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Is there a future role for immunoscintigraphy in the diagnosis of colorectal carcinoma?

Minireview

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Immunoscintigraphy combines the advances in immunology and nuclear medicine to target tumor sites. Visualization of colorectal carcinomas is based on different monoclonal antibodies and their fragments against tumor-associated antigens labeled with gamma emitting radionuclides which accumulate in the tumor tissue due to their interaction with corresponding antigens. Available data on the role of immunoscintigraphy in detection of recurrence and metastases of colorectal carcinomas are reviewed. Despite a variety of investigations related to the application of immunoscintigraphy in diagnostics of colorectal cancer, using different radiolabeled immunoreactive agents and imaging methods there has not been a consensus among the investigators regarding the best modality of the method, including the specific radiopharmaceutical for this purpose. Some general conclusions concerning potentials of immunoscintigraphy in such diagnostics, including expectancy of the newly developed SPECT/CT systems, are suggested. The possibilities of PET imaging of colorectal carcinomas using monoclonal antibodies labeled with positron emitting radionuclides, as well as of the radioimmunoguided surgery and radioimmunotherapy are also discussed.

Key words: Immunoscintigraphy, colorectal cancer, recurrences, metastases, radioimmunoguided surgery, SPECT/CT

Introduction. Colorectal cancer is the third most common cancer worldwide in man and second in woman. The incidence is higher in the developed countries, where it is the second most common cancer. The World Health Organization estimates that there are over 940,000 cases annually worldwide, with almost 500,000 deaths. [1]

Optimal treatment depends on the stage of the disease. Surgery is the treatment of choice in early stage, while in advanced disease chemotherapy and drugs that target growth factor receptors are only treatment options. Recurrent disease and/or locoregional and distant metastases can occur in about 30% patients who undergo surgical resection. Early detection of primary colorectal cancer increases the patient's chance of survival, while identification of recurrent and metastatic diseases before evident symptoms enhance positive clinical outcome.

Ultrasonography (US), barium enema examination, computed tomography (CT), and magnetic resonance imaging (MRI), as well as colonoscopy, are commonly used for staging of colorectal cancer, including detection of metastases and recurrences. Functional imaging techniques, such as immunoscintigraphy (planar and single photon emission computerized tomography –SPECT) modalities, as well as positron emission tomography (PET), image viable tumor tissue, and can contribute in diagnosis of metastatic and recurrent disease. Recently, fusion techniques (PET/CT and SPECT/CT) provide information on both anatomical characteristics and viability of detected tumors and have great diagnostic potentials in all aspects of staging patients with metastatic and reccurent colorectal carcinomas. Intraoperative detection of recurrences and metastases of colorectal carcinomas is also currently employed.

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This paper reviews the usefulness of immunoscintigraphy in diagnostics of colorectal carcinomas and its future role.

Immunoscintigraphy with high energy and long half- life radiopharmaceuticals. The first immunoscintigraphic studies for diagnostics of colorectal carcinomas, were performed with Iodine-131 (^{131}I).

One of commercially available radiopharmaceuticals widely used earlier was a cocktail of ^{131}I MoAb 19-9 F (ab')$_2$ and MoAb anti CEA F(ab')$_2$ *(IMACIS)*. Potassium iodide was administered orally in order to block the uptake of free ^{131}I into the thyroid gland. Following administration, a quantity of radioiodinated MoAbs can undergo dehalogenation in normal tissue, especially in the liver. Planar images of thorax, abdomen and pelvis could be obtained using large field-of-view cameras, fitted with parallel hole high energy collimators. Because of the very low count rate, it was very difficult to perform whole body scintigraphy and SPECT. In order to improve the sensitivity of the study, the dual isotope acquisition and subtraction of the obtained images are carried out. Thus, subtracted images were those of the vascular system (^{99m}Tc red blood cells/human serum albumin), the liver and spleen (^{99m}Tc sulphur colloid) or the kidney (^{99m}Tc DTPA).

Chatal et al, using ^{131}I labeled monoclonal antibodies 19-9, or its F(ab')$_2$ fragments, showed significant accumulation in 66% colorectal carcinoma sites while the other authors with ^{131}I labeled F (ab')$_2$ fragments of monoclonal antibodies against CA 19-9 and CEA ("radioimmunococktail" IMACIS 1) reported even higher sensitivity (82%) and specificity (90%), especially in the diagnosis of pelvic recurrences and intra-abdominal metastases [2-5]. Better results can be obtained after peritoneal application in comparison to intravenous [6].

On the contrary, some authors, using immunococktail of ^{131}I labeled F(ab')$_2$ fragments of monoclonal antibodies against CEA, with Ca 19-9 found immunoscintigraphy results disappointing in comparison to other diagnostic modalities, especially concerning the diagnosis of extrahepatic tumors. They reported that accuracy could not be improved even by changing of the antibodies, radiolabels or imaging techniques [7].

The other most commonly used radionuclide with high energy and longer half life for immunoscintigraphy is Indium-111 (^{111}In). It has favorable physical characteristics for gamma camera imaging (principal photons of 173 and 247 keV, half-life of 67h) and allow SPECT to be easily performed. However, it is not easily available and its use is expensive. Both ^{111}In labeled antibodies and the free radionuclide can be partly accumulated in the liver. Because of the transchelation, there is also high nespecific activity in the liver, spleen and bone marrow, as well as in the blood, because partly released ^{111}In from antibodies is bound to transferin. Urine and fecal excretions are very slow, and thus, high activity in blood pool and kidneys can also be observed.

Two most widely used ^{111} In-labeled radiopharmaceuticals for immunoscintigraphy are *OncoScint CR 103* and *INDIMACIS 19.9*. *OncoScint CR 103* a murine immunoglobulin which is specific for glycoprotein (TAG-72) expressed by the majority of adenocarcinomas [8]. *INDIMACIS 19.9*, contains 19.9 F(ab')$_2$/DTPA monoclonal antibody fragments. Anterior and posterior planar scintigraphy of the abdomen, pelvis and/or chest can be obtained on two separate day as well as whole body imaging. SPECT of abdominal and pelvic regions is nearly always performed and if the findings obtained by planar or whole-body scintigraphy with regards to the extra-abdominal regions are suspicious for tumors, evaluation by SPECT is also required. Like immunoscintigraphy with ^{131}I, dual isotope acquisition and subsequent subtraction of the obtained images can be performed.

The sensitivity of immunoscintigraphy with *OncoScint CR 103*, depends on the density of TAG-72 antigen expression of the particular carcinoma, but no current *in vivo* method is available for its estimation [9]. *Volpe et al* reported that cocktail-antibody imaging of ^{111}In-CYT-103 and CYT-37 improved the sensitivity of immunoscintigraphy for the detection of colorectal carcinoma compared to that obtained with a single MoAb imaging and may enhance staging and management of the disease [10]. According to the results of *Pinkas et al* and our previous results, OncoScint scintigraphy is a sensitive method for the detection of local recurrence and extra-hepatic metastases in colorectal carcinoma and has an important role in therapeutic decision making process [11,12]. In adition, this radiopharmaceutical proved its clinical value in the detection of liver metastases and viability assessment after radiotherapy and surgery [5,12]. SPECT improved the sensitivity of the method, although small recurrences can sometimes be overlooked. However, in initial staging of primary colorectal carcinoma apart from high sensitivity of both planar immunoscintigraphy and SPECT in the diagnosis of primary lesions, and SPECT in the detection of lymph node metastases, false-positive scans were also reported [13]. SPECT is strongly recommended in all patients undergoing immunoscintigraphy, since it identified tumours missed on planar scans in 35% of patients and provided additional information regarding tumour burden in 23% of patients [14, 15]. Several studies compared immunoscintigraphy with CT or MRI findigs. According to *Dominguez et al*, immunoscintigraphy with ^{111}In-CYT-103 was more accurate compared with a CT scan, but it was beneficial in only 13% of patients [16]. Some authors show cases of recurrence of colorectal carcinoma not detected by MRI and CT [17]. *Goldenberg* point out a particular application of these antibodies in disease staging and disclosure of occult lesions [18].

The immunoscintigraphy with radiolabeled monoclonal antibody fragments has also been performed, mainly with *INDIMACIS 19.9* (19.9 F (ab')$_2$/DTPA MoAb). Our results

with this radiopharmaceutical proved its clinical value in the detection of recurrences, liver metastases, and viability assessment after therapy, with the emphasize of SPECT application [4, 12, and 19]. *Chetanneau et al* confirmed the advantage of immunoscintigraphy using ^{111}In labeled carcinoembryonic antigen (CEA)-specific and/or 19-9 F $(ab')_2$ fragments over conventional methods, particularly in the diagnosis of pelvic recurrences. In order to improve sensitivity of the method, subtraction method was introduced [20, 21].

Immunoscintigraphy with low energy and short half- life radiopharmaceuticals. One of the low energy and short half-life radionuclide for immunoscintigraphy is Iodine-123 (^{123}I). ^{123}I has more favorable physical characteristics, delivering smaller radiation dose to the patient in comparison to ^{131}I. It is not suitable for labeling with intact MoAbs, because the delayed acquisition (even up to 36h) should be required in order to achieve high target-to-backgroung ratio resulting in the decrease in the count rate. When ^{123}I antibody fragments (Fab and Fab') are used, earlier acquisition can be performed, as well as SPECT with very high count rate even with a small dose. Similarly to ^{131}I, pretreatment with potassium iodide is necessary, and there is a dehalogenation problem. Anterior and posterior images, a whole body scan, as well as SPECT are recommended. Disadvantage of ^{123}I use is its high cost and limited availability.

However, good results in the detection of recurrences or metastases of colorectal carcinomas were achieved in combined clinical studies with ^{123}I labeled fragments and whole anti CEA MoAbs. *Goldenberg et al* found that immunoscintigraphy with ^{123}I labeled fragments, F(ab')2 and Fab', of IMMU-4, and anti-CEA monoclonal antibody (Immu-RAID-CEA) complemented CT findings by confirming suspected tumors and disclosing occult lesions with a very low possibility of developing human antimouse antibody reaction (HAMA) [22]. Other authors, proved that immunoscintigraphy with SPECT based on ^{123}I-labeled anti-CEA MoAb allows early detection of recurrence or metastasis of colorectal carcinoma, thus reducing the delay between diagnosis and treatment [23]. *Wong et al* evaluated an engineered intermediate-molecular-mass radiolabeled antibody construct directed against CEA (cT84.66) [24]. It demonstrated tumor targeting to colorectal carcinoma and a faster clearance in comparison with intact antibodies, making it appropriate for further evaluation as an imaging and therapeutic agent.

Radiopharmaceuticals labeled with 99m-technetium pertechnetate (^{99m}Tc) for immunoscintigraphy can be labeled either with antibody fragments (*CEA-Scan*, etc.) or whole antibodies (*Scintimun CEA*, etc)

The most widely used ^{99}Tc labeled radiopharmaceutical for immunoscintigraphy of colorectal carcinomas is *CEA-Scan,* an antibody fragment (Fab') against carcinoembryonic antigen (CEA, IMMU-4). Posterior and anterior whole body imaging and if needed, delayed images of the extra-hepatic abdomen should be acquired. SPECT of the pelvis and abdomen is recommended. Delayed 24h images, spot views, are indicated only when there is equivocal abnormal uptake seen on early images in the abdomen that could be bowel activity.

In spite of the short half-life of ^{99m}Tc, labeled whole MoAb (*Scintimun CEA/*anti CEA MoAb ^{99}Tc – BW 431/26) were also used with the similar acquisition and recommended delayed imaging.

The most of the studies compare the immunoscintigraphy with a ^{99m}Tc labeled antibody fragment (Fab') against carcinoembryonic antigen (CEA, IMMU-4), *CEA-Scan* with conventional diagnostic methods such as CT in detection recurrences/metastases of colorectal carcinomas. Thus*, Moffat et al,* found that the sensitivity of this method was superior to that of conventional diagnostic methods (CT) in the extrahepatic abdomen and pelvis, while it complemented the conventional ones in the liver [25]. According to authors, method affords high-quality, same-day imaging, uses an inexpensive and readily available radionuclide, and adds clinically significant information in assessing the extent and location of the disease in colorectal carcinoma patients. Similarly*, García Vicente et al,* achieved the values of sensitivity, specificity, positive and negative predictive value for the immunoscintigraphy with *CEA-Scan* higher than using CT and CEA blood level [26]. *Moffat et al,* using CT plus immunoscintigraphy in patients with recurrent or metastatic colorectal carcinoma, improved the correct prediction of resectability by 40% as well as of unresectability by 100%, compared with CT alone and concluded that immunoscintigraphy should be used in combination with conventional modalities to contribute to diagnostic accuracy in patients with known or suspected recurrent disease [27], which is supported by the results of *Behr et al* [28].

Some authors presented their results with *Scintimun CEA* that are almost the same as with immunoscintigraphy with a ^{99m}Tc labeled antibody fragment (Fab') against carcinoembryonic antigen (CEA, IMMU-4). They obtained the 87% overall accuracy in the diagnosis of recurrent colorectal carcinoma and reported sensitivity in the detection of locoregional or abdominal recurrence and liver metastases was 97% and 89% respectively. Immunoscintigraphy is most useful in patents with rising CEA levels on clinical follow-up while the other diagnostic investigations are negative. The advantages of immunoscintigraphy include the ability to detect tumor recurrence prior to other investigations and to identify tumor recurrence in areas such as the pelvis, where CT and MRI have their greatest weaknesses. The imaging accuracy is significantly increased when combined CT and antibody imaging is performed. [29].

Apart from commercially available radiopharmaceuticals, certain authors obtained similar results using either

whole monoclonal antibodies or antibody fragments for the detection of colorectal carcinoma that are not widely available such as: anti-CEA antibody PR1A3, IOR C-5, Ior-CEA1 as well as the most recent CL-58 [30-33].

Comparative immunoscintigraphic studies. Despite a variety of investigations in the last decades related to the application of immunoscintigraphy in diagnostics of colorectal cancer, using different radiolabeled immunoreactive agents and imaging methods there has not been established the best imaging modality nor the best radiopharmaceutical for this purpose. Some authors tried to use several radiopharmaceuticals in the same study in order to achieve the most accurate diagnosis and compared the results. Thus, *Bares et al,* used antibody preparations labeled with all three radionuclides (^{99m}Tc labeled complete anti-CEA antibodies – BW 431/26, ^{111}In labeled F (ab') $_2$-fragments against CEA – BW 431/31, and a mixture of ^{131}I labeled F (ab') $_2$-fragments against CEA and CA 19-9 – IMACIS-1) and yielded equal diagnostic sensitivities (65%, range 60-78%), except for liver metastases [34].

The best outcomes were obtained for abdominal and pelvic recurrences and lymph nodes lesions, while, the lowest levels of sensitivity were observed for liver metastases using monoclonal antibodies anti-CEA F(ab') $_2$, labeled with ^{131}I or ^{111}In [35]. Also, *Muxi Pradas et al*, [28] with anti-CEA MoAb ^{99m}Tc-BW 431/26 obtained worse results in comparison to anti TAG-72 MoAb ^{111}In-CYT-103, but both methods were proved to be useful in the detection of primary tumors and recurrences. Also, immunoscintigraphy was confirmed as complementary technique to other diagnostic procedures.

State-of-art and future direction. With the development of contemporary nuclear medicine equipment, as well as radiopharmaceuticals for scintigraphy, possibilities for broader application of immunoscintigraphy are widely opened. Thus, there have been attempts to apply radiolabeled monoclonal antibodies in radioimmunodetection, radioimmunotherapy, as well as using SPECT/CT and PET/CT. Thus, beside standard immunoscintigraphy (planar and SPECT), nowedays the great expectances are related to introduction of such diagnostics using the hybrid SPECT/CT and PET/CT systems, as well as of radioimmunoguided surgery and radioimmunotherapy

Recently, immunoscintigraphy is being combined with gamma detecting probe-guided surgery of colorectal carcinoma. It is based on the concept of sentinel-node-diagnosis, and is just being clinically evaluated for the potential future applications (*Kuhn et al* [36]). *Lechner et al*, applied ^{99m}Tc -CEA-Scan to patients 24 h before surgery [37], and excised the lymph nodes with increased radioactivity measured by gamma detecting probe. In 30% of cases this method led to an up-staging of the disease, and metastatic spread to lymph nodes was not regionary for the primary tumor. This is the way to precisely identify even very small tumor deposits [38], leading to accurate staging even during surgery [39]. While treating the primary disease, the use of radioimmunoguided surgery may help in assessing the necessary extent of operation, as well as in staging of the disease by revealing occult lymph nodes involved. Preoperative immunoscintigraphy seems to be a useful diagnostic method for the detection of tumor recurrence [40]. According to *Mery et al* [41] despite the good sensitivity of the technique, some concerns revolve around the high rate of false positives. Additionally, according to *Sun et al* [42] fluorescence image-guided surgery using ^{125}I-labeled anti-TAG-72 antibodies may provide opportunities for intraoperative carcinoma detection of both large and occult tumors. However, more studies are warranted to further develop the technique and determine the specific role it will play on the diagnosis and management of surgical disease.

During the last few decades, there has been attempts to extend and accomplish the results of radioimmunoscintigraphy with radioimmunotherapy. It is based on the application of radionuclides (mainly ß) conjugated to monoclonal antibodies in order to deliver high radiation doses to tumors. The effect depends upon an interaction between radiolabeled antibody and a tumor cell that persists long enough to deliver a tumoricidal radiation dose. However, colorectal, as well as other solid tumor malignancies are usually more heterogeneous regarding the antigen expression and density. Furthermore, agent delivery can also be prevented by large tumor size, location in solid organs or on peritoneal surfaces, limited tumor vascularity, reduced tumor immunogenicity or rapid cell proliferation, as well as lower sensitivity to radiation. [43]. Up to now, this method has not been widely applied. The principal antibodies studied thus far are directed against the shed antigens, carcinoembryonic antigen and tumor-associated glycoprotein 72 [43], or the transmembrane A33 antigen [44]. In order to improve the effect of radioimmunotherapy, *Wong et al* [45], propose combined radioimmunotherapy with other systemic, potentially radiation-enhancing chemotherapy agents (continuous infusion 5-fluorouracil with ^{90}Y-chimeric T84.66 anti-carcinoembryonic antigen). Similarly, according to *Behr et al* [46], preclinical results with ^{131}I-labeled humanized anti-CEA antibody hMN-14 in small-volume disease of colorectal cancer, in an adjuvant setting are promising. The future role of radioimmunotherapy depends on the ability to increase the tumor radiation burden in various ways, such as with fractionated delivery of radioimmunotherapy, concurrent application of external beam radiation, administration of marrow-ablative radioimmunotherapy doses with stem cell transplantation, or combination with radiation-sensitizing chemotherapy. Advanced colorectal cancer is a common and highly lethal disease, and new systemic therapies are needed to improve treatment outcomes for these patients [43]. Future studies should focus on combination therapies in populations most likely to achieve clinical benefit.

There have been a few studies comparing the results obtained by PET and immunoscintigraphy in diagnostics of colorectal carcinomas. According to *Ito et al,* [47] although PET reflects the biological features of tumor and makes a more accurate diagnosis by combined use with regular CT and MRI, this technique can not provide the specificity of an antibody based functional imaging agent, and can not help in selecting patients for the antibody-based therapy. However, both FDG PET and ^{99m}Tc-labeled anti-CEA Fab' are suitable for the diagnosis of local recurrence of colorectal carcinoma, but FDG PET is clearly superior in the detection of distant metastases (liver, bone, lung) and lymph node involvement [48].

There have also recently been experiments of using PET radiopharmaceuticals for immunoscintigraphy of colorectal carcinomas, mainly using ^{68}Ga labeled antibodies [49]. *Cai et al* [50] claimed that the results obtained with ^{64}Cu-DOTA-cetuximab, a chimeric monoclonal antibody targeting epidermal growth factor receptor (EGFR) on the surface of carcinoma cells, can be translated into the clinic to characterize the pharmacokinetics, to select the right population of patients for EGFR-targeted therapy, to monitor the therapeutic efficacy of anti-EGFR treatment, and to optimize the dosage of either cetuximab alone or in combination with other therapeutic agents. The same author [51] investigated the ^{18}F-labeled anti-carcinoembryonic antigen (CEA) T84.66 diabody, and concluded that it can be translated to the clinic for PET of CEA-positive malignancies.

In order to improve the results of immunoscintigraphy, a lot of methods and mathematical models have been used. The most recently, for either diagnostic imaging, such as with immuno PET and immuno SPECT, or radioimmunotherapy, various pretargeting methods have been recently proposed in order to allow the rapid elimination of radioactivity from normal tissues, resulting in a significant increase in tumor-to-normal tissue ratios. [52-55].

Conclusion

Scintigraphy with radiolabeled monoclonal antibodies and fragments have been playing an important clinical role during the past decades in the evaluation of patients with colorectal carcinomas. As a functional modality, it can estimate tumor viability and can be used for staging in the patients before and after surgery and other types of oncological therapy. It is mainly recommended in the patients with suspected metastases as well as recurrences, while its role in the detection of primary tumor has not been established. In most of the cases it may be a useful complementary tool to other diagnostic methods, by adding very high specificity. Immunoscintigraphy contributes to the detection of extrahepatic abdominal metastases, and is complementary with anatomical imaging methods in detection of liver metastases. Also, it can be used for the assessment of the resectablility of the tumor, as well as in the patients with inconclusive outcome of routine diagnostic workup. Furthermore, it is indicated after therapy when it is not possible to distinguish tumor necrosis from viable tissue (CT, MRI) as well as in patients in whom other diagnostic methods (barium enema and colonoscopy) can not be performed.

Regarding the radiopharmaceuticals used, the limitations of the method are high background activity and/or non-specific uptake of the radiopharmaceutical in different tissues as well as immunogenicity of injected murine antibodies, which prevent the repetition of the examinations. Thus, further investigations should be directed towards the reduction of the non-specific accumulation and diminishing the immunogenicity of the radiopharmaceutical.

One of the disadvantages in standard nuclear medicine is relatively low resolution in comparison to other visualization methods. However, with contemporary gamma cameras this problem is partly overcome. Thus, the particular advantage of immunoscintigraphy in comparison to other diagnostic methods is possibility to image the whole body in the single procedure, with low radiation dose, allowing visualization of distant metastases. Also, SPECT allows a more accurate diagnosis and assessment of localisation, as well as discovery of smaller lesions. Furthermore, the fusion images and recently developed hybrid SPECT/CT and PET/CT systems, are expected to significantly improve the possibilities of the both modalities in diagnostics of colorectal carcinomas, owing to combined anatomical/functional imaging. Up to now, ^{18}FDG PET can not provide the specificity of an antibody-based functional imaging agent, although PET may have a higher lesion sensitivity. However, radioimmunodetection using positron emitting radionuclides can provide new opportunities for and more sensitive functional imaging. Similarly, radioimmunoguided surgery is expanding and promising, and has been advocated as a method of more accurate detection of tumor extension and accomplishing radical resection, with the future potentials in clinical practice. On the contrary, radioimmunotherapy is still limited. Its future role depends on the ability to increase the tumor radiation burden in various ways, with minor side effects on other organs and tissues.

With the development of contemporary nuclear medicine equipment, as well as radiopharmaceuticals for scintigraphy, possibilities for broader application of immunoscintigraphy are widely opened. In the future, pre-targeting techniques should allow the rapid elimination of radioactivity from normal tissues, resulting in a significant increase in tumor-to-normal tissue ratios which will contribute to diagnosis as well as in the therapy. Progress is also required in the choice of radionuclides and labeling techniques. With contemporary equipment, beside standard immunoscintigraphy (planar and SPECT), nowadays the great expectances are related to introduction mainly of diagnostics using the hybrid SPECT/CT and PET/CT

systems, as well as of radioimmunoguided surgery and radioimmunotherapy.

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