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# Value of scintigraphic imaging in the detection of pancreatic tumors – the role of FDG-PET

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*One of the main challenges in diagnostic radiology is the early and the accurate detection of pancreatic carcinoma, which is indeed difficult by morphologically orientated methods, i.e. US, CT, MRI. Therefore, functional imaging using nuclear medicine procedures may be useful. In patients with suspected pancreatic cancer, several imaging procedures have been investigated i.e. immunoscintigraphy, receptor scintigraphy, unspecific perfusion scintigraphy. However, none of them convinced in routine patient management. Best diagnostic results with an overal accuracy of about 80% were obtained using F-18-fluorodeoxyglucose – positron emmission tomography (F-18-FDG-PET). Due to inherent technical limitations PET probably cannot depict lesions smaller than 10–15 mm in diameter even when using a high resolution PET scanner. Thus, it is probably not suitable for early detection of pancreatic carcinoma. It is not yet clear, whether the performance of FDG-PET is high enough to reduce the current number of diagnostic laparotomies. Prospectively performed comparative studies with CT, US, ERCP and MRI using state of the art equipment are still needed to establish an optimal diagnostic strategy. Beside lesion detection, FDG-PET may offer valid data on both the prognosis of pancreatic masses, and the effectiveness of therapeutic procedures. However, further effort is still necessary to define the exact position of nuclear medicine in the management of pancreatic cancer.*

*Key words:* pancreatic – neoplasms – radionuclide imaging; tomography, emission – computed – methods, fenorine radioisotopes; FDG-PET – diagnostic value

## The clinical problem

One of the current challenges in diagnostic radiology is the early and the accurate detection of pancreatic carcinoma and its differentiation from mass-forming pancreatitis using noninvasive imaging methods.[1, 2] The diagnostic accuracy of morphologically oriented imaging techniques is presently suboptimal. Ultrasonography is hampered by the dorsal position of the pancreas in the abdomen and the bowel located in front of it. CT and MRI have an excellent geometric resolution, but the differentiation between malignant and benign lesions remains difficult even with this leading edge technology. On the other hand, functionally oriented nuclear medicine procedures offer the possibility of imaging organ metabolism when using appropriate radiolabelled tracers. At the beginning, the aim of radioisotope studies was merely the visualization of the pancreatic tissue. For this purpose Selenium-75-selenmethionine and (I-125)-N,N,N'-trimethyl-N'(2-hydroxy-3-methyl-5-iodobenzyl)-1,3-propanediamine (I-123-HIPDM) were tested. Both tracers are accumulated in the normal pancreatic tissue, but they can not differentiate between malignant tu-

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mors and benign lesions.[3,4] Thus, in the era of high resolution radiological methods they are of a more historical value. Recently, the introduction of several new types of tracers opened exciting perspectives. Therefore, the possibilities of these radiopharmaceuticals will be discussed.

## Immunoscintigraphy

Since the mid eighties big expectations have been connected to the introduction of radiolabelled monoclonal antibodies against tumor associated antigenes in oncologic nuclear medicine. The characteristic feature of these antibodies is their extremely high specificity. Using chemical procedures, they can be broken either into Fc and F(ab')2 fragments or into Fc and Fab fragments. The F(ab')2 of Fab fragments are responsible for the antigen specificity of the antibodies. These antibodies can be labelled with I-123, I-131, In-111 or, recently with Tc-99m.

Different types of monoclonal antibodies have been tested for the detection of pancreatic cancer. A coctail of I-131 labelled F(ab')2 fragments of antibodies directed against the tumor associated antigenes CA 19-9 and CEA was used by Montz.[5] Despite the detection of some large tumors without elevated level of tumor markers in the peripheral blood, this tracer is considered of only limited diagnostic value due to its relatively poor sensitivity. Using In-111 for labelling and SPECT acquisition at least 3 days after the tracer injection some increase in diagnostic accuracy, due to elimination of unspecific early tracer accumulation, was reported by Bares in various gastrointestinal carcinomas.[6] As a further attempt, preliminary results have been reported with the I-131 labelled murine monoclonal antibody AR-3-IgG1 directed against the mucin-like antigen CAR-3.[7]

Investigations with the In-111 or I-131 labelled F(ab')2 fragments of the monoclonal antibody BW 494/32, the corresponding antigene which is often expressed by pancreatic carcinomas, failed as well in presenting a break through in immunoscintigraphy.[8] Nevertheless, in a study with only 3 patients, Abdel Nabi and coworkers presented favourable images of primary tumors as well as of their metastases using In-111 labelled monoclonal anti CEA antibody ZCE 025.[9]

In conclusion, at present there is no radiolabelled monoclonal antibody available with clearly documented high clinical performance necessary for routine patient management. Despite of this, immunoscintigraphy can be considered as a possible investigation in diagnostically problematic cases.

## Receptor scintigraphy

New possibilities in tumor imaging have been offered recently by the introduction of small receptor analogue molecules. A subgroup of these compounds, the radiolabelled somatostatine analogues can be used for imaging of endocrine tumors i.e. of those derived from the so called APUD cells. Somatostatine analogues have been primarily used for imaging of carcinoids and islet cell tumors of the pancreas. Bakker and coworkers reported the successful localization of pancreatic tumors in rats with I-123-Tyr-3-octreotide.[10] However, the main disadvantage of this radiopharmaceutical is its predominantly hepatic clearance and therefore its high liver accumulation, which may mask pancreatic tracer uptake.

When labelling octreotide with In-111-DTPA, the longer halflife of In-111 can be combined with the facilitated renal clearance of the DTPA-containing compound. These features offer the advantage of 24 hours imaging when interferring background activity is already minimized by renal clearance. Bakker and coworkers reported successful investigations of pancreatic tumors in a rat model using (In-111-DTPA-D-Phe1)-octreotide.[11] They documented an increasing tracer uptake with time within the tumor tissue, which could be clearly visualized by gamma camera scintigraphy in somatostatin receptor positive rat pancreatic carcinoma.[11] As an attempt for supporting surgical interventions, Ohrvall and coworkers introduced a non imaging method for the intraoperative detection of tumors and its metastases by using a hand-held gamma probe. However, the feasibility of this interesting method is limited by the relatively high background activity.[12]

## Unspecific perfusion tracers

Thallium-201 uptake is considered to reflect the regional perfusion as well as the viability of tumor cells.[13] The theoretical background of this feature of TI-201 is the correlation of the growth of malignant transformed cells and the activity of the Na/K-ATPase.[14]

In 1993 Suga and coworkers demonstrated the possibility of monitoring the efficacy of antineopla-

stic treatment using quantified TI-201 uptake in pancreatic cancer. In three patients, the TI-201 uptake by the tumor correlated well with the serum level of the tumor marker CA 19-9.[15] In a subsequent publication of this group results with subtraction scintigraphy were presented.[16] When the boundary between abnormal TI-201 uptake and adjacent liver activity was unclear on the TI-201 SPECT image a SPECT image of the liver using Tc-99m-phytate was acquired and subtracted from the TI-201 image in order to separate hepatic and pancreatic TI-201 uptake. Using this technique a favorable sensitivity of 91% could be demonstrated. However, in the same study, four of sixteen patients with benign pancreatic disorders exhibited abnormal increased TI-201 uptake. Based on these data, TI-201 scintigraphy is a nuclear medicine method with relatively low cost and acceptable clinical performance for detecting pancreatic cancer and can be recommended, especially when PET facility is not available.

## PET investigations using FDG

The rational of using radiolabelled glucose analogues for tumor imaging is based on the increased metabolic activity of tumor tissue. The accelerated rate of glykolysis in aggressive malignant transformed tumors was published first by Warburg in 1956.[17]

Fluorodeoxyglucose (FDG), a glucose analogue, is supposed to enter the cells by the same transport mechanisms as used by native glucose. After phosphorylation, however, FDG-phosphate is trapped intracellulary due to its extremely slow dephosporylation as compared to native glucose. This feature enables imaging of FDG distribution by positron emission tomography (PET). Experimental and human studies have demonstrated an increase in FDG uptake in various malignant tumors.[18–20] All of these studies have confirmed that an increased FDG uptake is a reliable indicator of the presence of viable malignant tumor tissue. In contrast, benign processes or metabolically less active neoplasms generally have lower or even normal levels of glucose uptake.[21] The mechanism of FDG accumulation in tumors is probably multifactorial. First, it is induced by activation of glucose transporter proteins and elevated glucose consumption, which both are considered to be early and prominent features of an oncogene-mediated malignant transformation in cell culture systems.[22] Second, tumor associated tissue inflammation produces an increased FDG uptake as well.[23]

The value of F18-FDG for the detection of malignant pancreatic processes was first documented in patients by Zanzi and coworkers in 1990.[24] Based on the results of F18-FDG-PET, Klever and coworkers reported clear differentiation of pancreatic carcinoma and chronic pancreatitis.[25] Bares and coworkers[26] found focally increased FDG accumulation in 12 out of 13 patients with histologically proven pancreatic adenocarcinoma. Eight of nine known lymph nodes and four of five known liver metastases were detected in their study. In contrast, in two patients with chronic pancreatitis no FDG uptake was documented. One patient suffering from an adenocarcinoma and lacking of FDG uptake had diabetes, probably because the fasting state could not be established sufficiently prior to the study. In a second study with 40 patients investigated by the same group,[27] PET helped to correctly classify 25 of 27 malignant pancreatic tumors and 11 of 13 benign disorders of the pancreas. False negative findings were obtained again in 2 patients with insulin-dependent diabetes. False-positive findings were associated either to retroperitoneal fibrosis or, in one patient, to pancreas divisum with chronic pancreatitits. However, FDG-PET was shown to be superior to both CT and ultrasound in the detection of lymph node metastases. These results have been confirmed by Friess and coworkers.[28] Fourty one of fourty two patients with pancreatic cancer and four of six patients with a periampullary carcinoma presented a focally increased FDG uptake. In contrast, in 28 of 32 patients with chronic pancreatitis no FDG accumulation occured.

In a comparative study of 46 patients suspected of having a pancreatic cancer the diagnostic performance of FDG-PET was superior to both CT and transabdominal and endoscopic ultrasound.[29] This superiority of FDG-PET over CT was also demonstrated by Stollfuss and coworkers.[30] Based on the result of a recent comparative study with FDG-PET and TI-201 SPECT in patients with histologically proven pancreatic cancer it can be concluded that, if PET facility is available, FDG-PET is at present the nuclear medicine method of choice.[31]

An exciting and widely discussed possibility to increase the performance of PET studies is the use of quantitative methods to obtain numerical values of the phosphorylation rate of deoxyglucose. For this purpose, several methods have been suggested.

Most of them are based on the three-compartment model introduced by Sokoloff.[32] However, there are some practical and theoretical difficulties connected to the application of the three compartment model of FDG metabolism, especially to the determination of the velocity constants of the biochemical reactions and to that of the lumped constant.[33–35] Therefore, most investigators are simply using ratios of FDG uptake in tumors as compared to that in normal tissue. A further possibility of quantification is the estimation of the net tumor uptake of FDG in the tumor tissue normalized to the body surface or body weight.

The most widely used quantitative method of estimation of FDG uptake in tissue is the determination of standardized uptake values (SUV). The main advantage of the SUV method is its methodologic simplicity. The main disadvantage is the fact, that the SUV itself is time-dependent and, therefore, potentially subject to error if images are not obtained at the same time interval after tracer injection.[36, 37]

The impact of quantification of FDG uptake by SUV could be shown in patients with pancreatic cancer. The tumor region exhibited significantly higher values compared to pancreatic regions in patients with pancreatitis.[28] Using ROC analysis it could be demonstrated that an SUV value of about 1.5 optimally separates malignant and benign pancreatic processes.[30]

However, very recent investigations in clinical patients report a lower accuracy as found in the early works.[38, 39] Dohmen and coworkers found an accuracy of about 80% regarding the differentiation of pancreatic cancer from chronic pancreatitis. Furthermore, they could not demonstrate any advantage of using quantitative parameters as compared to the simple visual analysis.[38] The limited performance of the SUV was also reported by Vomocil and coworkers.[39]

## PET tracers for endocrine pancreatic tumors

Results with C-11-labelled L-dihydroxyphenylalanine (L-DOPA) and hydroxytryptophane (HTP) have been recently reported in pancreatic endocrine tumors with promising results particularly regarding glucagonomas.[40] These findings, based on the investigation of 22 patients, suggest further possibilities in metabolic characterization of tumors. However, the role of FDG in this type of tumors has not yet been explored.

## Multimodality imaging

The combination of morphologic and functional information is a very new and exciting trend in diagnostic imaging. It is especially helpful in the exact anatomic localization of functional disorders. Detailed morphologic information presented by the excellent geometric resolution of CT or MRI can be combined with the visualization of metabolic parameters and presented in one single image. However, for the coregistration of tomographic images from different modalities sophisticated external or anatomical markers are needed. The first successful fusion of F-18-FDG-PET and MR images using a system of surface markers in patients with pancreatic adenocarcinoma was demonstrated by Benyounes and coworkers.[41] The combined images were impressive for exact delineation of the tumor on the high quality slices of the MR study. Thus, multimodality imaging might be of increasing interest in future studies.

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