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Detection of Primary Colorectal Cancer With Indium 111 Monoclonal Antibody B72.3

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• B72.3 is a murine monoclonal antibody of the immunoglobulin subclass IgG1 directed against TAG-72, a cell surface antigen present on colorectal carcinoma cells. We investigated the utility of scanning with indium 111–labeled B72.3 in 16 patients with a high clinical suspicion of or biopsy-proven primary colorectal cancer. Each patient received 1 or 2 mg of B72.3 monoclonal antibody labeled with 152 MBq of indium 111. Patients underwent scanning 2 to 3 days and 7 days after infusion by planar and emission computed tomography. Nineteen lesions were confirmed in 12 patients. Three patients with benign polyps had true-negative monoclonal antibody scans. Indium 111–labeled imaging of B72.3 detected nine of 19 lesions. Unsuspected tumor sites were identified by monoclonal antibody scan in three patients. By detection of additional abdominal disease and extra-abdominal spread, indium 111–labeled scanning of B72.3 directly affected treatment in 18% of patients.

(*Arch Surg.* 1990;125:1601-1605)

Primary colorectal carcinoma is usually diagnosed with a combination of physical examination, barium enema, sigmoidoscopy, or colonoscopy with biopsy. Accurately determining the extent of tumor both locoregionally and at distant sites forms the basis for staging and influences the therapeutic approach. Despite new advances in cross-sectional imaging with ultrasound, computed tomographic (CT) scan, and magnetic resonance imaging, staging is incomplete and ordinarily awaits histopathologic examination of the specimen. Recently, the strategy for presurgical detection and staging has been expanded by the use of monoclonal antibodies (MoAbs) labeled with radioisotopes directed against tumor-associated antigens.[1-7] Excellent tumor localization has been achieved with minimal reported toxicity.[8]

Monoclonal antibody B72.3 targets the tumor-associated glycoprotein TAG-72 found on the cell surface of up to 94% of colon adenocarcinomas.[9] In previous studies, B72.3 labeled with iodine 131 demonstrated 75% of tumor lesions with excellent ratios of tumor to normal tissue.[10] A variety of tumor sites including primary, recurrent, and metastatic colorectal lesions have been identified by radioisotope concentration, including occult tumors missed by conventional diagnostic tests.[5]

In this study, we present the effectiveness of indium 111–labeled B72.3 immunoscintigraphy in localizing primary colorectal cancers and the locoregional and distant spread at the time of presentation.

MATERIALS AND METHODS

A total of 16 patients were studied under this prospective, multi-institutional, open-labeled, nonrandomized trial. All patients were men whose ages ranged from 60 to 79 years, with a mean ± SD of 67.9 ± 5.4 years. Thirteen patients were suspected of having primary colorectal cancer. All 13 patients had colonoscopy- or biopsy-proven adenocarcinoma of the colon and/or rectum. Three patients had multiple polyps. The preinfusion workup in all the patients included the following: (1) physical examination, (2) history pertinent to previous MoAb injection and concomitant medications, (3) blood workup including complete blood cell count with differential, platelets, liver functions, kidney functions, and tests. Patients also had serum TAG-72 level evaluations. Prior to the antibody infusions, a baseline serum sample was obtained for the evaluation and the study of the development of human antimouse antibodies. Diagnostic workup included a colonoscopy on all patients, barium enema (double contrast in all patients), CT scan of the abdomen and pelvis, chest roentgenograms, and baseline electrocardiogram.

After giving informed consent according to the local institutional review board requirements, each patient received either 1 or 2 mg of B72.3 labeled with 162.8 to 185 MBq of ^{111}In. The B72.3 ^{111}In labeled by the carbohydrate linker specific technique of glycyl-tyrosyl-diethylenetriaminepentaacetic acid is referred to as CYT-103. Planar and single photon emission CT imaging was performed 3 days and 5 to 7 days following the infusion. All patients went to surgery within 3 to 16 days after the second scanning session. The results of the scans were communicated to the surgeon prior to the scheduled surgery.

Accepted for publication September 30, 1990.

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Read before the 14th Annual Surgical Symposium of the Association of Veterans Affairs Surgeons, Charleston, SC, May 8, 1990.

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Findings in Patients With CYT-103 Immunoscintigraphy*

Patient No./ Age, y	Disease Site at Presentation	Histologic Findings†	Tumor Cells Expressing TAG-72, %	Additional Lesions Found on MoAb
1/68	Sigmoid colon‡	Adenocarcinoma	50	Right iliac bone
	Rectum‡	Adenocarcinoma	50	...
2/60	Ascending colon	MWD adenocarcinoma, metastatic lymph node (2/3)	...	...
3/59	Ascending colon, transverse colon	Polyps: necrosis and marked dysplasia	...	...
4/60	Suspected hepatic flexure	Not done	...	Left 6th rib
	Right lobe of liver	MWD adenocarcinoma	...	7th, 8th thoracic vertebrae, iliac bone bilaterally
5/66	Rectum	WD adenocarcinoma	...	...
6/66	Ascending colon‡	MWD	15	Left supraclavicular lymph node
	Liver	Metastatic adenocarcinoma with necrosis, metastatic lymph node (11/25)	...	...
7/69	Colonic polyps	Multiple polyposis	...	...
8/67	Hepatic flexure‡	MWD	90	...
9/75	Ascending colon polyp	Adenocarcinoma in situ	...	...
10/72	Ascending colon‡	Adenocarcinoma	60	...
11/79	Sigmoid	MWD adenocarcinoma	...	...
12/69	Hepatic flexure‡	MWD adenocarcinoma	60	...
	Liver	Metastatic adenocarcinoma, metastatic lymph node (2/2)	30	...
13/64	Rectum	Focus adenocarcinoma in villous adenocarcinoma	ND	...
14/68	Cecum	WD adenocarcinoma in a villous adenoma	...	...
15/62	Rectum‡	MWD adenocarcinoma arising from villous adenoma	10	...
16/64	Ascending colon	Tubular adenomas (5)	...	...

*MWD indicates moderately well differentiated; WD, well differentiated; TAG-72, a cell surface antigen present on colorectal carcinoma; MoAb, monoclonal antibody; and ND, not done.

†Numbers in parentheses indicate number of lymph nodes.

‡Positive findings on MoAb scan. Patient 4 had a negative cold defect finding on MoAb scan.

RESULTS

Nineteen separate adenocarcinoma lesions were identified in 12 patients (Table) at the following locations: bowel, 12 (five in the rectosigmoid, one in the transverse colon, and six in the cecum and ascending colon); lymph node, four (three in the mesenteric and one in the neck); and liver, three. Three patients with a preoperative diagnosis of polyps were confirmed at surgery to have benign polyps. One patient had complete excision of adenocarcinoma in situ in a rectal villous adenoma. In these four patients, the ^{111}In scans had negative results and were considered to be true negative findings. In the remaining 12 patients, seven had only one lesion, while five had several lesions either in the regional site of the tumor or distant metastases to the liver, lymph nodes, or bone.

Results of CYT-103 imaging were true-positive in seven of 12 bowel lesions and two of four lymph node metastatic lesions. Liver lesions were missed in two patients and appeared as cold defect in a third patient. In three patients, previously unsuspected additional lesions were identified with the MoAb scan and were confirmed. These lesions were in the right iliac bone in one patient (patient 1), consistent with bone metastasis confirmed by a bone scan. In another patient (patient 4), there was a lesion in the left sixth rib and in the seventh and eighth thoracic vertebrae (Figs 1 and 2), as well as the sacroiliac joints, highly suggestive of metastatic disease to the bone. By open biopsy, the left sixth rib lesion was proved to be metastatic adenocarcinoma. In the third patient (patient 6), the antibody scan identified a left supraclavicular lymph node (Fig 3, left) that was resected and confirmed to be a metastatic adenocarcinoma from a bowel primary site (Fig 3, right). Incidentally, this patient also presented with a right colon lesion and was worked up with the possibility of another primary tumor in the head and neck region. The patient was subsequently treated with a radical neck dissection that tested negative for a primary tumor. All lymph nodes were adenocarcinoma, consistent with a finding of primary tumor in the bowel.

The sensitivity of the MoAb scan in this cohort of patients is slightly lower than expected, identifying only nine of 19 lesions. However, one of these lesions was carcinoma in situ and well beyond the resolution of existing gamma camera capabilities. If we exclude this patient, then the MoAb scan successfully identified nine of 18 lesions. Seven of 11 bowel primary sites were imaged and confirmed, for a sensitivity of 63%. In the remaining bowel lesions that tested negative for tumor, there was no expression of the antigen TAG-72. Thus, from an immunoaffinity point of view, ^{111}In-labeled CYT-103 identified all primary lesions that expressed TAG-72, for a sensitivity of 100%. The expression of TAG-72 in the lesions varied

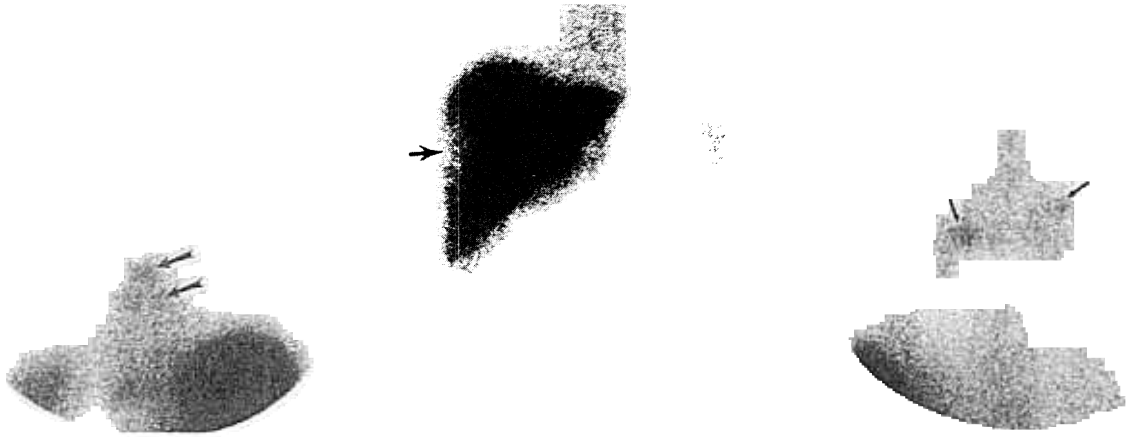

Fig 1.—Left, Patient 6. Posterior view of the chest following CYT-103 administration, showing two previously unsuspected lesions at the level of the seventh and eighth thoracic vertebrae (arrows). Center, Same patient with a large liver mass (arrows). Right, Bony metastases were also demonstrated (arrows) in the pelvis posteriorly.

from 15% to 90%. Those lesions that were TAG-negative or had TAG in less than 5% of the cancer cells were not imaged with the CYT-103, thus confirming our previous observation.[11] Serum TAG-72 levels, elevated in only four patients, had no influence on immunoscintigraphy.

Human antimouse antibody formation was identified in three patients (18%). No adverse reactions or clinically significant changes in bone marrow, liver, or kidney functions were detected in patients receiving ^{111}In B72.3.

COMMENT

Colorectal cancer remains the most common visceral malignancy in the United States.[12] Despite newer diagnostic adjuncts, 50% of patients harbor undetected micrometastases at the time of their presentation and will die of their disease.[13] More accurate staging at presentation would permit tailoring of adjunctive therapy to individual patients. This would require detection of tumor deposits in lymph nodes and other soft tissues in the abdomen and retroperitoneal area and distant sites commonly missed by other diagnostic modalities. The identification of occult disease could help define the surgical procedure to be undertaken or dictate further directed diagnostic workup.

Locoregional recurrence of colorectal carcinoma is related to the depth of the tumor bowel wall penetration (Dukes' B), presence of lymph node metastases (Dukes' C), and invasion of adjacent organs (Dukes' B_3-C_3).[14] Advancing Dukes' classification predicts local recurrence as well as declining 5-year survival.[15] Involvement of regional lymph nodes, while the most common form of colorectal cancer spread, remains difficult to detect preoperatively. Ultrasound study and CT scan are of limited value in detecting pathologic lymph nodes. If 1.5 cm represents the upper limit of normal lymph node size, CT scan reliably identifies lymph node metastases in only one third of the cases. The preponderance of nodal metastases are found in normal-sized lymph nodes.[16] Recent reports of improved 5-year survival with wider, more extensive lymphadectomy at the time of resection of a primary colorectal cancer makes the question of detecting lymph node metastases preoperatively more important.[17]

Recent observations of survival benefit accruing from en bloc resection of adherent or tumor-infiltrated adjacent viscera or abdominal wall at the time of the primary colorectal resection direct attention to a more accurate preoperative staging of local tumor extent.[18]

Metastatic spread to the liver will be found in approximately 20% of patients at the time of diagnosis of primary colorectal carcinoma.[19] Among the available cross-sectional imaging agents, CT scan remains superior, with a sensitivity of 73% and specificity of 99%.[20] Magnetic resonance imaging has been useful in evaluating anatomic disposition of metastases relative to hilar vessels and hepatic veins, crucial to planning operative removal. Again, smaller liver metastases are missed with CT scan, even with contrast-enhanced hepatic artery injection.

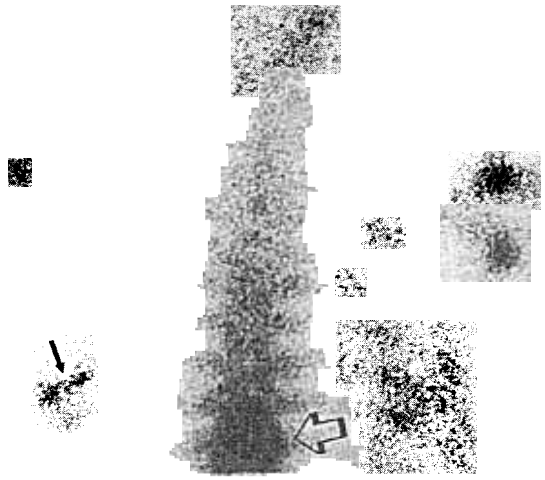

Fig 2.—Patient 6. Scan showing posterior projection. In addition to the thoracic spine lesions (open arrow), involvement of the left sixth rib is also demonstrated (closed arrow).

The discovery of carcinoembryonic antigen led to a new concept in immunodiagnosis.[21] Several radiolabeled polyclonal antibodies, and, more recently, MoAbs, were raised to these tumor-associated antigens. Subsequent work demonstrated that radiolabeled MoAbs could be safely injected and could detect tumors with a reasonable sensitivity and specificity.[1-7,22]

In this study, we successfully detected 63% of primary colorectal carcinomas. As we have noted before, there is a

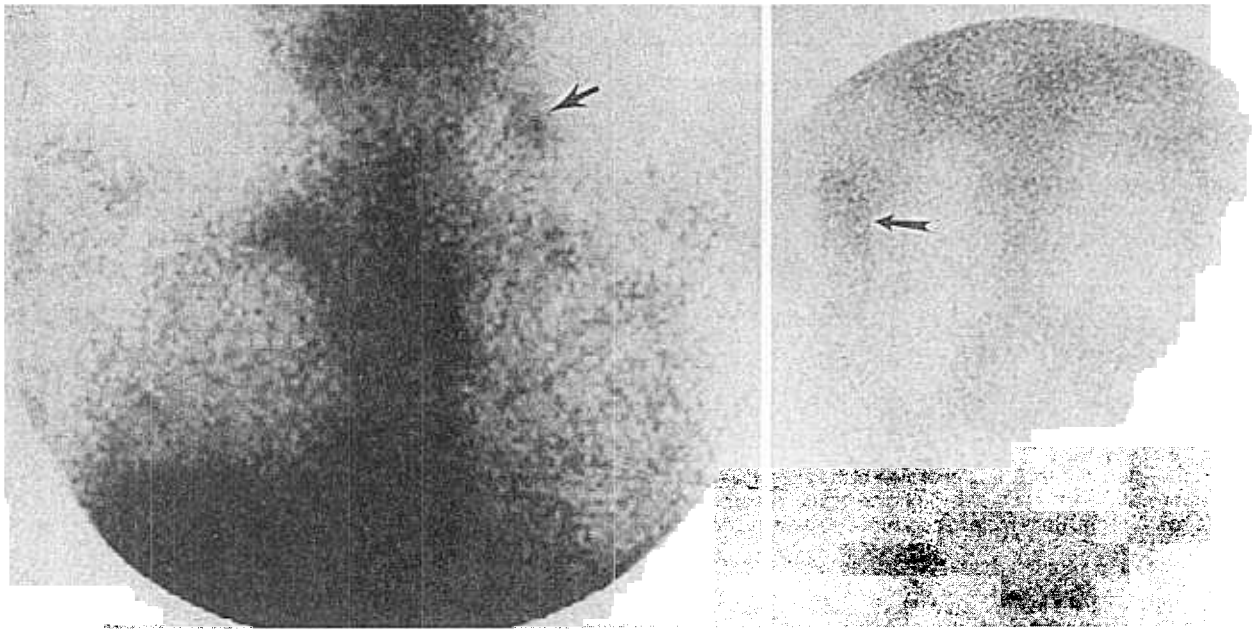

Fig 3.—Left, Abnormal CYT-103 accumulation identified in the left supraclavicular region (arrow). Right, Primary adenocarcinoma of the ascending colon (arrow) in the same patient.

correlation between the presence of TAG-72 in resected specimens and ^{111}In-labeled B72.3 detectability of these lesions.[11] In contrast, there is no correlation between serum TAG-72 levels and successive tumor imaging with CYT-103. Difficulty in interpretation arises because of nonspecific radioaccumulation in the bowel. If the two cases with predominant bowel activity are excluded, the sensitivity of CYT-103 for primary colon lesion is 100%. The high specificity of CYT-103 is demonstrated in the three patients who presented with equivocal biopsies of polypoid colonic lesions. While suspicious for adenocarcinoma preoperatively, the MoAb scans showing negative results were confirmed by the finding of benign polyps on resected specimens. The addition of single photon emission CT imaging provided better anatomic definition of the primary tumors and resulted in improvement in tumor detection in four patients.

The low rate of human antimouse antibody formation and absence of adverse reactions observed in this study are in accordance with results of recent studies with this MoAb.[22] In the four patients with mesenteric lymph node involvement, ^{111}In-labeled MoAb imaging failed to detect these lesions. Positive lymph nodes less than 1 cm in diameter in the mesentery or retroperitoneum are below the detection capability of the gamma camera, even with the use of single photon emission CT. If the lymph nodes are close to a primary tumor with a high uptake of radiolabeled antibodies, they are not distinguishable from the primary lesion.[23]

As has been previously observed, hepatic metastases can appear on MoAb scan as filling defects, positive accumulations, or both.[24] The degree of differentiation of these synchronous liver lesions, irrespective of mucin production or the presence of necrosis, also affects imaging accuracy.[22]

The most important aspect of immunoscintigraphy is the ultimate impact on treatment of patients. Beatty et al[25] reported that the major advantage of MoAb scanning is in the detection of extra-abdominal metastases. In reviewing a large European patient experience, Baum et al[26] found immunoscintigraphy to be helpful, primarily complementing other diagnostic methods, in 46% of patients. In 20% of their cases, the MoAb scan contributed unique formation, eg, identifying abdominal or lymph node metastases and pelvic recurrences missed by conventional workup. Finally, immunoscintigraphy was felt to be decisive for a change in treatment strategy, eg, institution of radiotherapy or second laparotomy in 13%.

In a large multicentered trial, CYT-103 radiolabeled with ^{111}In correctly identified colorectal adenocarcinoma lesions at a 70% sensitivity and a 90% specificity. The investigators considered immunoscintigraphy to be beneficial or very beneficial in 26% of patients. The benefit accrued from detecting previously occult synchronous lesions, identifying localized disease without regional or metastatic spread, and confirming adenocarcinoma when other diagnostic test results were equivocal.[27]

In this study, the sensitivity of the MoAb scan is slightly lower than expected, identifying only nine of the 19 confirmed lesions. If the in situ carcinoma is excluded, and one only looks at lesions that express TAG-72 in the resected specimen, then CYT-103 identified all primary tumors. The variability of TAG-72 expression in the tumor dictates the success of immunoscintigraphy with CYT-103.

We found MoAb scan results to directly affect the diagnostic and treatment strategy in 18% of our patients. In keeping with the observations of Beatty et al[25] in these patients with primary colorectal cancer, the MoAb scan was seen to affect their treatment with the detection of additional abdominal disease (hepatic metastasis) and extra-abdominal spread (bone and distant lymph node metastases). The addition of targeted cross-sectional imaging and needle biopsies of MoAb-detected lesions followed by the institution of systemic therapy and radiotherapy defines the advantage of immunoscintigraphy in this study.

The high specificity and documented safety combine to make ^{111}In-labeled B72.3 a promising clinical tool in the evaluation and staging of primary colorectal cancer.

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ARCHIVES OF DERMATOLOGY

Neurologic Disease in Human Immunodeficiency Virus–Infected Drug Abusers

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Previous studies of human immunodeficiency virus–related neurologic disease have been either retrospective or have included mostly homosexual patients. We sought to determine (1) the true prevalence of neurologic abnormalities in patients with acquired immunodeficiency syndrome or lymphadenopathy acquired immunodeficiency–related complex, and (2) whether differences in prevalence or type of neurological abnormality exist between parenteral drug abusers and non–parenteral drug abusers. We prospectively evaluated 190 adult inpatients with either acquired immunodeficiency syndrome (129) or lymphadenopathy acquired immunodeficiency–related complex (61); 151 (80%) were parenteral drug abusers, and 172 patients (91%) had neurologic symptoms or signs. There was no significant difference in prevalence of neurologic disease between parenteral drug abusers and non–parenteral drug abusers, or between patients with acquired immunodeficiency syndrome and those with lymphadenopathy acquired immunodeficiency–related complex. The prevalence of neurologic symptoms in these patients with lymphadenopathy acquired immunodeficiency–related complex and acquired immunodeficiency syndrome is the highest reported to date and appears to reflect the prospective nature of the study (*Arch Neurol.* 1990;47:1002-1007).

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