without changing the affinity of the Ab for the Ag. Special techniques are available that can result in site-specific attachment of a radionuclide. Modifications of Abs may reduce their immunogenicity. Smaller molecules also may penetrate the tissues more quickly and be eliminated from the blood and background more quickly. Antibody fragments do indeed have less immunogenicity and an accelerated intravascular half-life. Newer techniques include the production of chimeric, humanized and human Abs, each of which results in progressively less immunogenicity (6).

Satumomab pentitide (OncoScint® CR/OV; Cytogen Corporation, Princeton, NJ) was the first Mab approved by the Food and Drug Administration (FDA) for tumor imaging. It is a conjugate produced from the murine monoclonal antibody B72.3 (CYT-099). B72.3 is an IgG molecule that is directed against a tumor-associated antigen, TAG-72, which is found in many adenocarcinomas. B72.3 is reactive with most colorectal and ovarian cancers, and the majority of breast, nonsmall cell lung, pancreatic, gastric and esophageal cancers. The OncoScint CR/OV is prepared by site-specific conjugation of a linker-chelator to the oxidized oligosaccharide component of the B72.3 molecule (CYT-103). B72.3 usually is not reactive with normal adult tissues, however, it is reactive with salivary gland ducts, normal postovulatory endometrium, some benign ovarian tumors and fetal gastrointestinal tissues. Indium-111 OncoScint CR/OV also localizes in non-Ag-dependent regions (likely secondary to catabolism), including localization in the liver, spleen and bone marrow. Activity also is normally seen in the blood pool, bowel, kidneys, urinary bladder, male genitalia and breast nipples in women (7).

THE APPROVAL PROCESS FOR MABS IN THE U.S.

The following summarizes the major steps that need to occur before a Mab can be used in humans in the U.S. OncoScint® CR/OV was the first of four radiolabeled Mabs or fragments, at the time of this writing, to be approved for tumor imaging by the FDA. The FDA derives its authority from the Federal Food, Drug and Cosmetic Act and Section 351 of the Public Health Service Act and has jurisdiction over drugs, which include biologic products (such as Mabs), that will be marketed through interstate commerce. The sponsoring individual or company first needs to file a "Notice of Claimed Investigational Exemption for a New Drug," known as an IND. The IND includes relevant preclinical animal data and in vitro data as well as the qualifications of the investigators and a research plan for proposed human studies. If the IND is approved, Phase I clinical trials investigating the safety, possible toxicity and dose escalation may proceed. Subsequently, Phase II studies evaluate the effectiveness of the agent for a specific disease or condition, as well as to further evaluate for possible side effects, risks and the approximate optimal dose. If approved, Phase III trials may begin which must be well controlled, statistically designed studies to evaluate efficacy and risk benefit (6).

When Phase III clinical trials are concluded, the sponsoring individual or company presents relevant clinical data and its plans for manufacturing, including quality control of the agent, to the FDA in a biologic license application (BLA). The BLA combines what was previously known as a product license application (PLA) and an establishment license application (ELA). The FDA may use expert advisory panels and community and patient representatives. The FDA may defer approval of the BLA if there are unanswered questions or concerns that must be readdressed by the applicant on a subsequent resubmission. When the BLA is approved, an official "label" indication is assigned to the product, which refers to the strict context in which efficacy was demonstrated. Other uses of the approved agent usually are considered a physician's prerogative. However, "off-label" usage may not be reimbursable (6).

Although the FDA serves an important role in assuring that agents injected into humans are safe and effective, the approval process is expensive, tedious and time consuming. The approval process can result in extensive delay of the development of new agents for use in humans and may discourage individuals or companies with limited financial resources from obtaining approval of a promising agent (6).

PHASE TRIAL RESULTS FOR ONCOSCINT® CR/OV

Colorectal Carcinoma: OncoScint versus Computed Tomography

There were 151 patients with surgically confirmed colon carcinoma evaluated by both OncoScint CR/OV imaging and x-ray computed tomography (CT). OncoScint revealed a greater proportion of lesions in the pelvis (75% versus 55%; $n = 20$) and in the extrahepatic abdomen (67% versus 28%; $n = 18$), while CT revealed a greater proportion of liver lesions (88% versus 38%; $n = 40$). The aggregate sensitivity of the two tests used in combination was 88%. The specificities of OncoScint and CT were identical (76.9% for patients found to be surgically free of disease imaged with both modalities). Of 124 positive OncoScint scans, 120 were confirmed at surgery resulting in a positive predictive value of 97%. However, only 13 of 67 negative OncoScint scans were confirmed as occurring in patients without tumor, for a negative predictive value of 19%. It was concluded that a negative scan is not informative about disease and should not be used to guide clinical practice. There were seven false-positive OncoScint scans in this trial which correlated histopathologically with four sites of inflammation, two benign colonic polyps and one site with pathologically normal colonic tissue (7).

Ovarian Carcinoma: OncoScint versus Computed Tomography

Of 51 patients with surgically confirmed ovarian cancer who were imaged by both OncoScint and CT, the overall sensitivity of OncoScint was 59%, which was significantly greater than the 29% sensitivity of CT. Of the 27 patients with carcinomatosis (diffuse miliary spread of disease intraperitoneally), OncoScint was more sensitive than CT (59% versus 30%) for detecting

carcinomatosis. Because there were five false-positive studies in patients evaluated for primary ovarian cancer who were later found to have benign ovarian tumors, it was concluded that OncoScint should not be used to distinguish benign from malignant primary ovarian tumors. Of 36 positive OncoScint studies, 30 were confirmed at surgery as tumors, resulting in a positive predictive value of 82%. However, only 9 of 31 negative OncoScint scans were confirmed as occurring in patients without tumors, for a negative predictive value of 29%. Therefore, it was concluded that a negative antibody scan is not informative about the presence of ovarian cancer and should not be used to guide clinical practice (7). According to Krag, 18 study sites evaluated 103 patients, and Mab imaging resulted in a sensitivity of 69% (44% for CT). The specificities were 57% for the Mab and 79% for CT. The sensitivities for carcinomatosis were 71% and 45%, respectively. OncoScint revealed tumors in 19 patients who had negative CT scans, whereas CT showed tumors in only two patients with negative Mab studies (8).

Safety and Adverse Reactions

A total of 1188 intravenous doses of OncoScint were administered to 1041 patients in the clinical trials. Adverse reactions occurred in approximately 45 patients. There were no deaths or anaphylactic reactions. The most common adverse reaction was fever (1%). Other adverse reactions, occurring in less than 1% of patients, are listed in order of decreasing frequency: hypotension, hypertension, nausea, chills, rash, injection site reaction, pruritus, allergic reactions, sweating, abdominal pain, asthenia, chest pain, headache, hypothermia, pain, bradycardia, vasodilatation, diarrhea, arthralgia, confusion, dizziness, nervousness, crying and angioedema. Although it may not have been related to OncoScint administration, an isolated occurrence of reversible thrombocytopenia was observed in one patient (7).

The overall incidence of adverse reactions reported in patients who received repeat administrations of OncoScint was approximately 4%, similar to that observed after the administration of a single dose. Two fevers, one incident of abdominal pain and two readily reversible hypersensitivity reactions (characterized primarily by flank pain) were reported after repeat doses of OncoScint intravenously. The latter two patients had positive preinjection human antimurine Ab (HAMA) titers and a history of allergies (7).

Human Antimurine Antibody Response

Because murine Mabs are foreign proteins to humans, their administration can induce an immunologic response inducing human antimurine Ab (HAMA) production in humans. HAMA may interfere with murine Ab-based immunoassays and could compromise the efficacy of diagnostic or therapeutic murine Ab-based agents, as well as possibly increase the risk of adverse reactions. For these reasons patients should be informed that the use of a murine Mab could affect the future use of other similar agents, and patients should be advised to discuss the use of these products with their physicians. OncoScint has been shown to induce HAMA to murine IgG after

a single administration in about 55% of patients in the trials. The HAMA levels became negative in one third of these patients by 6 mo after infusion resulting in approximately 37% of patients being HAMA-positive at 6 mo (7).

Patients with persistently elevated HAMA levels have altered clearance and tissue biodistribution of Mabs. Before the administration of OncoScint, patients who previously received this or other murine Ab-based products should be tested for HAMA using approved methodology. Specialty Laboratories, Inc., in Santa Monica, CA (phone: 1-800-421-7110) has a Cytogen-approved methodology to measure HAMA. Clinical trials demonstrated that if serum HAMA levels are less than 50 ng/ml, there is a high probability that the images will be of normal quality with a normal biodistribution of OncoScint. If the levels are between 50 and 400 ng/ml, the biodistribution is likely to be abnormal with a more rapid clearance of the product from the blood and most of the organs with increased deposition of the radiolabeled product in the liver. If the HAMA level is greater than 400 ng/ml, repeat imaging studies should not be performed (7).

Ninety-five patients who were at risk of colorectal carcinoma recurrence received a total of 147 repeat doses of OncoScint, including 37 patients who received three or more doses (with a minimum interval of 4 mo between doses). The imaging results of the 147 repeat injections included 30 true-positive, 89 true-negative, 1 false-positive, 8 false-negative and 19 indeterminate scans. The overall sensitivity was calculated at 79%, which is similar to the results for single doses. However, surgical confirmation was not obtained in most patients and therefore repeat dose sensitivity, specificity and true/false-positive and negative categorizations could not be verified. Again, negative studies were felt to be noninformative about disease and should not be used to guide clinical practice (7).

HAMA may interfere with two-site murine Ab-based immunoassays, including assays for carcinoembryonic antigen (CEA) and CA-125. When HAMA is present the interference generally results in falsely high values, and the clinical laboratory should be notified so that appropriate measures can be taken to prevent this interference (by using nonmurine immunoassays or removing HAMA by adsorption, blocking or heat inactivation) (7).

LIMITATIONS OF OTHER DIAGNOSTIC AND LABORATORY STUDIES

One third of all colorectal cancer recurrences do not have an elevated CEA. CA-125 lacks both sensitivity and specificity as a screening test for ovarian cancer and, although positive CA-125 titers are useful in predicting the presence of disease in patients with known ovarian cancer, negative titers do not preclude disease. The negative predictive value of CA-125 was only 56% in a prospective study using a cutoff value of 35 units/ml (2).

As described above, OncoScint is superior to CT for detecting disease in the extrahepatic abdomen and pelvis, and it is much more sensitive for detecting carcinomatosis. Radio-

graphic imaging modalities are suboptimal for various reasons. For both CT and MR imaging of lymph nodes, size is the criterion used to determine whether or not a lymph node is positive for disease. However, tumor may be present in normal-sized nodes, and nodes may be enlarged on an inflammatory basis rather than secondary to malignancy. The barium enema examination as well as colonoscopy primarily evaluate the mucosal surface of the bowel and do not evaluate the wall or the serosal surface. OncoScint may prove useful as an imaging study to identify tumors in any portion of the bowel or in lymph nodes of normal size.

INDICATIONS FOR ONCOSCINT® CR/OV IMAGING

Suggested indications for imaging with OncoScint include: (a) the presence of a rising serum tumor marker in the absence of a known source (negative imaging studies); (b) further evaluation of patients with presumed solitary disease who are being contemplated for curative surgical resection; and (c) the presence of equivocal lesions as imaged by CT or MR (for example, to help distinguish fibrosis from tumor in patients who have had surgery or radiation therapy). OncoScint is indicated for determining the extent and location of extrahepatic malignant disease in patients with known colorectal or ovarian cancer. This study should follow the completion of standard diagnostic tests and be interpreted in conjunction with these tests (7).

PROTOCOL

Typical imaging protocols usually incorporate 10-min spot images, more than 1 day of imaging, the use of oral cathartics, and SPECT imaging to allow for evaluation in multiple planes. Interpretation requires knowledge of normal variants and the causes of false-positive studies. Nontumor causes of OncoScint uptake and normal variants include inflammation at the surgical site, colitis, infection, arthritis, fractures, ostomy sites, activity in bladder and rectum, blood-pool activity in the aortic knob and in the left upper quadrant (which decreases with time), and bowel activity (which moves with time) (2,7,9). Sagittal imaging is helpful in distinguishing bladder, rectal and tumor activity when interpreted in conjunction with MRI (10). Quantitation using computer regions-of-interest may be helpful in identifying carcinomatosis (11).

At my institution, the nuclear medicine physician explains the study to the patient, including the potential for an anaphylactic reaction or for serum sickness, although stressing that neither of these occurred during the multicenter clinical trials. Although injection and imaging days are flexible, an ideal day for injection of OncoScint is on a Friday with imaging performed the next Monday and Wednesday mornings. The study is not scheduled until 6 wk after radiation therapy, chemotherapy or surgery. The patient must not be pregnant and a detailed history of allergies and previous exposure to murine antibodies is obtained. If there is a history of a prior murine antibody test, a HAMA level is obtained.

If there is no medical contraindication, such as colonic obstruction, the patient is asked to take an oral cathartic the

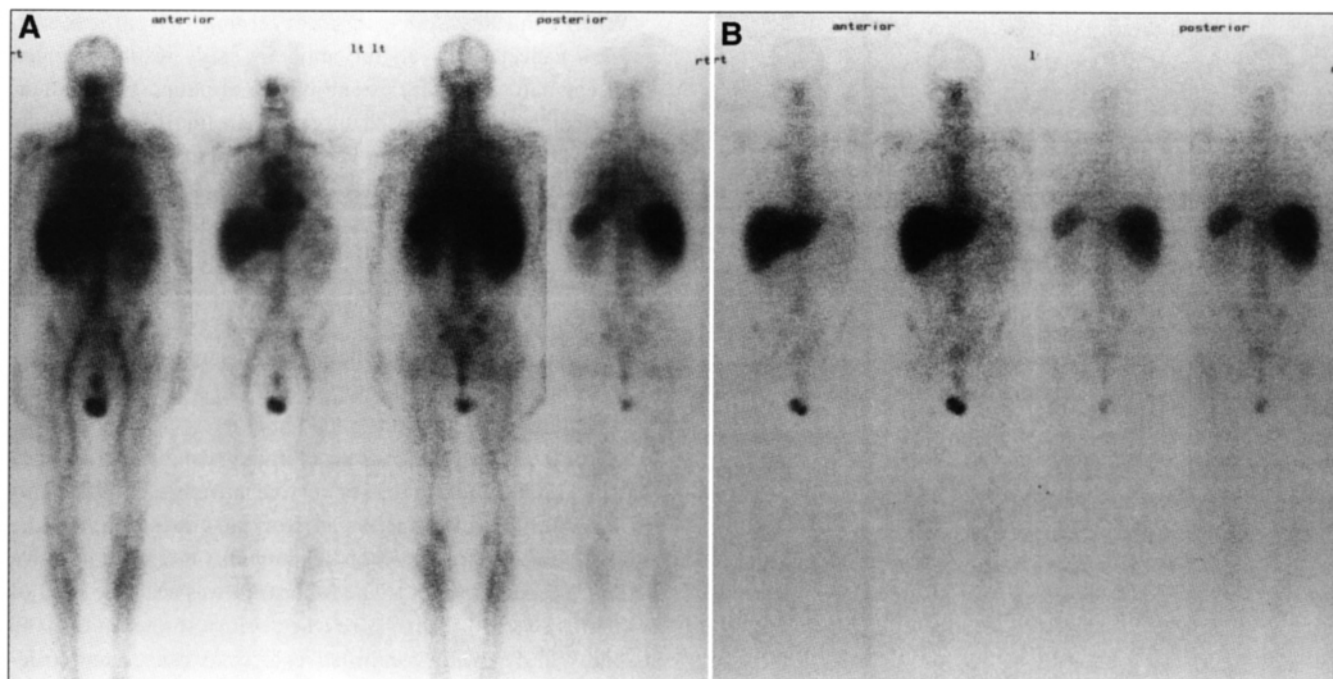


FIGURE 1. (A) Anterior and posterior whole-body images, obtained 48 hr after the intravenous administration of ^{111}In OncoScint® CR/OV in a 58-yr-old man with previously resected carcinoma of the colon and rising CEA values, demonstrate the normal biodistribution of OncoScint 48 hr after injection. (B) Anterior and posterior whole-body images performed 7 days after injection demonstrate the normal biodistribution of OncoScint at 7 days. Note the significant clearing of cardiac and vascular blood-pool activity over time. These whole-body images illustrate the normal biodistribution of OncoScint over time. (Ten-minute spot images of the anterior and posterior chest, abdomen and pelvis, rather than whole-body imaging, are usually recommended for clinical imaging.)

evening before the second day of imaging. The patient should void before imaging and any colostomy or urine collection bags should be changed immediately before scanning.

One milligram of satumomab pendetide is radiolabeled with 5.0 mCi ^{111}In -chloride. A medium-energy collimator is used with dual-pulse height analyzer at 173 and 247 keV photopeaks with 20% symmetric windows. Planar images are set to be obtained using a $128 \times 128 \times 16$ matrix.

A 21-gauge or larger angiocatheter is inserted intravenously. The physician or technologist (with a physician in the immediate area) then injects the ^{111}In OncoScint over a 5-min time period. The patient is not left unattended.

Ten-minute anterior and posterior images of the chest, abdomen and pelvis are obtained on the first imaging day (usually 72 hr after injection) and again 120 hr after injection. The chest and pelvis views ideally should include only one edge of the liver. SPECT images of selected regions of interest are usually obtained on the second day of imaging.

Until recently a single-headed SPECT camera was used for medium-energy isotope SPECT imaging in our institution. All OncoScint images were obtained with this single-head ADAC camera. Imaging results are excellent using a $64 \times 64 \times 646$ matrix for SPECT with 360° rotation, 120 stops and 20 sec per stop. A Butterworth filter is used with an approximate frequency cutoff of 0.4 cycles/cm and an order of 5. Attenuation correction is applied and a 0.11-per-cm attenuation coefficient used. Two-dimensional displays in axial, coronal and sagittal planes, as well as rotating volume-rendered images of the SPECT data, are viewed on the computer monitor.

REPRESENTATIVE CASES

Four cases are presented for illustration. Information regarding each case is contained in the figure legends.

Case 1 shows normal biodistribution of OncoScint in a patient with colon cancer and rising CEA values (Fig. 1).

Case 2 illustrates carcinomatosis and focal tumor recurrence in a patient with metastatic cancer of the cecum (Fig. 2).

Case 3 shows metastatic sigmoid carcinoma in mesenteric and retroperitoneal lymph nodes in a patient with rising CEA values (Fig. 3).

Case 4 is a false-negative OncoScint scan with a true positive ^{18}F -FDG PET study in a patient with a sigmoid cancer recurrence (Fig. 4).

Case 5 illustrates multiple focal sites of abnormal uptake in a patient with metastatic rectal cancer (Fig. 5).

STRENGTHS AND WEAKNESSES OF ONCOSCINT® IMAGING

OncoScint's ability to detect carcinomatosis currently is unsurpassed and can be extremely helpful to the patient and physician. Carcinomatosis is more accurately diagnosed with planar OncoScint images than with SPECT OncoScint images, FDG PET or CT (10). Carcinomatosis often is seen in ovarian cancer but can be seen in colorectal cancer as well. (Fig. 2). The ability to diagnose carcinomatosis is useful particularly before a planned second-look laparotomy for patients with ovarian cancer (12). The carcinomatosis pattern in the setting of either colorectal or ovarian cancer indicates inoperability.

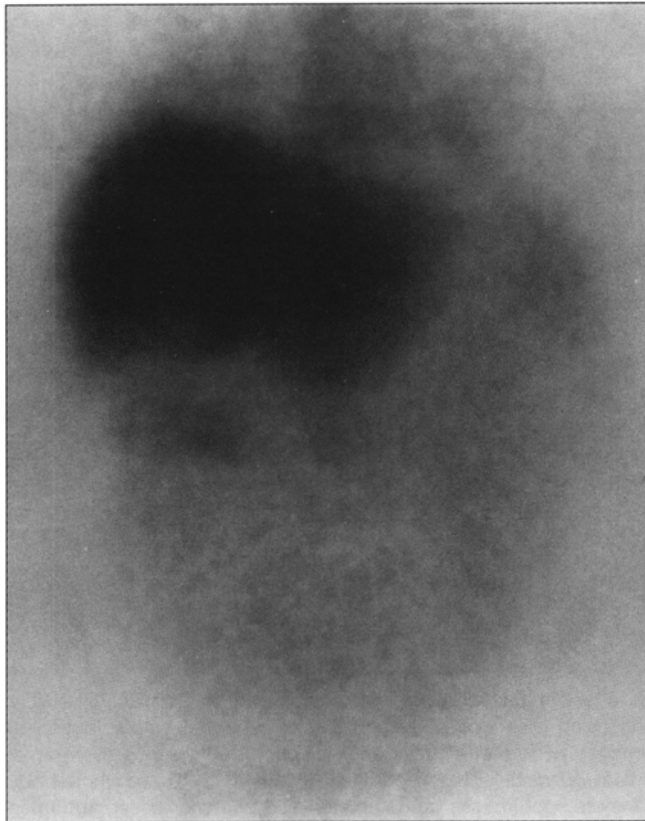


FIGURE 2. Anterior image of the abdomen performed 72 hr after intravenous administration of OncoScint® in a 65-yr-old man who had surgery 8 mo previously for cecal cancer. A diffuse haze of activity over the entire abdominal/pelvic peritoneal cavity is typical in appearance for carcinomatosis. (The same pattern is seen more often in patients with ovarian cancer.) In addition, focal abnormal increased activity is visible in the right upper quadrant, which persisted on 120-hr images and represented focal tumor recurrence.

When clinicians were polled concerning 103 patients with ovarian cancer, they felt the antibody study results changed their estimate of disease extent in 27% of patients and potentially changed the proposed surgical plan for 16%. The study was considered beneficial or very beneficial in 16 of 68 patients (24%) evaluated for recurrent ovarian cancer and 12 of 35 patients (35%) evaluated for primary disease. This study was felt to be negative/very negative in only 2 of 103 patients (2%) for all patients with ovarian cancer evaluated in the 18 study sites (12).

The impact of Mab imaging in patients with colorectal cancer was addressed in articles by Doerr (13), Corman (14) and Dominguez (15). Clinicians polled in Doerr's article found the effect of the study to be beneficial or very beneficial in 18 of 69 patients (26%) and negative or very negative in 2 of 69 patients (3%) (13). The investigators in Corman's article found the study to be beneficial in 45 of 103 patients (44%) and negative in 2 of 103 patients (2%). The Mab study was accurate in 71 of 84 patients (85%). There were true-positive studies in 36 of 49 patients (73%) with confirmed colorectal cancer and true-negative studies in all 35 patients (100%) with no evidence of colorectal cancer. The results of the Mab study prompted a change in treatment in 17 of 103 patients (16.5%) (14). The clinicians polled in Dominguez' article found the study effect to be beneficial or very beneficial in 2 of 15 patients (13%) and negative or very negative in 3 of 15 patients (20%) (15). It is possible that the results in Dominguez' study were not as favorable because of the small size of the patient population and because SPECT imaging was not always performed in that series.

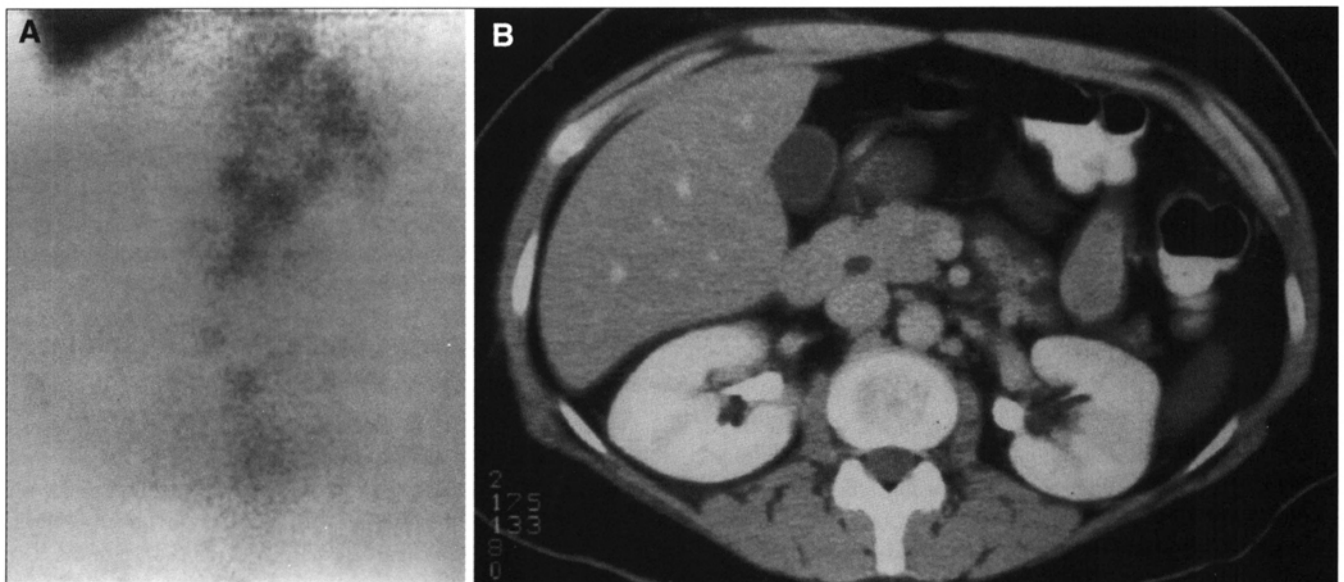


FIGURE 3. (A) Anterior image of the abdomen, 96 hr after intravenous administration of ^{111}In OncoScint® in a 52-yr-old woman with rising CEA values who had resection of a sigmoid carcinoma 1 yr before, demonstrates abnormal activity in the region of the retroperitoneal and mesenteric lymph nodes. The abnormal activity persisted on repeat imaging. (Lymph node biopsy was positive for metastases in retroperitoneal and mesenteric lymph nodes.) (B) An axial slice from the same patient's CT scan demonstrates highly suspicious enlarged lymph nodes in the periaortic region (positive for tumor on biopsy).

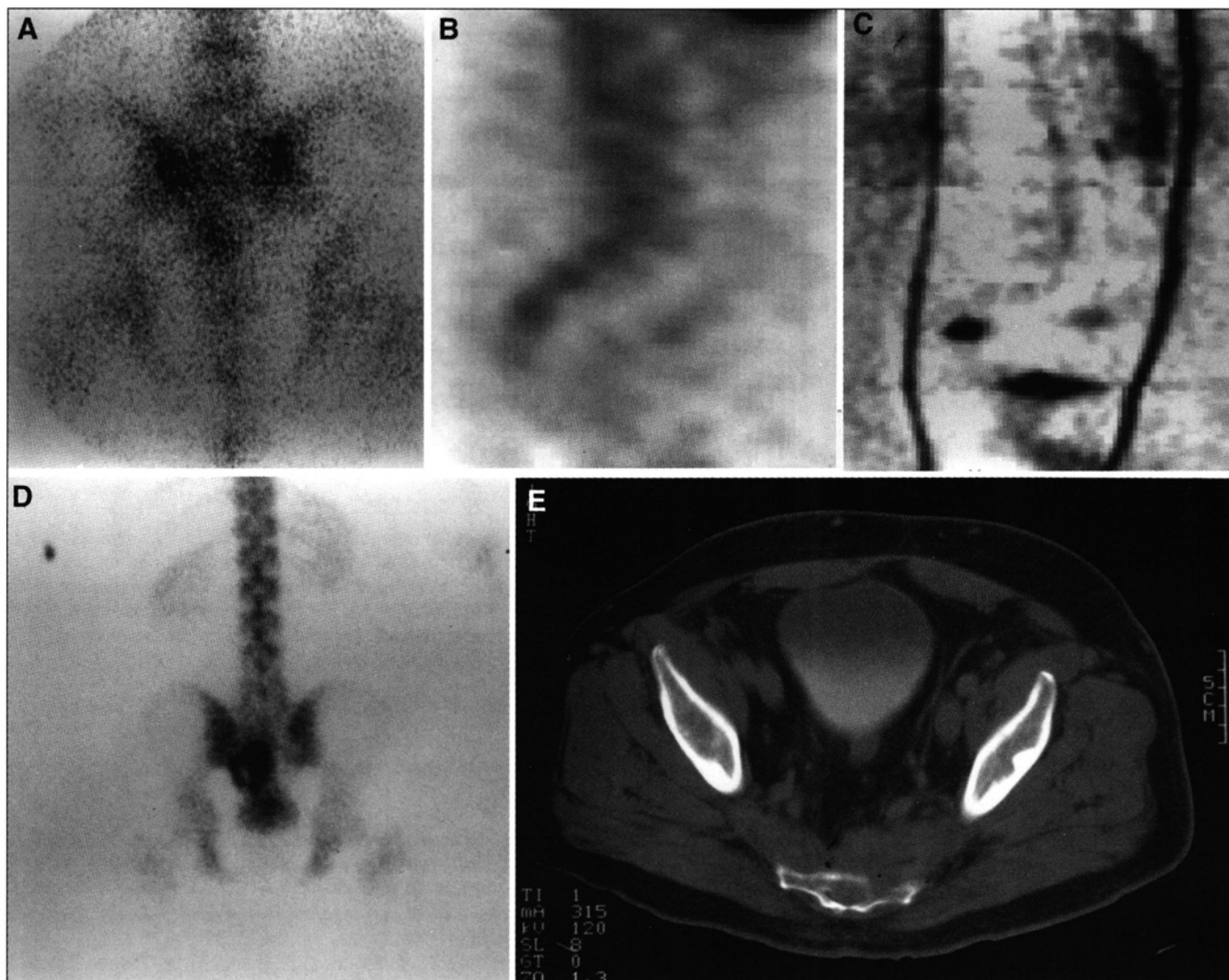


FIGURE 4. False-negative OncoScint® study and true-positive ^{18}F -FDG PET study of a 58-yr-old man who previously had surgical resection of a sigmoid carcinoma and right hepatectomy for hepatic metastases, and was imaged because of rising CEA values and a negative CT. (A) Posterior image of the pelvis 5 days after intravenous administration of ^{111}In OncoScint® demonstrates no abnormality. Images at 3 and 7 days appeared the same. (B) Sagittal SPECT image demonstrates normal-appearing lumbar and sacral vertebrae and normal activity in the rectosigmoid. No abnormal presacral or sacral activity is noted. (Posterior is to the left in this image.) (C) Sagittal PET image 1 hr after intravenous administration of ^{18}F -FDG demonstrates the bladder and a true-positive focal area of abnormal increased activity in the sacral/presacral region posterior and superior to the bladder. (Posterior is to the left in this image.) (D) Posterior image from a bone scan, performed after the positive PET study, demonstrates focal abnormal increased activity in the left sacrum which corresponds to bony involvement by recurrent tumor. (E) An axial image from a repeat CT scan with bone windows (performed after the positive bone scan) demonstrates a soft-tissue mass anterior to the left and central aspects of the sacrum, with cortical destruction of the anterior aspect of the left sacrum secondary to tumor extension.

CT and MR cannot reliably distinguish fibrosis from tumor after surgery or radiation therapy and cannot reliably differentiate lymph nodes with tumors from those without tumors by size criteria. Indium-111 satumomab pentetide is a "positive" tumor imaging agent which should result in a hot spot at the site of the tumor. The Mab study is more sensitive for extrahepatic abdominal and pelvic disease, whereas CT is more sensitive for tumor detection in the liver. Thus, RIS is strong in regions where CT and MR are relatively weak, which is in the extrahepatic abdomen and pelvis. The two studies are complementary. Liver lesions tend to be photopenic on OncoScint

imaging because the normal liver has nonspecific increased uptake of OncoScint.

A disadvantage of tumor detection with Mabs in general is that the tumors are usually small compared to surrounding normal organs, such as the kidneys or liver. Even a large tumor (baseball sized) weighing approximately 188 g (which is slightly larger than a kidney) receives, at best, 38 ml of blood per minute. The kidney (approximately 150 g), on the other hand, receives approximately 300 ml/min (eight times more). The liver receives approximately 700 ml/min. To make matters worse, as the tumor size increases, the blood flow per gram of

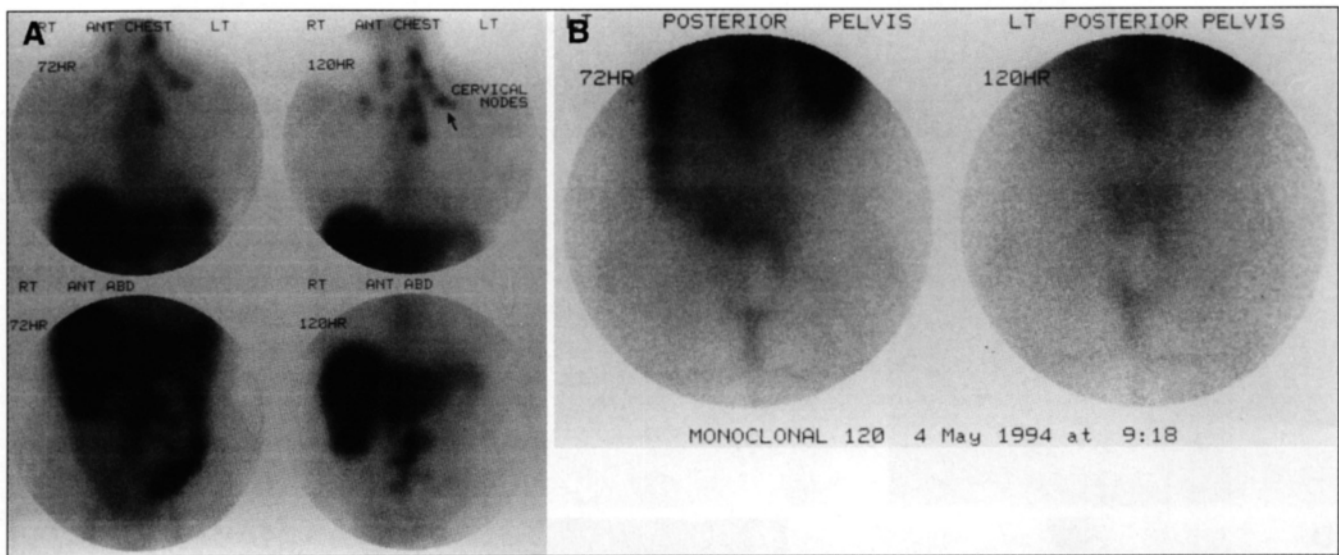


FIGURE 5. (A) Anterior images of the chest and abdomen, obtained 72 and 120 hr after intravenous administration of ^{111}In OncoScint® in a 53-yr-old woman who had abdominoperineal resection 2 yr before for adenocarcinoma of the rectum, demonstrate abnormal increased activity in cervical, supraclavicular, mediastinal and retroperitoneal lymph nodes. Lymph node biopsy was positive for adenocarcinoma. (Note the normal significant clearance of left-sided bowel activity between 72 and 120 hr.) (B) Posterior images of the pelvis obtained 72 and 120 hr after injection demonstrate a rim-like area of increased activity with a central photopenic defect. Computed tomography revealed a cystic region in the pelvis which was biopsied and demonstrated recurrent rectal carcinoma. (Figure 5 images are provided courtesy of Fouada Panah, MD, St. Mary Hospital, Livonia, MI.)

tumor decreases. The distribution of flow within the tumor also changes with increasing tumor size, and much of the flow may not even perfuse the tumor due to arteriovenous shunting (4).

HAMA is a significant concern to clinicians especially since it can alter CEA or CA-125 values (even though there is a way around this as described earlier in this paper). One solution is the use of human Abs. However, human monoclonal IgG Abs tend to be of low affinity and are relatively difficult to produce (4).

Another disadvantage of OncoScint imaging is its low negative predictive value. A low negative predictive value almost can be expected because of the high pretest probability of disease in the highly selected patients who are imaged with OncoScint.

CONCLUSION

OncoScint can detect tumor in the extrahepatic abdomen and pelvis not seen on CT, can usually be repeated and can prevent unnecessary surgery. However, since OncoScint imaging is relatively time consuming and considered expensive by clinicians, and since the relatively high incidence of HAMA formation is looked upon negatively by clinicians, OncoScint is not being used frequently in the U.S. at this time. Nonetheless, there is no question that OncoScint has done a great deal for the field of nuclear oncology, leading the way for other antibody, and antibody fragment, imaging studies.

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