

Monoclonal immunoscintigraphy for detection of metastasis and recurrence of colorectal cancer

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cinoma suspected of local recurrence and metastatic disease. The results were compared with conventional diagnostics.

RESULTS: Immunoscintigraphic investigation was done in 53 patients. Tumor recurrence occurred in 38 patients, and was confirmed by other diagnostic modalities in 35. In 15 patients, immunoscintigraphic findings were negative, and confirmed in 14 with other diagnostic methods. Comparative analysis confirmed good correlation of immunoscintigraphic findings and the results of conventional diagnostics and the level of tumor marker carcinoembryonic antigen. Statistical analysis of parameters of radiopharmaceutical groups imacis, indimacis and oncoscint presented homogenous characteristics all of three radiopharmaceuticals. The analysis of immunoscintigraphic target focus was clearly improved using tomography.

CONCLUSION: Immunoscintigraphy is highly specific and has a good predictive value in local recurrence of colorectal cancer.

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Key words: Immunoscintigraphy; Monoclonal antibodies; Colorectal carcinoma; Tumor metastasis; Tumor recurrence

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Abstract

AIM: To assess the clinical role of monoclonal immunoscintigraphy for the detection of metastasis and recurrence of colorectal cancer.

METHODS: Monoclonal immunoscintigraphy was performed in patients operated on for colorectal adenocar-

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INTRODUCTION

Radiolabeled monoclonal antibodies (mAbs) against tumor-associated antigens enable imaging of primary tumors of the gastrointestinal system, and their metastases and/or recurrence, with high sensitivity and specificity. Whole body immunoscintigraphy and/or single photon emission computed tomography (SPECT) are accessible imaging methods focusing on specific type of tumors. Nuclear medicine imaging enables determination of the pathophysiological and biochemical parameters of the viable tumor tissue, including metabolic changes as well as the presence of specific proteins/receptors on the surface of the tumor cells. Positron emission tomography (PET) is the best method for imaging metabolic changes based on increased rate of tumor glycolysis and/or protein metabolism. Dual modality hybrid imaging techniques PET/CT enable precise morphological and anatomical localization.

Radio-immunoguided surgery has been introduced as a method of more accurate detection of tumor extension and enables radical resection. Radioimmunotherapy with mAbs as postoperative adjuvant treatment is currently been investigated^[1].

The aim of the present study was to evaluate the clinical reliability of immunoscintigraphy for detection of metastasis and recurrence of colorectal carcinoma, using three different radiopharmaceuticals.

MATERIALS AND METHODS

Methodology

Imacis 1 contains a cocktail of (111 MBq ¹³¹I) mAb 19-F (ab)² and mAb anti CEA F (ab)². It is labeled with ¹³¹I. Its half-life of 8 d and β -minus emission leads to significant radiation exposure of the patient. In addition, its high energy (364 KeV) makes it less than optimal for imaging, necessitating special collimation for contemporary gamma cameras. The two other radiopharmaceuticals used in this study were labeled with ¹¹¹In. Indimacis 19-9 contains 19-9 F(ab)²/DTPA fragments of mAbs. It is a pure γ emitting isotope with a physical half life of 67 h, an abundance of photon emissions at 173 and 247 keV, while Oncoscint CR 103 is an immunoconjugate produced by site-specific modification of the mAb B72.3, which is a murine immunoglobulin that is able to recognize high molecular weight glycoprotein (TAG-72) expressed by a majority of adenocarcinomas^[2-6].

Imacis 1 was administered by slow injection for approximately 30 min. Potassium iodide (600 mg/d) was administered orally for 10 d (starting 24 h before injection) to block the uptake of free iodine into the thyroid gland. Imaging was carried out after 96-120 h. Planar images (6 min/image or at least 200000 counts over the whole field of view) including anterior and posterior projections of the thorax, abdomen and pelvis, were taken using large

field-of-view cameras, fitted with parallel hole high energy collimators. Indimacis 19-9 at a dose of 185 MBq was administered by slow infusion of 100 mL 0.9% sodium chloride over 30 min. Anterior and posterior spot views of the abdomen, pelvis and/or chest (500000 counts/view) were obtained 24 h and 48 h following the infusion. SPECT of abdominal and pelvic regions, including 360° rotating orbit, sampling every 6° with an 40-s acquisition per stop, using a 128 × 128 or 64 × 640 word matrix was carried out. Reconstruction was performed using Butterworth filter, order 6-10. Oncoscint CR 103 at a dose of 185-200 MBq was administered by slow injection for approximately 5 min, following the same acquisition protocol as above. To achieve more precise localization of the pathological lesions, as well as to increase target-to-background ratio, the dual isotope acquisition and subsequent subtraction of the obtained images were carried out. Thus, images of the vascular system (^{99m}Tc-red blood cells), liver and spleen (^{99m}Tc-sulfur colloid) or kidney (^{99m}Tc-DTPA) are obtained and used for subtraction. Scintigraphy was performed with a ROTA/Orbiter scintillation camera and Micro Delta computer.

Patients

The selection of patients was based upon complete diagnostic records [anamnesic data, physical examination, blood analysis, ultrasonography, contrast radiography, rectoscopy/colonoscopy, CT, magnetic resonance imaging (MRI), tumor marker assay] and clinical follow-up of at least 6 mo. The investigation was performed whenever there was a rise in serum levels of tumor markers [carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19-9)], and metastasis or recurrence could not be located according to clinical, radiological (chest X-rays), sonographic or endoscopic findings.

In all the patients, tumor marker (CEA and CA 19-9) blood levels were estimated every month in the same laboratory. Blood samples for tumor marker estimation were taken from the cubital vein of the patients and stored at -20°C until analysis. Physiological values of CEA were considered up to 7 U/L, while for CA 19-9, they were up to 33 U/mL. Fifteen patients were treated with Imacis 1, 18 with Indimacis 19-9, and 20 with Oncoscint CR 103.

Statistical analysis

The study data were analyzed in program R version 2.8.1. Tables and graphs were created in Microsoft Office Excel 2007. For statistical analysis of inter-rater agreement of samples with normal distribution, the following graphs were used: Normal Q-Q plot, histogram, and Kolmogorov-Smirnov's and Shapiro-Wilk's tests. In order to test the differences between parameters based on their nature, we used Kruskal-Wallis's test, exact Wilcoxon's rank sum test and Fisher's exact test. The value of $\alpha = 0.05$ was accepted as statistically significant. In case of multiple testing of the same set of data, Bonferroni's correction was used ($\alpha_1 = 0.05/\beta = 0.0167$). For the inter-rater agreement of significant parameters, Cohen's κ coefficient test was used.

Table 1 General parameters in patients examined by all three radiopharmaceuticals

Parameter	Imacis 1	Indimacis 19-9	Oncoscint CR 20	Test
No. of patients	15	18	20	-
CEA (µg/L)				Kruskal-Wallis
Mean (SD)	11.6 (12.2)	8.6 (6.5)	41.2 (60.4)	$\chi^2 = 5.71$
Median (rang)	8.9 (1.2-40)	5.9 (3.2-21)	14 (1.3-234)	$P = 0.0577$
NA	2/15 (13.3%)	8/18 (44.4%)	1/20 (5.0%)	
CA 19-9 (U/mL)				Kruskal Wallis
Mean (SD)	27.6 (10.4)	16.2 (4.5)	49.3 (56.5)	$\chi^2 = 10.71$
Median (rang)	22.0 (15-42)	14.6 (11.2-27)	24.5 (14-183)	$P = 0.0047$
NA	6/15 (40.0%)	8/18 (44.4%)	6/20 (30.0%)	
US				Fisher's exact
0	9 (60.0%)	12 (66.7%)	16 (80.0%)	$P = 0.5838$
1	5 (33.3%)	6 (33.3%)	4 (20.0%)	
NA	1 (6.7%)	-	-	
CT				
0	8 (53.3%)	6 (33.3%)	8 (40.0%)	
1	5 (33.3%)	5 (27.8%)	3 (15.0%)	Fisher's exact
2	-	5 (27.8%)	6 (30.0%)	$P = 0.1787$
3	-	1 (5.6%)	2 (10.0%)	
4	-	-	1 (5.0%)	
NA	2 (13.3%)	1 (5.6%)	-	
MR				
0	2 (13.3%)	-	4 (20.0%)	
1	-	-	3 (15.0%)	Fisher's exact
2	-	-	1 (5%)	$P = 0.6$
NA	13 (86.67%)		12 (60.0%)	
Colonoscopy				
0	2 (13.3%)	9 (50.0%)	5 (25.0%)	
1	1 (6.67%)	3 (15.0%)	3 (15.0%)	Fisher's exact
2	3 (20.0%)	2 (11.1%)	2 (10.0%)	$P = 0.55942$
NA	9 (60.0%)	4 (22.2%)	10 (50.0%)	
Rectoscopy				
0	5 (33.3%)	8 (44.4%)	5 (25.0%)	
1	4 (26.7%)	1 (5.6%)	2 (10.0%)	Fisher's exact
2	4 (26.7%)	1 (5.6%)	1 (5.0%)	$P = 0.42891$
NA	2 (13.3%)	8 (44.4%)	12 (60.0%)	
Immunoscintigraphy				
0	7 (46.7%)	5 (27.8%)	4 (20.0%)	
1	2 (13.3%)	5 (27.8%)	3 (15.0%)	Fisher's exact
2	5 (33.3%)	6 (33.3%)	5 (25.0%)	$P = 0.31134$
3	1 (6.7%)	2 (11.1%)	7 (35.0%)	
NA				
SPECT				
0	-	2 (11.1%)	3 (15.0%)	
1	-	6 (33.0%)	1 (5.0%)	
2	-	6 (33.0%)	3 (15.0%)	Fisher's exact
3	-	2 (11.1%)	7 (35.0%)	$P = 0.06137$
NA		2 (11.1%)	6 (30.0%)	

Type 0- no disease; 1- liver metastases; 2- recurrence; in colonoscopy and rectoscopy: 1- recurrence; 2- stricture and polyposis; 3- liver metastases and recurrence; 4- peritoneal carcinosis. CEA: Carcinoembryonic antigen; NA: Not Analyzed; US: Ultrasound; CT: Computed tomography; MR: Magnetic resonance; SPECT: Single photon emission computed tomography. Oncoscint CR 20: Indium In 111 satumomab pendetide; CA 19-9: Carbohydrate antigen 19-9.

RESULTS

Analysis of general parameters in three radiopharmaceutical groups-homogeneity

Data from various patients were statistically analyzed using Fisher's exact test in a study group consisting of 53 patients investigated with three radiopharmaceuticals. Analyzed parameters were: age, sex, surgical treatment, pathological verification and diagnostic examination findings. These analyses showed the homogeneity between the three different radiopharmaceuticals (Table 1).

Tumor marker CEA

With Kruskal-Wallis's test, levels of tumor markers CEA and CA 19-9 were analyzed in 53 patients. CA 19-9 level in the Indimacis 19-9 group was lower than in the other two groups, but it was still elevated. CEA level was elevated in all patients, but was significantly lower in those without pathological findings, and elevated in those with metastatic disease and/or recurrence (Table 2).

Complementary diagnostics

The findings of the complementary diagnostic methods

Table 2 Median carcinoembryonic antigen in types of immunoscintigraphy

Type of disease	<i>n</i>	CEA median
0	14	5
1	8	16.25
2	10	9.45
3	9	10
4	1	40

Type 0-no disease; 1-liver metastases; 2-recurrence; 3-liver metastases and recurrence; 4-peritoneal carcinosis. CEA: Carcinoembryonic antigen.

Table 3 Comparison of Cohen's κ coefficient for immunoscintigraphy and other diagnostic methods

Method	<i>n</i>	κ
US	52	0.157
CT	50	0.384
MRI	10	0.667
Colonoscopy	31	0.469
Rectoscopy	30	0.655

US: Ultrasound; CT: Computed tomography; MRI: Magnetic resonance imaging.

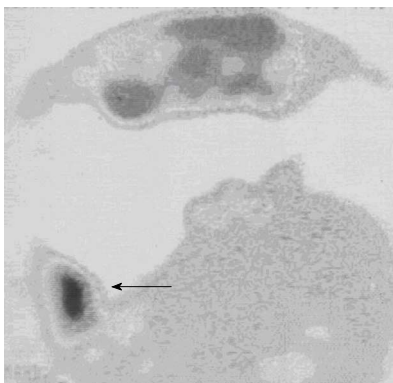


Figure 1 Immunoscintigraphy, planar, anterior view. Accumulation of radiopharmaceutical (IMACIS 1) in metastatic tumor of the right lower part of the liver (arrow).

and immunoscintigraphy were analyzed with Cohen's κ coefficient for the statistical analysis of inter-rater agreement: ultrasonography, slight; rectoscopy, substantial; colonoscopy, moderate; CT, fair; and MRI, substantial (Table 3). Whole body immunoscintigraphy was superior in correlation with complementary diagnostic methods for the detection of pelvic and extrahepatic metastases. Tumor recurrence occurred in 38 patients, and was confirmed by other diagnostic modalities in 35. In three patients, immunoscintigraphic findings were false positive, because hepatic metastases were not confirmed by other imaging modalities. This can be explained by the local inflammation after liver surgery. Thus, sensitivity of the method was 97%, specificity 82%, positive predictive value 92%, negative predictive value 93%, and accuracy 92% (Figures 1-3).

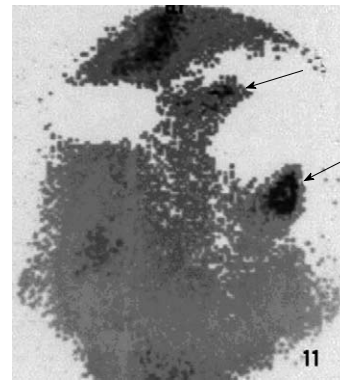


Figure 2 Immunoscintigraphy, planar, posterior view. Accumulation of radiopharmaceutical (INDIMACIS 19-9) in liver metastases (arrows).

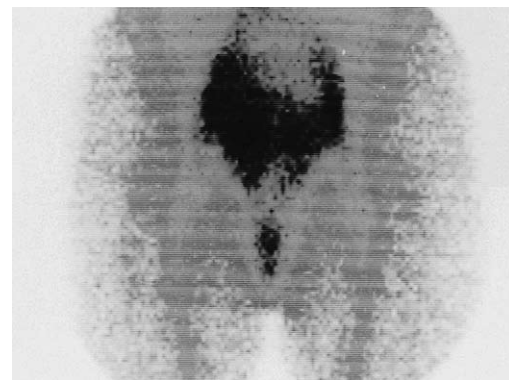


Figure 3 Immunoscintigraphy, planar, anterior view. Accumulation of radiopharmaceutical (Oncoscint) in peritoneal carcinosis.

Target background ratio

In 28 patients with positive immunoscintigraphic findings (both Indimacis 19-9 and Oncoscint), target/background (tg/bg) ratio was analyzed. Higher tg/bg ratio was found in metastatic foci with Indimacis 19-9 (Table 4). Further analysis of SPECT tg/bg ratio and planar tg/bg ratio points out the advantages of SPECT acquisition in immunoscintigraphic detection of metastases (exact Wilcoxon's rank sum test: planar images $W = 169$, $P = 0.0005$ and SPECT images $W = 174.5$, $P = 0.0001$).

DISCUSSION

The analyses showed homogeneity between the groups for the three different radiopharmaceuticals. CEA and CA 19-9 were analyzed in 53 patients. The CA 19-9 level was lower in the Indimacis 19-9 group compared with the other two groups, but it was still elevated. Tumor marker CEA was elevated in all patients, but significantly lower in those without pathological findings, and elevated in those with metastatic disease and/or recurrence. Thus, we can conclude that both parameters are valuable for evaluation and follow-up of disease.

The findings of the complementary diagnostic methods and immunoscintigraphy were analyzed and whole body immunoscintigraphy was superior in correlation

with complementary diagnostic methods for the detection of pelvic and extrahepatic metastases.

Tumor recurrence occurred in 38 patients, and was confirmed by other diagnostic modalities in 35 (Figures 1-3). In three patients, immunoscintigraphic findings were false positive due to local inflammation after liver surgery. In 15 patients, findings were negative, which were confirmed in 14 patients using other diagnostic methods, and one patient had a false-negative result, which was a small lesion in the rectal lumen (1 cm) that was confirmed by rectoscopy. Thus, sensitivity of the method was 97%, specificity 82%, positive predictive value 92%, negative predictive value 93%, and accuracy 92%.

A higher tg/bg ratio was found for metastatic foci with Indimacis 19-9. Further analysis pointed out the advantages of SPECT acquisition for immunoscintigraphic detection of metastases.

In most of the investigated cases, immunoscintigraphy was complementary to other imaging methods and significantly influenced the patient management. The most appropriate applications of this method should be the detection of recurrence, assessment of viability, as well as follow-up of disease progression and regression after therapy. Its diagnostic role is complementary to the radiological methods, which show limitations such as viability assessment after surgery, radio- and chemotherapy (CT, MRI), as well as when contrast radiography and colonoscopy cannot be performed (patients with colostomas and strictures), or when recurrence has an extraluminal position. However, other morphological methods (CT, ultrasonography, MRI) are superior for detection of liver metastases, while immunoscintigraphy is more sensitive and specific for the discovery of recurrences of colorectal carcinoma.

With regard to the false-negative findings for small intraluminal tumors, we conclude that for intraluminal tumors, endoscopic methods such as rectoscopy are the methods of choice. Apart from localization, the disadvantage of immunoscintigraphy is low spatial resolution of gamma cameras, which can lead to overlooking of small lesions (1 cm). These disadvantages can be overcome by using new generation gamma cameras with increased resolution as well as fusion images with CT and MRI, and especially hybrid systems. Thus, the recent introduction of a hybrid imaging device that contains a low-dose CT system and a gamma camera (SPECT/CT) on a single gantry has enabled the sequential acquisition of the two imaging modalities, with subsequent merging of data into a composite image display. These hybrid studies have led to a revolution in the field of imaging, with highly accurate localization of tumor sites, assessment of invasion into surrounding tissues, and characterization of their functional status^[7-9]. In the absence of SPECT/CT systems, tomography (SPECT) for a better distinction of the tumor is highly recommended. Further improvement in the detection of small tumor recurrences with immunoscintigraphy, using radioimmunoguided surgery (RIGS) and intraoperative detection of tumor deposits using special gamma probe systems, after i.v. application of radiopharmaceuticals, is discussed later.

Table 4 Target/background ratio (mean and SD) in planar and single photon emission computed tomography immunoscintigraphic foci

	Planar	SPECT	n
Indimacis 19-9 mean (SD)			
Recurrence	1.2	3.5	1/13
Metastasis	2.03 (0.44)	3.04 (0.8)	13/13
Oncoscent mean (SD)			
Recurrence	1.6 (0.24)	2.15 (0.29)	4/5
Metastasis	1.45 (0.26)	1.84 (0.28)	15/15

SPECT: Single photon emission computed tomography.

For accurate diagnosis, it is necessary to estimate tg/bg ratio, especially for the detection of liver metastases (subtraction method is highly recommended), and non-specific uptake of the radiopharmaceuticals in organs due to metabolism and excretion (liver and kidneys), and tissues mainly due to local inflammation. In our patients, false-positive findings can be attributed to the accumulation of radiopharmaceuticals in inflammation. We must emphasize that in all three false-positive patients, tg/bg ratio was on the lower edge of values for positive findings, which means lower than in tumor tissue, but the difference was not obvious and it was not easy to make a clear cut-off. All three patients underwent liver surgery during 6 mo before our investigation, which caused local inflammation with increased accumulation of radiopharmaceuticals. This means that, to prevent false-positive findings, the time of investigation should be longer after surgery, or repeated after 1 or 2 mo, with the expectation of obtaining lower values in non-specific accumulation and higher values in the case of tumor tissue, with obligatory quantification, i.e. estimation of tg/bg ratio^[10,11]. Although the antibodies are tumor specific, there is a certain non-specific accumulation in tissues, due to increased vascularization and local inflammation because specific radioimmunotherapy has never been employed widely^[12]. Also, as in previously described methods recommended for detection of false-negative cases, apart from physiological methods (immunoscintigraphy with SPECT), additional morphological investigation is recommended, such as hybrid SPECT/CT imaging, in order to distinguish accumulation in the unchanged, inflamed tumor tissue from newly developed tumor formation. Furthermore, even tumor marker/antigen (CEA, CA19-9) levels can be moderately increased due to local inflammation, which results in binding with specific radiolabeled antibodies^[13,14]. This also confirms the importance of follow-up in unclear cases. However, even with the above-mentioned limitations, accuracy of the method is very high.

The results from the literature mainly correspond to ours. Thus, some authors have confirmed the significance of the method for detection of recurrence, but have not confirmed its validity for detection of liver metastases^[15,16], whereas many^[17-19] have emphasized the significance of tomography. However, on the contrary, some investigations^[20-22] have found immunoscintigraphy inferior to other imaging methods, especially for the detection of lymph node metastases and for planning adequate surgical

approaches for recurrent colorectal carcinoma.

Our previous results, as well as those of other authors^[23-29] have pointed out the particular application of these antibodies for disease staging, and detection of local recurrence and extra-hepatic metastases in colorectal carcinoma, and that they have an important role in the therapeutic decision making process. The clinical value of PET and immunoscintigraphy with ¹³¹I or ¹¹¹In anti-CEA mAb for diagnosis of recurrent colorectal cancer has been confirmed by Ito *et al.*^[30], who have concluded that PET/CT reflects more accurately the biological character of tumors, but cannot provide the specificity of immunoscintigraphy that enables us to distinguish patients for antibody-based therapy. The superior value of PET with fluorodeoxyglucose for detection of distant metastases (liver, bone, and lung) and lymph node involvement has been estimated in comparison to ^{99m}Tc-labeled anti-CEA Fab for detection of recurrence of colorectal carcinoma^[31]. Immunoscintigraphy is superior for detection of local recurrent colorectal cancer, whereas PET is better for detection of distal metastases^[32].

RIGS^[33] enables localization of small tumor deposits. Roveda *et al.*^[34] have performed immunoscintigraphy with ¹³¹I or ¹¹¹In anti-CEA and 19.9 mAb using a gamma probe, and have found it particularly useful for endoscopic study of the pelvis after anterior resection, which is difficult to achieve by other diagnostic procedures. Both immunoscintigraphy and RIGS enable a more accurate diagnosis according to Hladic *et al.*^[35]. Florio *et al.*^[36] have found positive intraoperative gamma probe detection, although negative for immunoscintigraphy. RIGS applied in primary colorectal cancer enables the detection of occult lymph node metastases^[37].

In summary, imaging methods (CT, US, MRI) have an advantage for detection of liver metastases, whereas immunoscintigraphy is more specific for the assessment of recurrence of abdominal tumors. Thus, immunoscintigraphy should be applied in patients with suspected local recurrence and inconclusive results of routine diagnostic workup.

COMMENTS

Background

Considering that some tumors produce characteristic antigens, scintigraphy with monoclonal antibodies to these antigens seems to be a very promising method for detection. The aim of this study was to evaluate the clinical reliability of immunoscintigraphy for the detection of metastasis and recurrence of colorectal carcinoma, using three different radiopharmaceuticals.

Research frontiers

The results demonstrate that immunoscintigraphy is an accurate method for the detection of cancer recurrence. Together with single photon emission computed tomography (SPECT)/CT and radioimmunoguided surgery, it could have potential for selection of patients for immunotherapy or, in the future, radioimmunotherapy.

Innovations and breakthroughs

Imaging methods (CT, ultrasonography, magnetic resonance imaging) have advantages for detection of liver metastases, whereas immunoscintigraphy is more specific for the assessment of recurrence of abdominal tumors.

Applications

Immunoscintigraphy should be used in patients with suspected local recurrence and inconclusive results from routine diagnostic workup.

Terminology

Monoclonal immunoscintigraphy is scintigraphy with radiolabeled monoclonal antibodies on tumor markers/antigens.

Peer review

The research article by Artiko and his team deals with the usefulness of immunoscintigraphy for the detection of metastases and the recurrence of colorectal cancer. The results indicate that immunoscintigraphy is reliable and has a specific advantage for the detection of tumor recurrence, and can also be useful for suspected local recurrence. There was a good correlation between immunoscintigraphic evaluation and the results of conventional diagnostic methods.

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