Radioimmunoscintigraphy of colorectal carcinomas with three different radiopharmaceuticals

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The aim of the study was evaluation of the clinical reliability of the immunoscintigraphy for the detection of metastases and recurrences of colorectal carcinomas using three different radiopharmaceutical substances.

With IMACIS 1, the number of true negative findings (TN) was 4/7 and true positive (TP) 3/7, while in one patient, the results of immunoscintigraphy significantly influenced the therapeutical management.

With INDIMACIS 19-9, there were 2/8 TN and 6/8 TP. In three patients, immunoscintigraphy results influenced patient further management.

With ONCOSCINT in 2 patients findings were TN, in one FN and in one FP. In 3 patients, immunoscintigraphy influenced the management of the patient. Other imaging methods (CT, US, MRI) have advantage in detection of liver metastases, while immunoscintigraphy is more specific for the assessment of reccurences of the abdominal tumors. Thus immunoscintigraphy should be applied in patients with suggested recurrences and inconclusive outcome of routine diagnostic workup.

Key words: immunoscintigraphy, colorectal carcinoma

While other imaging modalities can detect morphological changes of tissue, 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 tumor cells. Currently, positron emission tomography (PET) is the best method for imaging metabolic changes based on increased rate of tumor glucolysis and/or protein metabolism, but still, scintigraphic methods with whole body scintigraphy and/or single-photon emission computed tomography (SPECT) are more accessible, mostly focusing on specific type of tumors. Radiolabeled monoclonal antibodies (MoAb) against tumor-associated antigens make it possible to image primary tumors of gastrointestinal system, their metastases and/or recurrences with high sensitivity and specificity (immunoscintigraphy). Radioimmunoguided surgery has been introduced as a method of more accurate detection of tumor extension and enabling radical resection. Radioimmunotherapy with monoclonal antibodies as a postoperative adjuvant treatment is currently being investigated [1].

The aim of the study was evaluation of the clinical reliability of the immunoscintigraphy for the detection of metastases and recurrences of colorectal carcinomas using three different radiopharmaceuticals.

IMACIS 1 contains the cocktail of 111 MBq ^{131}I MoAb 19-9 F (ab')$_2$ and MoAb anti CEA F(ab')$_2$. ^{131}I has a half-life of 8 days and beta-minus emission, which leads to a great radiation exposure of the patient. In addition, its high energy (364 KeV) gamma emission 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 ^{111}In. It is a pure gamma emitting isotope with physical half life of 67 h, an abundance of photon emissions at 173 and 247 keV. INDIMACIS 19.9 contains 19.9 F (ab')$_2$/DTPA monoclonal antibody fragments, while OncoScint CR 103 is an immunoconjugate produced by site-specific modification of the monoclonal antibody B72.3, which is a murine immunoglobulin (IgG1) able to recognise high molecular weight glycoprotein (TAG-72) expressed by

the majority of adenocarcinomas [2–6]. The aim of the study was evaluation of the clinical reliability of the immunoscintigraphy for the detection of metastases and recurrences of colorectal carcinomas using these three radiopharmaceuticals.

Patients and methods

Selection of patients was based upon complete diagnostic records (anamnestic data, physical examination, blood analysis, ultrasonography, contrast radiography, rectoscopy/colonoscopy, computed tomography, magnetic resonance imaging, tumor marker assay), and clinical follow-up of at least 6 months. The investigation was performed whenever there was a rise in serum levels of the tumor markers (carcinoembryonic and carbohydratic Ca 19.9/CEA), and metastases or reccurences could be not located based on clinical, radiological (chest X-rays), sonographical or endoscopical findings.

In all the patients tumor marker values were estimated (CEA and Ca 19-9). Blood samples for tumor marker (CEA and Ca 19-9) estimation were taken from the cubital vein of the patients and sera separated and stored on –20 °C until the analysis. Physiological values of CEA are up to 7 micrograms/l, while for CA 19-9 up to 33 U/ml.

In 7 patients the study was performed with IMACIS 1 containing the cocktail of 111 MBq ^{131}I MoAb 19-9 F (ab')$_2$ and MoAb anti CEA F(ab')$_2$ per dosis, 8 patients with INDIMACIS 19-9 containing 150 MBq of ^{111}In labeled MoAb 19-9 F(ab')$_2$ and in 18 patients with ONCOSCINT CR 103, containing 150 MBq ^{111}In labeled B72.3 MoAb. Planar and/or tomoscintigraphy was performed with ROTA/Orbiter scintillation camera and MicroDelta computer, immediately after application of radiopharmaceutical substance, as well as after 24, 48, 72 and 96 h, using appropriate collimators (for high and medium energies), as well as energy settings (172 keV, 247 keV and 360 keV). In those examined with radioiodine labeled antibodies, thyroid uptake of the isotope had been prevented by Lugol's solution.

Results

In all patients examined with IMACIS 1 both tumor markers values were elevated. The number of TN was 4/7 and TP 3/7. One of the three TP patients with recurrences of the disease had also peritoneal carcinosis and liver metastases, respectively. In 4 patients with negative immunoscintigraphic findings, malignant process was not confirmed. Both US and CT were positive in the patient with recurrence and liver metastases, while CT and MRI were positive in the patient with recurrence and peritoneal carcinosis (Fig. 1), but negative in the one, with recurrence only. Recurrences were 3–5 cm in diameter, and metastases were multiple and distributed throughout the liver. Contrast radiography and rectoscopy/colonoscopy were positive in 2/3 patients with recurrences and negative in one with recurrence of extraluminal localization. Thus, in 1/7 patients, the results of immunoscintigraphy significantly influenced the therapeutical management.

With INDIMACIS 19-9, there were 2/8 TN, having borderline value of CEA and Ca 19-9. TP were 6/8 (all with elevated tumor marker values, four of them many times; 3 with recurrences, 1 with recurrence and liver metastases and two with liver metastases only). In two patients with proved liver metastases (Fig. 2) in whom the study was repeated after 4 i.e 6 months after surgery, tumor marker values were slightly elevated, and liver metastases were confirmed again (in one patient US, CT and MRI were negative). The size of recurrences was 4–6 cm and of liver metastases 1.8–4.5 cm. In two patients with only recurrences, only tomoscintigraphy (SPECT) was positive. In one patient without recurrences, CT finding and colonoscopy were both false positive (postradiation scar tissue), while immunoscintigraphy finding was true negative. In other patient with recurrence, CT finding, contrast radiography and rectoscopy/colonoscopy proved a mass due to postradiation necrosis while immunoscintigraphy finding was positive. In all patients with liver metastases, immunoscintigraphy was positive, while other diagnostic methods (MRI, CT, US) were negative. Thus, in 3/8 patients, immunoscintigraphy results influenced patient further management.

With ONCOSCINT immunoscintigraphy, recurrences of carcinomas (5–12 cm) were detected in 9 patients (Fig. 3), recurrence with peritoneal carcinosis in one, recurrences with liver metastasis in two, and only liver metastases in two were detected and confirmed by surgery (TP=14/18). Tomography (SPECT) contributed to diagnosis in 5 patients with recurrences. In 2 patients findings were TN, in one FN (false negative) and in one FP (false positive). The FN finding was in pa-

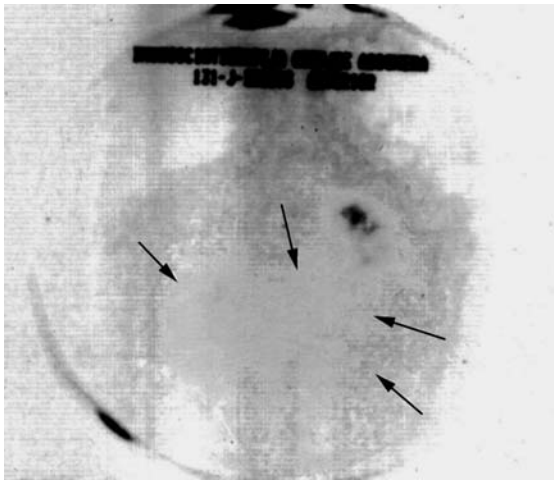

Figure 1. Immunoscintigraphy with IMACIS 1 anterior view shows increased accumulation of activity under the lower edge of the liver – peritoneal carcinosis.

tient with recurrence smaller than 2.5 cm, subsequently proven by colonoscopy. The FP one occured in a patient with granuloma. One of the immunoscintigraphically positive patients had been histopathologically diagnosed with squamocellular cancer instead of adenocarcinoma. At least one of the radiological examinations (US, CT or MRI) was positive in all patients with liver metastases. CT finding was false negative in two patients with recurrences, while MRI in one. In three patients with recurrences, CEA blood level was not increased. In 4 patients intensive accumulation of labeled antibodies was observed in colostomas. Immunoscintigraphy was positive also in one patient with squamocellulare carcinoma. Contrast radiography and rectoscopy/colonoscopy were TP in 13/16 patients with recurrences. In one, both methods were negative because of the extraluminal tumor localization, and in two patients both methods were impossible to perform (patients with colostoma and postoperative scar strictures, respectively). In 3/18 patients, immunoscintigraphy influenced the management of the patient.

Discussion

IMACIS 1 proved sensitivity and specificity in the detection of recurrences, liver and extrahepatic metastases, and influence the patient management.

INDIMACIS 1 proved sensitivity and specificity in the detection of recurrences as well as liver metastases, especially viability assessment (after radiotherapy) and follow up after surgery and proved to have significant influence on the patient management. When it was necessary, SPECT improved sensitivity of the method.

ONCOSCINT application proved sensitivity and specificity in the detection of recurrences as well as of liver metastases, especially viability assessment (after radiotherapy) and follow up after surgical treatment and significant influence the patient management. When it was necessary, SPECT improved sensitivity of the method. Oncoscint immunoscintigrahpy can also be useful in patients with squamocellular rectal carcinoma. Caution is necessary when interpreting immunoscintigraphy findings because of possible accumulation of radiopharmaceuticals in colostoma and/or granuloma. In addition, small recurrences (2.5 cm or smaller) sometimes can be overlooked by immunoscintigraphy.

With all three radiopharmaceuticals, in some cases (14%, 38% and 17%, respectively) immunoscintigraphy significantly influenced the patient management, while in other cases it was complementary. The most appropriate applications of this method should be the detection of recurrences, assessment of viability as well as follow up after the therapy. Its diagnostic role is complementary to the radiologic methods limitations of which involve CT and MRI viability assesment after surgery, radio and chemotherapy as well as contrast radiography and colonoscopy difficulties to be performed in some patients (colostomas, strictures, extraluminal tumor localizations, etc.). Disadvantages of immunoscintigraphy are poor spatial resolution (even with tomography), low target/background ratio (it is always advisable to perform subtraction technique) and nonspecific uptake of the radiopharmaceuticals in organs (liver, kidneys) and tissues (colostoma, granuloma). With tomography (SPECT), a better distinction of the tumor and estimation of its size can be achieved. Other imaging methods (CT, US, MRI) have advantage in detection of liver metastases, while immunoscintigraphy is more specific for the assessment of recurrences of the abdominal tumors.

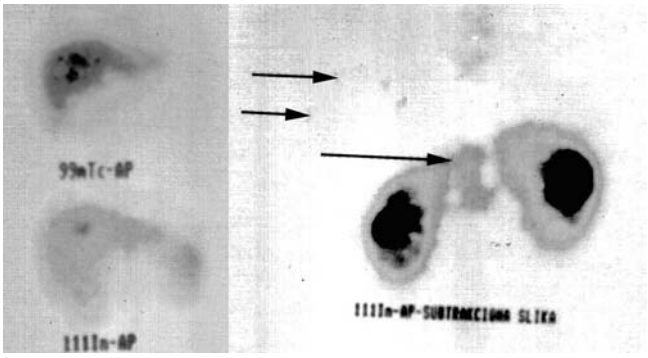

Figure 2. a) Planar radiocolloid scintigraphy anterior view shows almost physiological shape of the liver with almost physiological distribution of radiopharmaceutical in the right lobe, with absent accumulation in the lower part of the left liver lobe; b) Immunoscintigraphy (INDIMACIS 19-9) anterior view in the same patient revealed physiological shape of the liver with accumulation of the radiopharmaceutical in the lower part of the left liver lobe; c) resulting subtraction scintigram, anterior view, shows very small metastases of colorectal carcinoma (15–18 mm) in the upper part of the right liver lobe, interlobar indent and one larger metastases in the region of the lower part ogf the left liver lobe and abdominal lymph nodes.

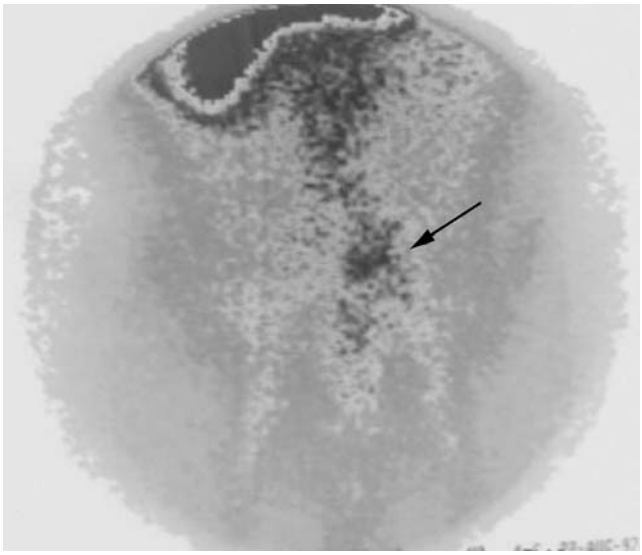

Figure 3. Immunoscintigraphy (ONCOSCINT) anterior view, revealed recurrence of the rectal adenocarcinoma.

Similarly to our findings, other authors [7–15] confirmed the significance of the method in the detection of recurrences, but denied its validity in the detection of liver metastases [16, 17]. Many authors [18–20] emphasized the significance of SPECT. Although some investigatiors confirmed the significance of the method in the detection of peritoneal carcinosis [21], which is also supported by our experience, others did not [10]. Unlike ours and the results of other authors, HOLTING et al and SCHLAG et al [22–24] found immunoscintigraphy disappointing in comparison to other diagnostic modalities, especially with regard to extrahepatic tumor diagnosis and concluded that it cannot give more information than conventional diagnostic tools. According to these authors, this is especially so in indicating and planning operative strategy for recurrent colorectal cancer.

Our previous results as well as results of other authors [25–28] point out the particular application of these antibodies in the disease staging, detection of local recurrence and extra-hepatic metastases in colorectal carcinoma and has an important role in the therapeutic decision making process.

In order to improve results of immunoscintigraphy, intraperitoneal application of the radiopharmaceuticals [16], combination of different antibodies [29], performance of quantitative analysis [21] as well as subtraction analysis [30] were also proposed. Some authors tried to increase the specificity of tumor uptake by simultaneous injection of an irrelevant antibody [17] while others proposed that antibodies used for radioimmunoscintigraphy should be selected on the basis of immunohistochemistry [31], although the method has several drawbacks [32].

Despite their theoretical appeal, the performance of these preparations can still be compromised by problems of poor tumor perfusion, low expression of tumor cell-surface antigen, antigen heterogeneity, and nonspecific uptake. One approach to reducing the confounding effects of high background activity has been the use of background subtraction techniques, as is the use of ^{99m}Tc-labeled albumin in conjunction with ^{99m}Tc-labeled antibody fragments; however, it is not clear whether improved specificity is in fact achieved. A more recent elaboration of this approach has been the fusion of bone scan or computed tomography (CT) images with single-photon emission tomography (SPECT) images of the radioantibody scan. Only limited experience with these approaches has been reported yet. An alternative approach attempts to apply the phenomenon of tumor antigen augmentation from exposure to cytokines such as interferon.

According to ITO et al [33] the usefulness of positron emission tomography (PET) and immunoscintigraphy by means of ^{131}I or ^{111}In anti-CEA monoclonal antibody for the diagnosis of the recurrent colorectal cancer had been confirmed already in clinical situation. PET reflects the biological character of tumor and makes the diagnosis more accurate, especially by combined use of PET and regular CT or MRI. PET can not provide the specificity of an antibody based functional imaging agent, and can not distuinguish the patients for the antibody-based therapy. However, WILLKOMM et al [34] point out that both FDG PET and ^{99m}Tc-labeled anti-CEA Fab' are suitable for the diagnosis of local recurrence of colorectal carcinoma, but that FDG PET is clearly superior in the detection of distant metastases (liver, bone, lung) and lymph node involvement.

Radioimmunoguided surgery (RIGS,35) is particularly useful in recurrences and in small tumor deposits which are difficult to localize. ROVEDA et al [36], performed immunoscintigraphy with ^{131}Iodine or ^{111}Indium anti-CEA and-19.9 monoclonal antibody, using a gamma-detecting probe (GDP) enabling to perform radioimmunodetection, and found it particularly useful in the endoscopic study of the pelvis after anterior resection, that can hardly be investigated by means of other instrumental diagnostic procedures. HLADIK et al [37] concluded that both immunoscintigraphy and RIGS enable a more accurate diagnosis. While treating the primary disease the use of RIGS may help in assessment of necessary extent of surgery and in staging of the disease by revealing an occult lymph nodes involvement. Pre-operative immunoscintigraphy seems to be a useful diagnostic method for detection of tumor recurrence (CEA-Scan, IMMU 4-Fab' fragments Moab against CEA, and Oncoscint CR 103, MoAb B72.3). According to FLORIO et al [38], immunoscintigraphy was obtained in 95% of cases. Radioimmunoguided surgery was performed in all cases. One case, which was negative at immunoscintigraphy, was found to be positive intraoperatively when radioimmunoguided surgery was performed. Radioimmunoguided surgery, in the authors' view, is a useful technique but needs to be validated in larger studies, particularly in cases of relapse.

We can conclude that other imaging methods (CT, US, MRI) have advantage in detection of liver metastases, while immunoscintigraphy is more specific for the assessment of reccurences of the abdominal tumors. Thus, immunoscintigraphy should be applied in patients with suspected local recurrences and inconclusive results of routine diagnostic workup.

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