

Radio-immunodetection of Colorectal Cancer using Tc-99m labeled Monoclonal Antibody ior-CEA1: Results of a Phase III Clinical Trial

Oliva JP¹, Pimentel G¹, Velasco M¹, Martinez A¹, Ortiz R², Abreu M¹, Diaz N¹, Oliver B¹, Sanchez I¹, Valladares T¹, Baum RP³

¹Department of Nuclear Medicine, National Institute of Oncology and Radiobiology (INOR), Habana, Cuba

²Clinical Trial Section, INOR, Habana, Cuba

³Department of Nuclear Medicine/Center for P.E.T., Zentralklinik Bad Berka, Germany

Abstract

The murine monoclonal IgG1 anti-CEA antibody (MAB) ior-CEA1 was developed in 1989 at the National Institute of Oncology and Radiobiology (INOR), characterized in collaboration with the Center for Genetic Engineering and Biotechnology and is produced at the Center of Molecular Immunology in Havana, Cuba. Phase I and phase II clinical trials had been performed to evaluate the safety, in vivo properties and diagnostic performance of the radiolabelled ior-CEA1 antibody for the detection of primary adenocarcinomas of the colon, colorectal cancer recurrences and metastases. This paper reports the results (obtained at the Nuclear Medicine Department of INOR) of a Phase III clinical trial in 61 patients using the intact Tc-99m labeled ior-CEA1 antibody for radioimmunodetection (RID) of colorectal malignancies. Three patients had a primary tumour; the remaining patients were evaluated for recurrences or metastases after resection of a colorectal cancer. Each patient received 1 mg of the MAB intravenously after labeling with 1.48 to 2.22 GBq (40-60 mCi) Tc-99m. Anterior and posterior images of the abdomen and pelvis as well as SPECT studies were obtained 18-24 hours after the antibody injection. All primary tumours and 18 of the 20 suspected recurrences were detected by RID, resulting in a sensitivity of 91% for the detection of recurrent disease.

Serum CEA and CA 19-9 levels and RID results did not correlate with the results of RID in all patients. Human anti-mouse antibodies (HAMA) developed in 17 patients, starting at day 15 after Mab injection and declining after 6 to 9 months. No toxicity was observed in any of the patients.

Key words: Monoclonal antibody, Colorectal Cancer, Radioimmunodetection

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Introduction

Colorectal cancer is one of the five most frequent malignant tumours in Cuba and worldwide (1). After initial surgery, and in more advanced cases adjuvant chemotherapy, the prognosis depends on the early diagnosis of intra or extra-abdominal recurrent disease (2,3). The colonic embryonic antigen (CEA), first reported by Gold and Freedman (4) as a marker of gastrointestinal cancer has been established as a tumour-associated antigen for monitoring of patients after resection of colorectal cancers (5,6). The rise of serum CEA in the follow-up after primary tumour treatment is indicative of tumour recurrence (7,8) and serial CEA-determination have been shown to be of clinical value for early detection of relapse (9,10).

The discovery of the hybridoma technology by Köhler and Milstein in 1975 (11) enabled the production of monoclonal antibodies (MAbs) and opened a new era in biomedicine. Radiolabelled MAbs against CEA allow the pre- and post-surgical evaluation of CEA-expressing tumours (12-20). MAbs are now extensively used in vitro as well as for in vivo diagnosis and therapy (21-27) and have shown a definite impact in the development of new diagnostic and therapeutic procedures (28-33).

MAB ior-CEA1 was developed in 1989 at the National Institute of Oncology and Radiobiology (INOR) and further characterized in collaboration with the Center for Genetic Engineering and Biotechnology. Already in 1993, therapeutic MAB preparations were routinely produced at the Center of Molecular Immunology in Havana, Cuba (34). After radiolabeling and preclinical testing of the ior-CEA1, phase I-II clinical trials were carried out to evaluate the diagnostic performance of the antibody in patients (35-37).

This paper reports the results of a Phase III clinical trial (performed at the Nuclear Medicine Department of the

Correspondence:

Prof. Dr. med. Juan P. Oliva Gonzalez
Departamento Medicina Nuclear
Instituto Nacional de Oncología y Radiobiología
Calle 29 y E. Vedado.
10400 C. Habana. Cuba
jpoliva@infomed.sld.cu

INOR) using the Tc-99m labeled ior-CEA1 MAb in order to evaluate the diagnostic efficacy of the antibody in a larger series of colorectal cancer patients.

Material and Methods

Patients

A total of 61 patients, 20 males and 41 females, were subjected to monoclonal antibody imaging (MAb imaging) between the January 2001 and June 2002. Three patients had primary adeno-carcinomas of the colon and 58 patients were suspected to have recurrent colorectal carcinoma following surgery due to rising serum CEA levels or clinical symptoms. None of the patients had any other treatment at the time of MAb imaging.

Measurement of tumour markers

Serum CEA levels were determined with an "in house" RIA kit or using a commercial IRMA (CIS-Bio-International). The cut-off values of the "in house" and commercial kits were 2.1 ng/ml and 7 ng/ml respectively. Serum CA 19-9 levels were determined using a commercial IRMA (CIS-Bio-International) with a cut-off value of 37 U/ml.

Human anti-mouse antibodies (HAMA) were measured by an ELISA developed at the Center of Molecular Immunology, Havana, Cuba.

ior-CEA1 Mab

The IgG1 murine ior-CEA1 MAb was produced by the hybridoma clone K3/5 derived from the fusion between P3/x63.Ag8.653 myeloma cells and spleen cells derived from Balb/C mice, immunized with purified CEA from a liver metastasis of a colonic adenocarcinoma patient. The MAb is directed against a specific carbohydrate epitope on cell-bound and free CEA and belongs to the GOLD I group, according to Hedin's classification (34).

Tc-99m labeling

Labeling of ior-CEA1 with Tc-99m was carried out applying the technique first reported by Schwarz and Steinstraesser (38). Briefly, the antibody was reduced with a molar ratio of 2000:1 of 2-mercaptoethanol and allowed to incubate at room temperature for 30 min. At the end of the incubation, the reduced IgG was purified by gel filtration on Sephadex G-50 (Pharmacia) using PBS solution as mobile phase. Aliquots of 1 mg of the reduced antibody were used for labeling. After reconstitution of a MDP kit (Amersham) with 5 ml of saline, 50 µl of this solution was added to the reduced monoclonal antibody. The antibody was then labeled with 1.5 to 3 GBq Tc-99m petchnetate and allowed to react for 15 min.

Imaging technique

Each patient received 1 mg of the MAb labeled with 1.48-2.20 Gbq Tc-99m. The labelled antibody was given as a slow intravenous injection (two minutes injection time) in

an antecubital vein. Patients were asked to empty the urinary bladder before imaging. Anterior and posterior planar images of the pelvis and abdomen were obtained 18 to 24 hours after the injection of the MAb. One million counts were acquired for each planar image (128 x 128 matrix) using a SOPHY DS7 gamma camera equipped with a HRLE parallel hole collimator.

SPECT studies (64 x 64 matrixes) of the abdomen and pelvis were recorded 18 to 24 hours after injection (30 seconds acquisition time per view, 360 degree circular orbit). Reconstruction of slices from raw data was performed using the Butterworth or Wiener filter and a conventional back-projection algorithm.

Interpretation of results

The images were interpreted independently by two experienced nuclear medicine specialists according to the following criteria: In the planar images, "hot" or "cold" spots in the liver were judged as metastases. "Hot" spots in the abdomen or pelvis were interpreted as lymph node metastases or local recurrences respectively.

The SPECT study was considered to be positive, if the suspicious lesion was clearly detected in two different contiguous slices and in two different tomographic views.

Efficacy Evaluation

Sensitivity, specificity and positive and negative predictive values of RID were determined for the detection of primary tumours and the diagnosis of recurrences.

Results

Radiochemical purity of the labelled MAb ranged from 96 to 99.4% as assessed by ITLC and FPLC. The Tc-99m labelled MAb had the same immunoreactivity as the "cold" MAb as determined by immunohistochemistry.

Table 1 shows the serum CEA and serum CA 19-9 levels of the patients which were determined immediately before MAb imaging.

Patients Nos.1, 52, and 59 had primary tumours (one well differentiated adenocarcinoma, one moderately differentiated adenocarcinoma, and one adenocarcinoma of the rectum) which were previously diagnosed by endoscopy and biopsy (Table 1). MAb scans were truly positive in all 3 patients as later verified by surgery. Figure 1 shows the scan of patient No. 1. The tumour could not be resected completely (infiltration of the sacrum). Six months later, a new surgical procedure was necessary because of persistent tumour. The patient is still alive.

Fifty-eight patients were examined for local recurrences and/or metastases (Table 2). In 28 patients, MAb scans showed uptake of the labelled antibody in the pelvic area. Figures 2 demonstrates pelvic recurrences as detected by the antibody scan in the patient #18, who was studied for suspicion of recurrence due to rising CEA serum levels, whereas conventional imaging, including CT scan, was

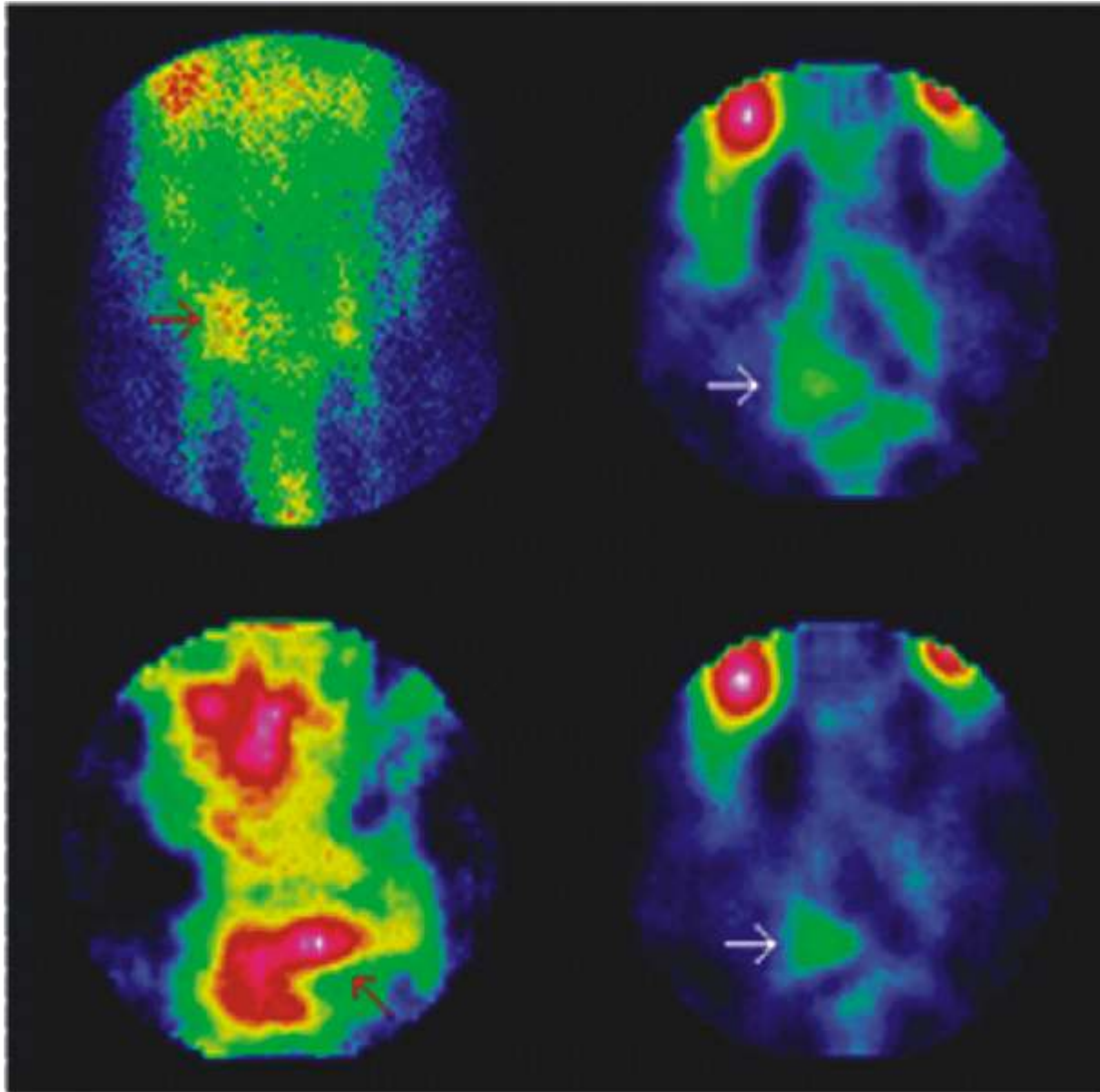


Figure 1 Tc-99m labeled anti-CEA antibody imaging in a patient with Primary Colorectal Cancer (Patient #1). Planar scan (upper left) and SPECT [sagittal (upper right) and coronal (Lower left and right)] images showing abnormal focal uptake of the radiotracer in the primary tumour.

negative.

In 10 of the 28 studies (patients #2, 3, 5, 18, 19, 24, 35, 42, 48 and 60), MAb scans revealed hepatic metastases. Liver metastases were known before the antibody scans only in patients #5 and #48, whereas in the other eight patients liver metastases were detected for the first time after antibody scans. In general, liver metastases were detectable by planar imaging; however, SPECT improved the diagnostic certainty. Pelvic recurrences and liver metastases were confirmed by ultrasound, histology and the clinical course of disease. The detection of multiple liver metastases in many of these patients avoided unnecessary surgery.

Hepatic abnormality in patient #42 was considered falsely positive at final diagnosis. This patient had received radiotherapy before surgery for a moderately differentiated

adenocarcinoma of the rectum. One year later, the patient presented with an elevated serum CA 19-9 and enterocolitis, whereas CEA was normal. The referring physician suspected a recurrence and ordered an immunoscintigraphy. MAb scans showed no signs of local recurrence, but focal abnormality was detected. On final diagnosis this was considered as false positive, because hepatic ultrasound was negative and the patient continued to live free of symptoms for more than five months after the antibody scan.

In the other 18 patients (patients # 4, 6, 7, 9, 20, 23, 34, 38, 41, 45, 46, 47, 49, 51, 53, 56, 57 and 61), MAb scans were positive for recurrence. Recurrent disease (True positive) was confirmed by ultrasound, endoscopy, histology and clinical course in 11 out of 18 patients. One patient (# 23),

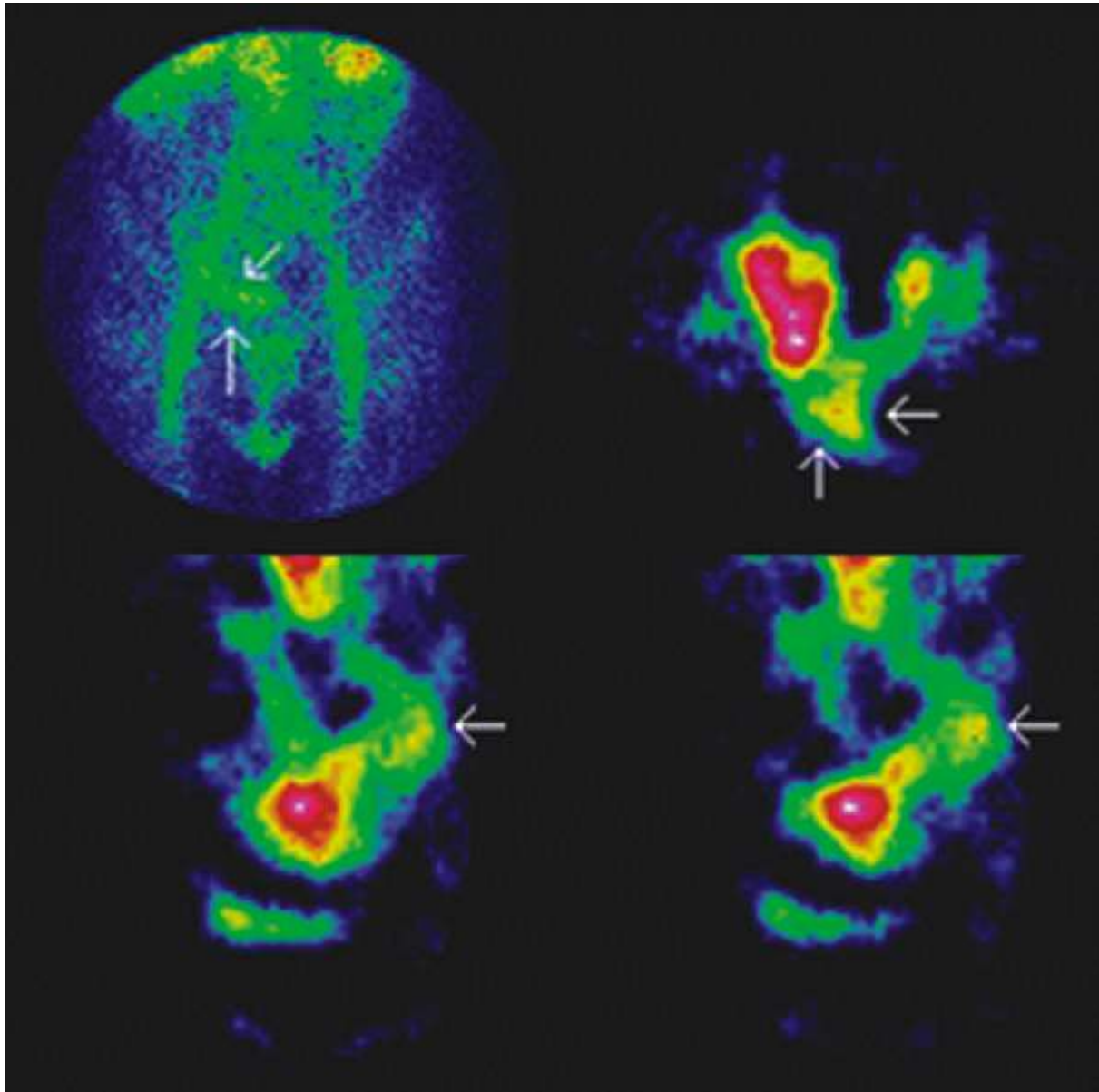


Figure 2 Tc-99m labeled anti-CEA antibody imaging in a patient with recurrent colorectal cancer (Patient # 18). Planar scan (upper left) and SPECT (upper right and lower row) images showing abnormal uptake of the radiotracer in the recurrent tumour.

with a positive MAb scan, had only elevated serum CEA, but no other evidence of disease during a follow-up period of more than 18 months following surgery. In the rest of the 6 patients (cases # 6, 42, 45, 46, 49 and 57) MAb scans were falsely positive. All these patients had normal serum CEA and CA 19-9 levels. These patients were referred for RID due to clinical symptoms indicating a probable recurrence 18-24 months post-surgery. The follow-up of these patients did not show any sign of local recurrence or liver metastases.

In the remaining 30 patients (# 8, 10, 11, 12, 13, 14, 15, 16, 17, 21, 22, 25, 26, 27, 28, 29, 30, 31, 32, 33, 36, 37, 39, 40, 43, 44, 50, 54, 55 and 58), MAb scans did not show any abnormal uptake in the pelvic region. In only two of these cases (patients 37 and 43), the results of the RID were incorrect. Pelvic recurrences were revealed by autopsy in

one patient (#37) and in another patient (#43) by colonoscopy and biopsy.

Sensitivity and specificity of RID for the detection of recurrence were 92.3% and 80%, respectively, with a positive predictive value of 77% and a negative predictive value of 93%, respectively.

Discussion

An ideal diagnostic approach for colorectal cancer detection would combine high sensitivity and specificity for the primary tumour or local recurrence with the ability to detect accurately regional and distant metastases. This would include the detection of tumour deposits in lymph nodes and other soft tissues in the abdomen and the retroperitoneal area that are commonly missed by current

Pat. N°	Histology	Duke Stage	Stage	CEA	CA 19-9	MAB Scan
1.	ADC Well Dif	B	II	N	N	+
2.	ADC	B	II	P	N	+
3.	ADC Well Dif	C	III	P	P	+
4.	ADC Well Dif	B	II	N	P	+
5.	ADC Well Dif	B	I	N	N	+
6.	ADC Well Dif	B	II	N	N	+
7.	ADC Well Dif	C	III	P	P	+
8.	ADC Well Dif	NA	NA	N	N	-
9.	ADC Well Dif	B	II	N	N	+
10.	ADC Well Dif	C	III	N	N	+
11.	ADC Well Dif	B	II	N	N	-
12.	ADC Well Dif	C	III	P	N	-
13.	ADC Well Dif	C	III	NA	NA	-
14.	ADC Mod Dif	B	II	NA	NA	-
15.	ADC Well Dif	C	III	P	N	-
46.	ADC	D	IV	P	N	-
17.	ADC Well Dif	B	II	N	NA	-
18.	ADC	D	IV	P	P	+
19.	ADC	C	III	P	P	+
20.	Ca Bas Ind	NA	NA	N	N	+
21.	ADC	C	III	P	N	-
23.	ADC Well Dif	C	III	N	N	-
24.	ADC	C	III	P	N	+
25.	ADC	NA	NA	P	NA	+
26.	ADC	C	III	N	N	-
27.	ADC Well Dif	B	II	N	N	-
28.	ADC Well Dif	B	II	N	N	-
29.	ADC	NA	NA	N	N	-
30.	ADC Mod Dif	B	II	N	NA	-
31.	ADC Well Dif	B	II	N	NA	-
32.	ADC Well Dif	C	III	NA	NA	-
33.	ADC	B	II	NA	NA	-
34.	ADC Well Dif	B	II	N	N	-
35.	ADC Well Dif	A	I	N	NA	+
36.	ADC	B	II	P	NA	+
37.	ADC Mucoprod	B	III	P	NA	-
38.	ADC Well Dif	C	III	P	N	-
39.	ADC	D	IV	P	N	+
40.	ADC	C	III	N	NA	-
41.	ADC Mod Dif	B	II	N	NA	-
42.	ADC Mod Dif	B	II	N	NA	+
43.	ADC Mod Dif	NA	NA	N	P	+
44.	ADC Well Dif	B	II	N	N	+
45.	ADC Well Dif	B	II	N	N	-
46.	ADC Mucoprod	NA	NA	N	N	+
47.	ADC Well Dif	B	II	N	NA	+
48.	ADC Mod Dif	C	III	P	P	+
49.	ADC	D	IV	NA	NA	+
50.	ADC Well Dif	B	II	N	N	+
51.	ADC	C	III	NA	NA	-
52.	ADC Well Dif	A	I	NA	NA	+
53.	ADC Mod Dif	C	III	NA	N	+
54.	ADC Well Dif	C	III	NA	NA	+
55.	ADC	B	II	N	N	-
56.	ADC Well Dif	C	III	N	N	-
57.	ADC Mod Dif	A	I	N	N	+
58.	NA	B	II	NA	NA	+
59.	ADC	A	I	NA	NA	-
60.	ADC	C	III	P	NA	+
61.	ADC Well Dif	D	IV	NA	NA	+
62.	ADC Well Dif	B	II	P	P	+

NA = Not Available P = Positive N = Negative ADC = Adenocarcinoma

Table 1 Results of MAb scan compared to Duke's Classification, clinical stage and serum CEA and CA19-9 levels

Pat. N°.	Localization	Histology	RID	TP	TN	FP	FN
2	Rectal	ADC	+	X			
3	Trans.Colon	ADC Well Dif	+	X			
4	Sigmoid	ADC Well Dif	+	X			
5	Sigmoid	ADC Mod Dif	+	X			
6	Sigmoid	ADC Well Dif	+			X	
7	Sigmoid	ADC Well Dif	+	X			
8	Rectal	ADC Well Dif	-		X		
9	Descend. Colon	ADC Well Dif	+	X			
10	Descend. Colon	ADC Well Dif	+		X		
11	Sigmoid	ADC Well Dif	-		X		
12	Rectal	ADC Well Dif	-		X		
13	Sigmoid	ADC Well Dif	-		X		
14	Sigmoid	ADC Mod Dif	-		X		
15	Descend Colon	ADC Well Dif	-		X		
16	Rectal	ADC	-		X		
17	Sigmoid	ADC Well Dif	-		X		
18	Rectal	ADC	+	X			
19	Descend Colon	ADC	+	X			
20	Anal Region	CA Basind	+	X			
21	Colon	ADC	-		X		
22	Sigmoid	ADC Well Dif	-		X		
23	Ascend Colon	ADC	+			X	
24	Descend Colon	ADC	+	X			
25	Ascend Colon	ADC	-		X		
26	Ascend Colon	ADC Well Dif	-		X		
27	Transv.Colon	ADC Well Dif	-		X		
28	Ascend Colon	ADC	-		X		
29	Rectal	ADC Mod DIF	-		X		
30	Colon	ADC Well Dif	-		X		
31	Sigmoid	ADC Well Dif	-		X		
32	Rectal	ADC	-		X		
33	Sigmoid	ADC Well Dif	-		X		
34	Rectal	ADC Well Dif	+	X			
35	Rectal	ADC	+	X			
36	Ascend Colon	ADC Mucoproductor	-		X		
37	Sigmoid	ADC Well Dif	-				X
38	Rectal	ADC	+	X			
39	Rectal	ADC	-		X		
40	Sigmoid	ADC MOD Dif	-		X		
41	Descend Colon	ADC Mod Dif	+	X			
42	Rectal	ADC Mod Dif	+			X	
43	Ascend Colon	ADC Well Dif	-				X
44	Sigmoid	ADC Well Dif	-		X		
45	Rectal	ADC Mucoproductor	+			X	
46	Ascend Colon	ADC Well Dif	+			X	
47	Esplenic Angulo	ADC Mod Dif	+	X			
48	Colon	ADC	+	X			
49	Rectal	ADC Well Dif	+			X	
50	Rectal	-			X		
51	Descend Colon	ADC Well Dif	+	X			
53	Ascend Colon	ADC Mod Dif	+	X			
54	Sigmoid	ADC	-		X		
55	Sigmoid	ADC Well Dif	-		X		
56	Rectal	ADC Mod Dif	+	X			
57	Descend Colon	NA	+			X	
58	Sigmoid	ADC	-		X		
60	Sigmoid	ADC Well Dif	+	X			
61	Sigmoid	ADC Mod Dif	+	X			

NA=Not Available, Y = Yes, TP=True +ve, TN = True -ve, FP=False +ve, FN=False -ve

Table 2 Patients suspected to have recurrence or metastases

available diagnostic tests (39,40). Any new diagnostic modality should have influence on the management of patients with colorectal cancer and should be able to compete with other diagnostic approaches in terms of relative costs, as well as of sensitivity and specificity (41). Based on our first encouraging clinical results (36,37), we carried out this clinical trial in order to establish country-wide routine clinical application of RID using the ior-CEA1 MAb for the detection of primary colorectal carcinomas, their recurrences and metastases. One important feature of this MAb is that high CEA serum levels have no or only a small influence on the immunoscintigraphic detection of CEA expressing tumours (36).

The detection of a pelvic recurrence of colorectal cancer is often a diagnostic dilemma due to the difficulty of distinguishing between scar tissue and tumour recurrence during the follow-up of asymptomatic patients. CT and ultrasound frequently lack sufficient specificity and sensitivity for this purpose (42, 43).

Imaging with ior-CEA1 MAb detected all primary tumours which confirms a high in vivo sensitivity for colorectal cancer detection. However, endoscopy with biopsy will remain the routine procedure for the diagnosis of primary tumours.

In 58 patients with suspicion of recurrence or metastases MAb scanning revealed abnormalities in 28 cases, out of which 21 turned out to be true positive for recurrence. MAb scanning also detected additional metastatic deposits in many of these patients which were not known before.

Another 28 studies were classified as being true negative. All of these patients live today free of any symptoms. SPECT was particularly valuable in those patients with occult metastases or suspected pelvic recurrences where it improved the diagnosis in equivocal findings on planar images (Figures 3 and 4).

In patients #37 and #43, MAb scans were falsely negative (Table 1 and 2), probably due to factors inhibiting the localization of the MAb in the tumour, e.g., tumour necrosis, reduced antigen expression, poor tumour blood flow or reduced vascular permeability, or increased interstitial pressure, as has been reported before (42, 44, 45).

False positive results of the MAb scanning were obtained in 7 patients for recurrence (Table 1 and 2), probably due to altered anatomy of the operated area.

SPECT images were clearly important for the evaluation of liver metastases. We were able to detect liver metastases missed by ultrasound in 7 patients, as has been described also by others authors (2, 14, 32, 46, 47). These findings can significantly change the therapeutic management and are especially helpful for the surgeons. The detection of occult tumour lesions or metastases allows also the selection of more appropriate non surgical treatments such as radiation therapy or chemotherapy. Hot liver lesions are highly predictive for metastases whereas cold lesions have a lower probability and can be caused also by benign lesions (e.g.,

cysts, hemangiomas or adenomas).

The CEA and CA 19-9 serum levels did not always correlate with positive RID findings. High CEA levels were associated frequently with a positive RID result, but normal CEA levels did not exclude a positive antibody scan (e.g., patients with a CEA positive tumour and no shedding of the antigen into the serum).

A positive HAMA response was seen in 17 cases, beginning with the 15th day after MAb application and declining after 6 to 9 months. No toxicity was observed in any of these patients.

Conclusions

Immunoscintigraphy using the ior-CEA1 MAb labeled with Tc-99m was able to detect primary colorectal malignant tumours, their recurrences and metastases with high sensitivity. No toxicity was observed which might enable repetitive use after HAMA measurement. SPECT improved the diagnosis in patients with occult liver metastases or suspected pelvic recurrences. These RID findings can help the clinicians to modify the treatment plan and select the optimal therapy (surgery, chemotherapy, radiotherapy).

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