TURUN YLIOPISTON JULKAISUJA
ANNALES UNIVERSITATIS TURKUENSIS

SARJA - SER. D OSA - TOM. 865

MEDICA - ODONTOLOGICA

POSITRON EMISSION TOMOGRAPHY IN THE DIAGNOSIS AND STAGING OF PANCREATIC AND NEUROENDOCRINE TUMORS

by

Saila Kauhanen

TURUN YLIOPISTO
UNIVERSITY OF TURKU
Turku 2009

Department of Surgery and Turku PET Centre, University of Turku, Turku Finland

Supervised by

Professor Pirjo Nuutila
Turku PET Centre and the Department of Medicine
University of Turku
Turku, Finland

and

Docent Jari Ovaska
Department of Surgery
University of Turku
Turku, Finland

Reviewed by

Professor Stefano Fanti
Department of Nuclear Medicine
University of Bologna
Bologna, Italy

and

Docent Juhani Sand
Department of Surgery, Gastroenterology and Oncology
University of Tampere
Tampere, Finland

Dissertation opponent

Docent Caj Haglund
Department of Surgery
University of Helsinki
Helsinki, Finland

ISBN 978-951-29-4029-5 (PRINT)
ISBN 978-951-29-4030-1 (PDF)
ISSN 0355-9483
Painosalama Oy – Turku, Finland 2009

To Ari and Otto

ABSTRACT

Saila Kauhanen: Positron emission tomography in the diagnosis and staging of pancreatic and neuroendocrine tumors.
Department of Surgery and Turku PET Centre, University of Turku
Annales Universitatis Turkuensis
Painosalama Oy, Turku, Finland 2009

Background and aims: Despite development in conventional imaging modalities, the diagnosis and staging of pancreatic and neuroendocrine tumors (NETs) are challenging. Positron emission tomography-computed tomography (PET/CT) using different tracers is a promising method in primary diagnosis, staging, and restaging of these tumors, although its role is still evolving.

The current series of studies was designed to define the feasibility of PET in the diagnosis of pancreatic tumors and NETs. To address these issues, a prospective series of patients with pancreatic tumors was imaged with PET/CT using tracer ^{18}F-fluorodeoxyglucose (^{18}F-FDG) to assess metabolism and radiowater (^{15}O-H_2O) to assess blood flow (BF) of the tumor. Moreover, further studies were designed to investigate the potential of ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA)-PET in the diagnosis and staging of different types of NETs.

Results: In primary diagnosis of pancreatic tumors, ^{18}F-FDG-PET/CT had a higher accuracy compared to both CT and magnetic resonance imaging (MRI) (89% *vs.* 76% and 79%, respectively). Especially in differential diagnosis of suspected malignant biliary stricture, ^{18}F-FDG-PET/CT had a high positive predictive value of 92%. In staging of pancreatic cancer, the sensitivity of ^{18}F-FDG-PET/CT was low (30%) in detecting local spreading of disease. Instead, ^{18}F-FDG-PET/CT had significantly higher sensitivity than CT or MRI in diagnosis of distant disease (M-staging) (88% *vs.* 38%). In assessment of metabolism and BF of different pancreatic tumors, metabolism/BF ratio was significantly higher in malignant lesions than in benign lesions or normal pancreatic tissue ($P<0.05$), and a high ratio was also a strong predictor of poor survival. When patients with insulinoma were imaged by ^{18}F-DOPA-PET, seven out of eight patients with insulinoma and two patients with β-cell hyperplasia showed increased focal ^{18}F-DOPA uptake. As compared to conventional imaging (CT or MRI), ^{18}F-DOPA-PET was a more sensitive diagnostic method. Futher, routine use of carbidopa premedication masked insulinoma lesions in two out of three patients in ^{18}F-DOPA-PET/CT imaging. In the study of 82 patients with suspected/known NET, ^{18}F-DOPA-PET had an overall accuracy of 90%. The accuracy was especially high in primary diagnosis of pheochromocytoma and restaging of known NET. Further, in 59% of the cases, ^{18}F-DOPA-PET imaging had an impact on the clinical management.

Conclusions: PET/CT using tracers ^{18}F-FDG and ^{15}O-H_2O was shown to be applicable in the differential diagnosis of pancreatic tumors. Further, ^{18}F-FDG-PET/CT was useful in M-staging of pancreatic cancer. This study also supported the efficacy of ^{18}F-DOPA-PET imaging in diagnosis of insulinoma, especially when carbidopa premedication was not used. Based on this study, ^{18}F-DOPA-PET is feasible method in primary diagnosis and restaging of different types of abdominal NETs, especially in patients with inconclusive findings in conventional imaging. Further, PET had a significant impact on the clinical management of patients with pancreatic tumors and NETs.

Keywords: pancreatic tumor, neuroendocrine tumor, positron emission tomography, fluorodeoxyglucose, dihydroxyphenylalanine, radiowater, diagnostic imaging

TIIVISTELMÄ

Saila Kauhanen: Positroniemissiotomografia haima- ja neuroendokriinisten kasvaimien diagnostiikassa
Kirurgian klinikka ja Valtakunnallinen PET keskus, Turun yliopisto
Annales Universitatis Turkuensis
Painosalama Oy, Turku, Finland 2009

Tutkimuksen tausta ja tavoitteet: Viimeaikaisesta perinteisten kuvantamismenetelmien kehityksestä huolimatta sekä haima- että neuroendokriinisten (NE) kasvaimien diagnostiikka on haastavaa. Uudentyyppinen kuvantamismenetelmä, fuusio positroniemissiotomografia-tietokonetomografia (PET/TT), on lupaava näiden kasvainten erotusdiagnostiikassa ja levinneisyyden arvioinnissa. Huolimatta alustavista lupaavista tutkimustuloksista, PET/TT:n rooli on toistaiseksi vielä epäselvä sekä haima- että NE-kasvaimissa eikä se näin ollen ole vakiintunut kliiniseen hoitokäytäntöön.

Väitöskirjatyön tavoitteena oli selvittää PET/TT-menetelmän käyttökelpoisuutta haima- ja NE-kasvaimien diagnostiikassa. Kahden ensimmäisen osatyön prospektiivisessa tutkimuksessa, potilaat, joilla epäiltiin haimakasvainta, kuvannettiin PET/TT:llä käyttäen merkkiaineena fluorideoxyglukoosia (^{18}F-FDG) kasvaimen aineenvaihdunnan arvioimiseksi ja kasvaimen verenvirtausta arviointiin käyttäen merkkiaineena radiovettä (^{15}O-H_2O). Kolmen muun osatyön tavoitteena oli selvittää dihydroxyfenylalaniini (^{18}F-DOPA)-PET-menetelmää erilaisten NE-kasvaimien diagnostiikassa ja levinneisyyden arvioinnissa.

Tulokset: Haimakasvaimien ensivaiheen diagnostiikassa ^{18}F-FDG-PET/TT:llä oli korkeampi diagnostinen tarkkuus verrattuna tietokonetomografiaan (TT) ja magneettikuvantamiseen (89% *vs.* 76% ja 79%). Etenkin pahanlaatuiseksi epäillyn sappitiehytahtauman erotusdiagnostiikassa ^{18}F-FDG-PET/TT:n positiivinen ennustearvo (92%) oli korkea. Haimasyövän levinneisyyden arvioinnissa ^{18}F-FDG-PET/TT:n herkkyys oli huono (30%) paikallisen taudin osoittamisessa. Sen sijaan etäpesäkkeiden osoittamisessa ^{18}F-FDG-PET/TT oli merkittävästi herkempi menetelmä verrattuna TT ja magneettikuvantamiseen (88% *vs.* 38%). Verrattaessa erilaisten haimakasvaimien ja normaalin haimakudoksen aineenvaihduntaa ja verenvirtausta, aineenvaihdunta/verenvirtaus suhde oli merkittävästi korkeampi pahanlaatuisissa haimakasvaimissa ($P<0.05$). Lisäksi kasvaimen korkea aineenvaihdunta/verenvirtaus suhde viittasi huonompaan taudin ennusteeseen. ^{18}F-DOPA-PET löysi seitsemän kahdeksasta insulinoomasta ja oli positiivinen myös kahdella potilaalla, joilla todettiin haiman saarakesoluhyperplasia. Perustuen alustaviin tuloksiin, rutiinikäytössä oleva karbidopa esilääke ennen ^{18}F-DOPA-PET kuvantamista peitti insulinooma löydöksen kahdella potilaalla kolmesta. NE-kasvaiminen diagnostiikassa 82 potilaan aineisto osoitti ^{18}F-DOPA PET kuvantamisen tarkkuudeksi 90%. Etenkin feokromosytoomien ensivaiheen diagnostiikassa ja NE-kasvaimen uusiutumaa epäiltäessä menetelmän tarkkuus oli korkea. Kokonaisuudessaan 59%:lla aineiston potilaista ^{18}F-DOPA-PET kuvantamisella oli vaikutusta kliinisiin hoitoratkaisuihin.

Johtopäätökset: PET/TT käyttäen merkkiaineena ^{18}F-FDG:tä ja radiovettä osoittautui käyttökelpoiseksi menetelmäksi haimakasvaimien erotusdiagnostiikassa. Lisäksi ^{18}F-FDG-PET/TT oli hyödyllinen haimasyövän etäpesäkkeiden löytämisessä. Tutkimus osoitti myös ^{18}F-DOPA-PET kuvantamisen olevan luotettava menetelmä insulinoomien ja muiden vatsan alueen NE-kasvaimien ensivaiheen diagnostiikassa sekä levinneisyyden arvioinnissa, etenkin muiden kuvantamislöydösten ollessa ristiriitaisia. PET kuvantamisella oli merkittävä vaikutus potilaiden kliiniseen hoitokäytäntöön sekä haima- että NE-kasvaimissa.

Avainsanat: haimakasvain, neuroendokriininen kasvain, positroniemissiotomografia, fluorideoxyglukoosi, dihydroksifenylalaniini, radiovesi, diagnostinen kuvantaminen

TABLE OF CONTENTS

ABBREVIATIONS

^{11}C-5-HTP	^{11}C-5-hydroxytryptophan
^{18}F-FDG	^{18}F-fluoro-2-deoxyglucose
^{18}F-FDG-6-PO_4	^{18}F- fluoro-2-deoxyglucose-6-phosphatase
^{18}F-DOPA	^{18}F-hydroxyphenylalanine
^{18}Ga-DOTA-NOC	^{68}Ga- DOTA -1-Nal^3-octreotide
^{18}Ga-DOTA-TOC	^{68}Ga-DOTA-D-Phe^1-Tyr^3-octreotide
^{15}O-H_2O	Radiowater
AADC	Aminoaciddecarboxylase
AIP	Autoimmune pancreatitis
APUD	Amine precursor uptake and decarboxylation
BF	Blood flow
Bq	Becquerel
Ca19-9	Carbohydrate antigen 19-9
Ce	Contrast-enhanced
CEA	Carcinoembryonic antigen
CP	Chronic pancreatitis
CrA	Chromogranin A
CRC	Colorectal cancer
CRP	C-reactive protein
CT	Computed tomography
CTA	Computed tomography angiography
ERCP	Endoscopic retrograde cholangiopancreaticography
EUS	Endoscopic ultrasonography
FDA	Fluoro-dopamine
FDOPAC	6-fluoro-L-3,4-dihydroxyphenylacetic acid
FHVA	6-fluorohomovanillic acid
FNA	Fine-needle aspiration
FWHM	Full-width half-maximum
GEP	Gastroenteropancreatic
GI	Gastrointestinal
HL	Hodgkin lymphoma
HT	Serotonin
IPMN	Intraductal papillary mucinous neoplasm
MCA	Mucinous cystadenoma
MDCT	Multidetector row computed tomography
MEN	Multiple endocrine neoplasia
MIB	Monoclonal antibody against the Ki-67 antigen

MIBG	Metaiodobenzylguanidine
MRCP	Magnetic resonance cholangiopancreaticography
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer
NET	Neuroendocrinetumor
NHL	Non-Hodgkin lymphoma
NOPR	National Oncologic PET Registry
NPV	Negative predictive value
OMFD	3-O-methyl-fluorodopa
PET	Positron emission tomography
PET/CT	Positron emission tomography-computed tomography
PHH	Primary hyperinsulinemic hypoglycemia
PPV	Positive predictive value
ROC	Receiver operating characteristics
ROI	Region of interest
RI	Retention index
SCA	Serous cystadenoma
SMA	Superior mesenteric artery
SR	Somatostatin receptor
SRS	Somatostatin receptor scintigraphy
SST	Somatostatin
SUV	Standardized uptake value
SUV/BF	Metabolism/blood flow ratio
Sv	Sievert
TAC	Time activity curve
UICC	The International Union Against Cancer
US	Ultrasonography
VIP	Vasoactive intestinal peptide
VMAT2	Vesicular monoamine transporter type 2
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which are referred to in the text by the corresponding Roman numerals, I–V.

I Saila Kauhanen, Gaber Komar, Marko Seppänen, Kirsti Dean, Heikki Minn, Sami Kajander, Irina Rinta-Kiikka, Kalle Alanen, Ronald Borra, Pauli Puolakkainen, Pirjo Nuutila, Jari Ovaska: A prospective diagnostic accuracy study of ^{18}F-FDG-PET/CT, MDCT and MR imaging in primary diagnosis and staging of pancreatic cancer, *in press,* Ann Surg (2009)

II Gaber Komar*, Saila Kauhanen*, Kaisa Liukko, Marko Seppänen, Sami Kajander, Jari Ovaska, Pirjo Nuutila, Heikki Minn: Decreased Blood Flow with Increased Metabolic Activity: a Novel Sign of Aggressive Tumor Aggressiveness, Clin Cancer Res 15;5511(2009)
** These authors contributed equally to this work*

III Saila Kauhanen, Marko Seppänen, Heikki Minn, Risto Gullichsen, Anna Salonen, Kalle Alanen, Riitta Parkkola, Olof Solin, Jörgen Bergman, Timo Sane, Jorma Salmi, Matti Välimäki, Pirjo Nuutila: Fluorine-L-Dihydroxyphenylalanine (^{18}F-DOPA) Positron Emission Tomography as a Tool to Localize an Insulinoma or β-cell Hyperplasia in Adult Patients. J Clin Endocrinol Metab 4;1237(2007)

IV Saila Kauhanen, Marko Seppänen, Pirjo Nuutila: Premedication with Carbidopa Masks Positive Finding of Insulinoma and Beta Cell Hyperplasia in ^{18}F-dihydroxy-phenyl-alanine Positron Emission Tomography. Correspondence. J Clinical Oncology 10;5307(2008)

V Saila Kauhanen, Marko Seppänen, Jari Ovaska, Heikki Minn, Jörgen Bergman, Pirkko Korsoff, Pasi Salmela, Juha Saltevo, Timo Sane, Matti Välimäki, Pirjo Nuutila: The Clinical Value of ^{18}F-Fluoro-Dihydroxyphenylalanine Positron Emission Tomography in Primary Diagnosis, Staging and Restaging of Neuroendocrine Tumors. Endocrine-Related Cancer 16;255(2009)

1 INTRODUCTION

Pancreatic and neuroendocrine tumors (NETs) share common diagnostic problems. The differential diagnosis of the lesion and the staging of the disease is a challenge for conventional imaging methods such as computed tomography (CT), magnetic resonance imaging (MRI), and somatostatin receptor scintigraphy (SRS). These modalities have shown limited ability in primary diagnosis of the tumor, or in detection of local invasion or small-volume metastatic disease.

In the case of pancreatic cancer, preoperative evaluation of resectability fails to identify up to 25% of patients who are found to be unresectable at surgical exploration. Pancreatic adenocarcinoma is an aggressive tumor with a propensity for early dissemination. At the time of diagnosis, approximately 40% of patients have metastatic disease, while another 40% present with locally advanced disease. Further, in patients with NETs, primary tumor is not localized in 20% to 50% of cases using conventional imaging, with gastrointestinal (GI) NETs being particularly elusive. The failure of conventional imaging to precisely define the primary tumor, and the extent of the tumor burden results in unnecessary surgical risk, delay in appropriate systemic oncological treatments, and increase in health costs. Therefore, the accurate identification of surgical candidates is crucial for the appropriate management of patients with pancreatic tumor or NET.

Diagnostic imaging of both pancreatic tumors and NETs has evolved during recent years, but current conventional imaging techniques still lack sensitivity. Positron emission tomography (PET) using different tracers has been introduced with promising results in these tumors. Especially integrated PET/CT has improved diagnostic accuracy with better anatomical orientation in image data. The most commonly used PET tracer, fluorodeoxyglucose (^{18}F-FDG), has been widely adopted in oncological imaging, although its role in pancreatic cancer is still unclear. Further, radiowater (^{15}O-H_2O) as tracer in PET imaging is a promising method in assessing tumor blood flow (BF). Antiangiogenesis agents are being developed, and the ability to monitor tissue perfusional changes before macroscopic changes are evident will be critical in patient management. In addition, perfusion imaging could be the method for differential diagnosis of pancreatic lesions. Recently, PET using the aminoacid precursor, dihydroxyphenylalanine (^{18}F-DOPA), has emerged as a new imaging tool for diagnosis of NETs, with improved tumor detection and staging compared to conventional imaging.

This study was initiated to investigate the role of PET imaging using different tracers including ^{18}F-FDG, ^{15}O-H_2O, and ^{18}F-DOPA, in patients with pancreatic tumors and NETs. The diagnostic accuracy of PET was compared to conventional imaging methods.

2 REVIEW OF THE LITERATURE

2.1 Positron emission tomography-computed tomography (PET/CT)

2.1.1 Principles of PET/CT

PET is a non-invasive nuclear imaging method, which enables *in vivo* measurements of physiological and biochemical processes quantitatively using short-lived positron emitting radionuclides, such as ^{18}F, ^{11}C, and ^{15}O. These radionuclides have a nuclear imbalance, *i.e.* an excess of protons. A wide range of natural substrates, substrate analogs or pharmaceuticals that are markers for specific biochemical processes can be labeled with a these positron emitting radioisotopes. After intravenous administration of the labeled compound, the positrons are emitted from the isotope nucleus. As the radioisotope undergoes positron emission decay to stabilize the nucleus, the excess proton is converted to a neutron and a positron is emitted. The emitted positron travels a short distance (0.35 millimeters) gradually losing its energy and finally it collides with an electron. The process is called annihilation, and two 511 kilo-electron volt photons are emitted in opposite directions.

The PET scanner detects the two simultaneously occurring high energy photons from the annihilation using detectors arranged in a ring-shaped pattern around the patient. The detectors record and send the raw data to the processing unit tomographic image reconstruction. To achieve quantitative measurements several corrections using mathematical models need to be applied (*i.e.* tissue attenuation). Standardized uptake values (SUVs) are a measure of the concentration of a radiotracer in a defined region divided by the injected dose normalized for the patient's body weight.

The introduction of hybrid PET/CT in the late 1990s (Beyer *et al.*, 2000) added a major dimension to the utility of PET, particularly in abdominal and oncological imaging. With PET/CT, areas of abnormal uptake can be localized to specific morphological structures such as lymph nodes, further aiding interpretation. CT performance has improved rapidly with the advent of multidetector arrays from the early 4-slice to more recent 64-slice scanners (2002). The increasing number of detector rows (slices) has been accompanied by faster rotation times. Further, significant advances have also been seen in hard- and softwares for CT.

2.1.2 Tracers

2.1.2.1 ^{18}F-fluorodeoxyglucose (^{18}F-FDG)

A glucose analogue, ^{18}F-FDG, is the most commonly used tracer in PET imaging. The utility of ^{18}F-FDG for imaging tumor cells is based on Warburg's observation that the increased metabolic demands of rapidly dividing tumor cells required adenosine

triphosphate generated by glycolysis (Miles & Williams, 2008). Like glucose, ^{18}F-FDG passes through cellular membrane and is phosphorylated by glucose 6-hexokinase *(Figure 1)*. After phosphorylation, phosphorylated ^{18}F-FDG (^{18}F-FDG-6-PO_4) enters the glycolytic pathway, but no significant dephosphorylation exists and it remains trapped. Therefore, the intracellular ^{18}F-FDG concentration increases with time in tissues with high glucose consumption. Malignant cells that demonstrate increased cellular metabolism have increased glycolysis and increased glucose transport (Bomanji *et al.*, 2001). The usefulness of ^{18}F-FDG-PET/CT in cancer diagnosis is based on this phenomenon. Overexpression of glucose transporter and increased enzyme activity of hexokinase lead to accelerated glucose and ^{18}F-FDG transport, phosphorylation, and intracellular trapping of phosphorylated ^{18}F-FDG.

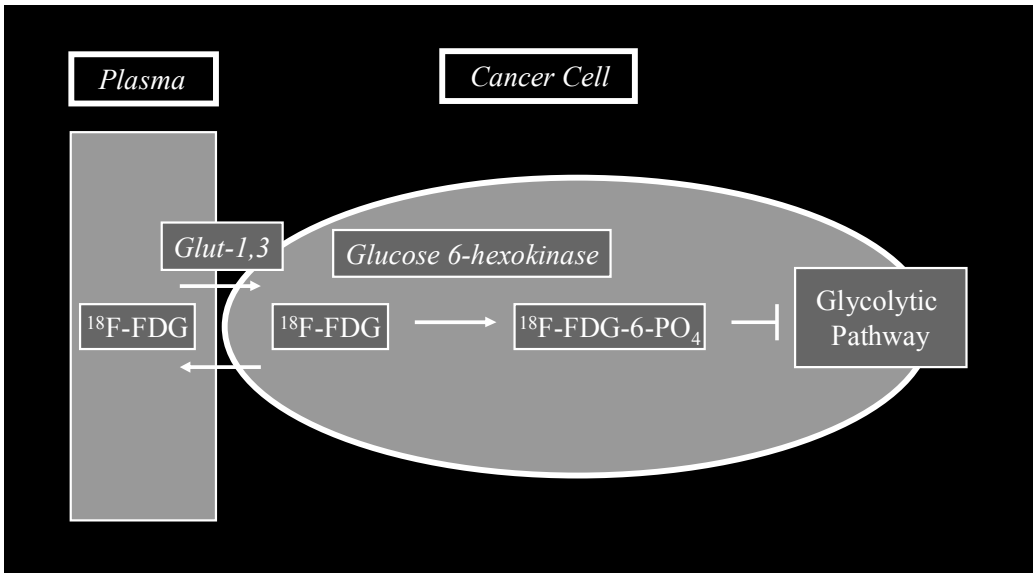


Figure 1. ^{18}F-FDG uptake by glucose transporters Glut 1 and 3, with subsequent phosphorylation and trapping of the phosphorylated ^{18}F-FDG (^{18}F-FDG-6-PO_4) in a cancer cell

2.1.2.1 Oxygen-15 labeled water (^{15}O-H_2O)

^{15}O-H_2O is an attractive tracer for monitoring tumor perfusion. It is metabolically and chemically inert, freely diffusible and has a short half-life (123 seconds), allowing rapid repetition of measurements. The method is based on the difference between arterial and tissue activity. ^{15}O-H_2O can be given to the patient intravenously as a bolus or infusion. To determine the tissue perfusion, blood from the artery is continuously withdrawn using a pump to measure radioactivity. The recent developments have also enabled extraction of the input curves directly from the images, making the procedure more patient-friendly compared to previously used invasive arterial blood sampling, and this new method has been found to be suitable for routine clinical applications (Liukko K.E *et al*., 2007).

2.1.2.3 [18]F-hydroxyphenylalanine ([18]F-DOPA)

NETs have the ability to take up amine precursors, like L-DOPA, which is then decarboxylated to dopamine. Increased activity of L-DOPA decarboxylase was found to be characteristic of NETs (Gazdar *et al.*, 1988). ^{18}F-DOPA was introduced as a specific tracer to image these tumors (Ahlström *et al.*, 1995). The radiolabeled DOPA is transported across the membrane by an aminoacid transporter, after which it is decarboxylated in fluoro-dopamine (FDA) and stored in vesicles *(Figure 2)*. The mechanism that influences the uptake of ^{18}F-DOPA in neuroendocrine tissues is not fully understood. ^{18}F-DOPA has been used for decades in neurological PET imaging, but so far only few studies of ^{18}F-DOPA- PET in NETs have been published. This is partly due to the demanding labeling procedure. Previous studies (Örlefors *et al.*, 2006;Koopmans *et al.*, 2006) have shown that oral premedication with carbidopa, an inhibitor of amino acid decarboxylase, improves the contrast in PET imaging by increasing the concentration and availability of ^{18}F-DOPA with NETs. Therefore, carbidopa premedication has become the standard procedure in patients undergoing ^{18}F-DOPA-PET imaging.

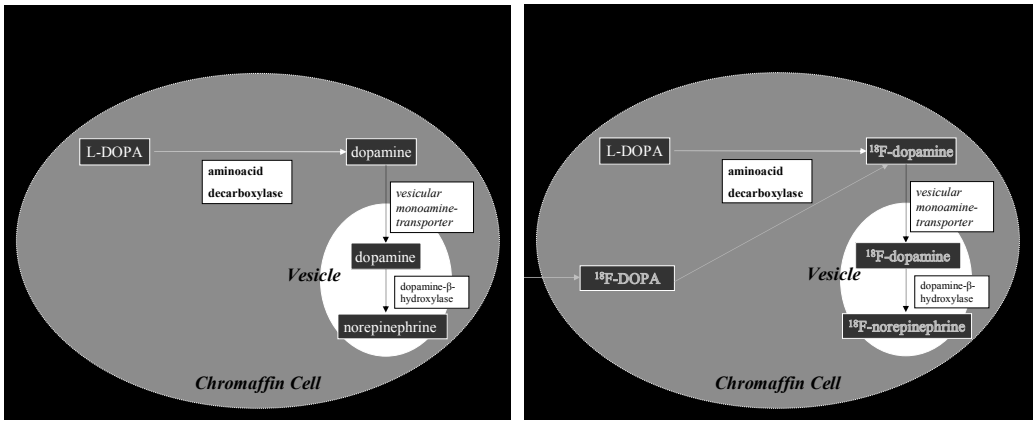


Figure 2. Uptake mechanism of aminoacid precursor ^{18}F-DOPA by NET chromaffin cell. The radiolabeled DOPA is transported across the membrane by an aminoacid transporter, after which it is decarboxylated in ^{18}F-dopamine and stored in vesicles.

2.2 [18]F-FDG-PET imaging in gastrointestinal (GI)-malignancies

At present, ^{18}F-FDG-PET is indicated in the primary diagnosis and staging of GI-malignancies by US Medicare in colorectal and esophageal cancer, and lymphoma. The National Oncologic PET Registry (NOPR) has been developed in response to the proposal to expand coverage for ^{18}F-FDG-PET/CT to include cancers and indications not presently eligible for Medicare reimbursement. *Table 1* shows coverages for ^{18}F-FDG-PET/CT in GI-malignancies both in US Medicare and in NOPR.

Table 1. Indications of ^{18}F-FDG-PET in GI-malignancies in US Medicare and the National Oncologic PET Registry (NOPR)

Currently covered by Medicare	Covered by NOPR
Colorectal cancer: diagnosis, staging, restaging	Pancreatic cancer Gallbladder cancer
Esophageal cancer: diagnosis, staging, restaging	Hepatocellular cancer Cholangiocarcinoma
Lymphoma: diagnosis, staging, restaging	Gastric cancer Peritoneal carcinosis

2.2.1 In primary tumor diagnosis

Esophageal cancer. Current clinical practice employs ^{18}F-FDG-PET imaging in preoperative staging of esophageal cancer. It has been shown by many to have diagnostic advantages in the initial staging of esophageal cancer over conventional imaging especially in detecting metastasis. According to a recent prospective multicenter study, the planned management was changed on the basis of the PET results in 38% of the patients (Chatterton *et al.*, 2009). *In primary diagnosis* of esophageal cancer, a prospective study of 74 patients reported that ^{18}F-FDG-PET detected the primary tumor in 95% of the patients but still included four false-negative findings in patients with pT1 lesions smaller than 8 mm (Flamen *et al.*, 2000). Similar poor sensitivities were reported by other study groups in patients with pT1-T2 tumors (Kato *et al.*, 2005;Pfau *et al.*, 2007). Kato and co-authors showed an association between the ^{18}F-FDG uptake and depth of invasion, occurrence of lymph node metastasis, and lymphatic invasion, but this finding has not been corroborated by others (Kato *et al.*, 2002). Nowadays, endoscopic ultrasonography (EUS) provides an accurate and cost-effective method for T-staging of disease, and has been shown to affect preoperatative management (Gan *et al.*, 2007). PET, on the contrary, is limited in its ability to demonstrate the depth of tumor invasion due to its reduced spatial resolution. Until recently, there were only few studies that had clearly demonstrated the superiority of integrated PET/CT over PET and CT performed separately in patients with esophageal cancer. Combined PET/CT can suggest the presence of pT4 disease, but has a minor role otherwise in T-staging (Bar-Shalom *et al.*, 2005).

Colorectal cancer (CRC). The evidence of the usefulness of ^{18}F-FDG-PET *in primary diagnosis* of CRC is limited so far (Abdel-Nabi *et al.*, 1998;Kantorova *et al.*, 2003;Heriot *et al.*, 2004). Both ^{18}F-FDG-PET and ^{18}F-FDG-PET/CT are very sensitive with a detection rate between 95-100% (Shin *et al.*, 2008). Kantorova and co-authors reported that ^{18}F-FDG-PET revealed extra lesions in 11 of 38 patients missed by conventional imaging and had an impact on treatment in 16% of the patients (Kantorova *et al.*, 2003). Although only a few studies have evaluated ^{18}F-FDG-PET in the initial staging of CRC, it is possible to hypothesize that integrated PET/CT may be more effective in primary CRC. A prospective study including one hundred patients, who underwent combined PET/CT in the evaluation of primary CRC, showed that 24% of the patients management was changed compared to the results of CT, and further, PET/CT scan detected 15 intra-abdominal metastatic lesions more than CT (Park *et al.*, 2006). This finding is extremely

important if neo-adjuvant chemoradiation therapy is being considered. However, PET/CT has limitations including the fact that small tumors (less than 5-10 mm) and those of mucinous type may show significantly lower ^{18}F-FDG uptake than other histologic types. PET/CT also has limited value in T-staging due to its weakness in differentiating pT2/pT3 and pT3/pT4 tumors. Further studies are needed to evaluate the cost-effectiveness of PET/CT as a replacement for CT in primary diagnosis of CRC, as well as to select most appropriate patients for application of PET/CT.

2.2.2 In staging

Esophageal cancer. In N-staging of esophageal cancer, ^{18}F-FDG-PET has been shown to have variable sensitivity of 24-82%, which although disappointing, has been shown in the same series to be superior to CT (11-62%) (Chowdhury *et al.*, 2008). According to a recent meta-analysis, the pooled sensitivities of EUS, CT, and ^{18}F-FDG-PET for regional lymph-node metastases were 80%, 50%, and 57%, and specificities 70%, 83%, 85%, respectively (van Vliet *et al.*, 2008). An important limitation of ^{18}F-FDG-PET in staging occurs in the lymphatic drainage adjacent to the site of the primary lesion. The uptake of the primary tumor obscures interpretation of the adjacent regional lymph node basins, and therefore EUS has shown better sensitivity in assessing local lymph node metastases in these regions (Flamen *et al.*, 2000;Kato *et al.*, 2002). The study of 74 patients with esophageal cancer showed a sensitivity of 33% for ^{18}F-FDG-PET when a corresponding sensitivity of 81% was achieved by EUS in the diagnosis of local nodal staging (Flamen *et al.*, 2000). Although the sensitivity of local lymph node spreading was lower than in EUS, still ^{18}F-FDG-PET had additional diagnostic value in 22% of the study patients according to this study. On the contrary, a prospective study in 48 patients who underwent esophagectomy and lymph node dissection, showed ^{18}F-FDG-PET to be more accurate than CT or EUS also in N-staging of disease (Choi *et al.*, 2000). The role of integrated ^{18}F-FDG-PET/CT was assessed by Yuan and co-authors and they demonstrated an additional value of integrated PET/CT in nodal staging (Yuan *et al.*, 2006). *In M-staging*, based on the meta-analysis, pooled sensitivity and specificity were 71% and 93% for ^{18}F-FDG-PET and 52% and 91% for CT, respectively (van Vliet *et al.*, 2008). Prospective studies have shown significantly higher sensitivities for ^{18}F-FDG-PET in detecting metastatic disease compared to combined findings of CT-EUS (78% *vs.* 37%) (Heeren *et al.*, 2004) or CT (100% *vs.* 29%) (Block *et al.*, 1997). Further, combined PET/CT has been shown to have superior accuracy in the staging and restaging of esophageal cancer compared with PET and CT performed separately (Bar-Shalom *et al.*, 2005). Especially better specificity was obtained by PET/CT compared with PET (81% *vs*. 59%).

CRC. The European consensus conference categorized ^{18}F-FDG-PET as an established technique to detect relapsing CRC (Reske & Kotzerke, 2001). The indications for ^{18}F-FDG-PET in CRC are staging, restaging, and detection of recurrence (Reske & Kotzerke, 2001;Larson *et al.*, 2004;Hustinx, 2004), as well as in recent studies in assessing the effect of oncological treatments (Stokkel *et al.*, 2001;Kostakoglu & Goldsmith,

2003). A meta-analysis of 11 articles has demonstrated the high accuracy of ^{18}F-FDG-PET in the evaluation of CRC compared with conventional imaging, with an impact on treatment in a third of the study patients (Huebner *et al.*, 2000). *In N-staging*, several study groups have reported low sensitivities combined with high specificities (29-37% and 83%-96%, respectively) (Shin *et al.*, 2008). Also limited advantages in N-staging have been observed when integrated PET/CT is used. On the other hand, *in M-staging* of CRC*,* both PET and PET/CT have been very successful. The study by Flamen estimated ^{18}F-FDG-PET to be more sensitive compared with CT in detecting pathological lymph nodes located in mesenterium, retroperitoneum, and peritoneum (Flamen *et al.*, 1999). Moreover, extrahepatic metastases located mainly in lungs are detected better using ^{18}F-FDG-PET compared to multidetector row CT (MDCT) (Lowe *et al.*, 1998;Flamen *et al.*, 1999). Several studies has compared ^{18}F-FDG-PET with conventional imaging (CT, ultrasonography (US), MRI) in the diagnosis of liver metastases with a sensitivity range of 76-90% *vs.* 52-66%, respectively (Ruers *et al.*, 2002;Kinkel *et al.*, 2002). When all metastases were analyzed, a sensitivity of 93% was achieved for ^{18}F-FDG-PET and of 69% for MDCT (Valk *et al.*, 1999). Very recently, PET/CT has also been compared to contrast-enhanced (ce) CT and liver MRI with encouraging results. A study by Kong et al. showed high sensitivities of 98% and specificities of 100% in both PET/CT and liver MRI, although PET/CT was less sensitive for subcentimeter liver lesions compared to liver MRI (Kong *et al.*, 2008).

Abdominal lymphoma. Based on the International Harmonization Project recommendations ^{18}F-FDG-PET is strongly recommended *in the initial staging* before treatment in patients with routinely ^{18}F-FDG avid lymphomas (Hodgkin lymphoma (HL) and aggressive non-Hodgkin lymphomas (NHL) such as diffuse large B-cell lymphoma as well as *in the restaging* (assessment of response to treatment after 6 to 8 weeks post-chemotherapy). Lymphomas differ with regard to their glucose metabolic activity. For instance, aggressive forms of NHL (large B-cell, mantle cell, and high-grade follicular lymphoma) have approximately three times higher SUVs than some other subtypes of NHL, predominantly low-grade lymphomas, marginal zone, or small cell lymphomas (Jerusalem *et al.*, 2001). Therefore, the staging accuracy of ^{18}F-FDG-PET is determined by the degree of ^{18}F-FDG uptake in individual lesions and potential limitations exist in the diagnosis of subtypes of NHL, such as mucosa-associated lymphoid tumor type and peripheral T-cell lymphoma (Elström *et al.*, 2003). Still more studies are needed to determine the diagnostic performance of ^{18}F-FDG-PET in the staging of the different histologic subtypes of NHL. Many studies have demonstrated the role of ^{18}F-FDG-PET *in the initial staging* of lymphoma. According to these studies, clinical management was changed in 18% to 40% of the patients (Jhanwar & Straus, 2006). The main advantage of the ^{18}F-FDG-PET scan is its ability to detect metabolic changes in areas involved in malignant lymphoma before structural changes become visible. Related to this, early studies already reported the usefulness of ^{18}F-FDG-PET in the evaluation of bone marrow involvement in lymphoma. In one prospective study of 78 patients, it showed

a sensitivity of 81% and a specificity of 100% for detection of bone marrow disease (Moog *et al.*, 1998).

2.2.3 In restaging

Esophageal cancer. In the diagnosis of recurrence, a high sensitivity of ^{18}F-FDG-PET was observed but it was combined with low specificity. The low specificity is explained by the high number of false-positive findings in patients with anastomotic stenosis (Flamen *et al.*, 2000). Based on this, reports concerning the usefulness of ^{18}F-FDG-PET/CT for recurrent esophageal cancer are limited (Flamen *et al.*, 2000;Kato *et al.*, 2004). At present, PET/CT is not necessary in the majority of patients with suspected disease relapse; most patients can be adequately investigated using MDCT.

CRC. In patients with elevated carcinoembryonic antigen (CEA), the sensitivity of ^{18}F-FDG-PET was as high as 100% combined with a specificity of 71% in localization of disease lesions (Tutt *et al.*, 2004). In addition, based on a study by Selzner and co-authors, ^{18}F-FDG-PET was a significantly more sentivitive imaging method compared to MDCT (93% *vs.* 53%) in detecting local recurrence (Selzner *et al.*, 2004). Good results have also been reported in showing local recurrence after radiotherapy (Moore *et al.*, 2003). Recent studies comparing PET and PET/CT, showed increased accuracy and certainty of locating lesions of postoperative CRC recurrence (from 74-75% to 90-96%)(Cohade *et al.*, 2003;Votrubova *et al.*, 2006). The value of contrast-enhancement in PET/CT scanning needs to be further studied. A recent retrospective study on recurrent CRC reported that cePET/CT revealed additional information in 39 of 54 patients compared with non-cePET/CT (Soyka *et al.*, 2008). Promising results are also expected in routine follow-up, although prospective studies on the real clinical advantage and cost-effectiviness are so far missing.

Abdominal lymphoma. During the last decade, several studies have shown ^{18}F-FDG-PET to be especially sensitive for *restaging,* in patients with HL sensitivity of 85% (lesion-based) and 100% (patient-based) and with NHL of 100% (lesion-based) and 60% (patient-based) (Kwee *et al.*, 2008). Further, the value of ^{18}F-FDG-PET in restaging has been shown to be the ability to distinguish between posttreatment fibrosis and residual viable tumor tissue (Kwee *et al.*, 2008). Concerning the role of integrated PET/CT, so far only five studies have been published on staging or restaging of lymphomas, although none of these studies was prospective (Freudenberg *et al.*, 2004;Schaefer *et al.*, 2004;Rhodes *et al.*, 2006;la Fougere *et al.*, 2006;Raanani *et al.*, 2006). The addition of PET/CT to CT changed the management decisions in 25% of NHL and 33% of HL patients, mostly in the early disease stage (Raanani *et al.*, 2006). According to a study by Schaefer et al., the sensitivity of non-cePET/CT and ceCT was 88% and 50%, while the specificity was 100% and 90%, respectively (Schaefer *et al.*, 2004). The role of cePET/CT versus non-cePET/CT is still unclear; some studies have found considerable impact of intravenous contrast in oncological imaging (Pfannenberg *et al.*, 2007). Baseline PET (Hernandez-Maraver *et al.*, 2006) or PET/CT (Kwee *et al.*, 2008) are observed to be superior to

CT for treatment monitoring and response assessment of lymphoma, but further studies should focus on measuring the response or prognostic indicator of ^{18}F-FDG-PET on the basis of SUV.

2.3 Pancreatic tumors

2.3.1 Pathology

Pathologically, tumors in the pancreas are divided into malignant tumors including adenocarcinoma, inflammatory tumors usually caused by *e.g.* chronic pancreatitis (CP), cystic neoplasms (benign, premalignant, malignant), and NETs. However, from the clinical point of view, tumors in the ampulla of Vateri, duodenum, and distal biliary tract can also be the cause of a pancreatic mass identified on imaging methods.

Adenocarcinoma. Pattern of spread. Ductal adenocarcinoma of the pancreas is a highly aggressive tumor with early local spread beyond the pancreas, predominantly to the retroperitoneum, but also with invasion of adjacent great vessels and organs. Tumor size and histologic grade influence the extent of spread. *Local spread* takes place predominantly within the pancreatic parenchyma and extension within the pancreatic duct. The most frequent direct extension beyond the pancreas involves the retroperitoneal tissues. The tumor extends in any direction in the retroperitoneum and may also invade great vessels such as the portal vein, the superior mesenteric artery (SMA) and vein, and the celiac artery. Anterior extension may lead to perforation of visceral peritoneum and spread within the peritoneal cavity. Invasion of intrapancreatic perineural structures and, subsequently, the retroperitoneal nerve plexus is a typical finding in pancreatic cancer (Hermanek, 1998). *Lymphatic spread*ing of the pancreas is multidirectional. Usually, the lymph nodes near the primary tumor are first involved. After lymphatic invasion, isolated tumor cells or small clusters of tumor cells may reach the sinus of regional lymph nodes. Isolated tumor cells in regional lymph nodes were found in 75% of node-negative patients with resection of adenocarcinoma (Hosch *et al.*, 1997). Instead, micrometastases can be diagnosed only after the adhesion, implantation, stromal resection, and proliferation of tumor cells within specific lymphatic tissue (Hermanek, 1999). *Venous invasion* is a frequent finding both in the advanced and in the early stages. Venous drainage follows the portal vein and, therefore, the liver is the first metastatic site. In more than 50% of small carcinomas (size less than 2 cm) the regional lymph nodes are involved. Even in carcinomas limited to the pancreas, lymph node metastases are frequent.

CP is an inflammatory process leading to irreversible damage of the parenchyma and ducts, and progressive exo- and endocrine functional impairment. The key histologic features of CP are pancreatic fibrosis, acinar atrophy, chronic inflammation, and distorted and blocked ducts. Additional histologic features have been described such as lymphocytic and plasma cell infiltrate in autoimmune pancreatitis (AIP) (Witt *et al*., 2007). Understanding of the pathogenesis of CP has improved in recent years. Especially important advances have been made with respect to the mechanism responsible for the

development of fibrosis following repeated acute attacks of pancreatic necroinflammation, the so-called fibrosis-necrosis concept. This concept is supported by both clinical and experimental data (Witt *et al.*, 2007). Pancreatic stellate cells play in the main role in fibrogenesis, particularly when activated directly by toxic factors (ethanol, oxidant stress).

Cystic neoplasms. Pancreatic cystic tumors are divided into four categories: serous tumors (serous cystadenoma (SCA), serous cystadenocarcinoma), mucinous tumors (mucinous cystadenoma (MCA), mucinous cystadenocarcinoma, intraductal papillary mucinous neoplasm (IPMN)) and solid pseudopapillary tumors (Garcea *et al.*, 2008). Of the cystic lesions of the pancreas, 10% are neoplastic including MCA and SCA. MCAs are malignant or premalignant, whereas only 1% of the SCAs are considered malignant. Pseudocysts, which comprise the majority of all cystic lesions in the pancreas, are collections arising from around the pancreas lacking of epithelial lining. Pseudocysts normally contain necrotic fat and a mixture of necrotic cells, including neutrophils surrounded by granulation tissue. This granulation tissue matures to form a fibrotic pseudocapsule. Serous cystic neoplasms are benign lesions in the pancreas with the macroscopic appearance of numerous tightly packed small cysts with a stellate scar. Mucinous cystic neoplasms of the pancreas are mucin-producing cystic tumors with an ovarian-like stroma, and they are usually found in the body and tail of the pancreas. They are solid lesions with a size range of 6-35 cm, consisting of several large cysts with thick fibrotic walls. They display no communication with the pancreatic ductal system unless fistulation has occurred. The content of the cyst is usually thick, haemorrhagic, watery or necrotic. Solid areas could include high-grade dysplasia or invasive carcinoma. IPMN histologically displays neoplastic mucin-producing cells arranged in a papillary pattern. Mucin production leads to intraductal mucin accumulation and, subsequently, dilation of pancreatic ducts. IPMN produces a lesion over 1 cm in size with a range of cell atypia (dysplasia → carcinoma), and a different grade of cell atypia is seen in the same lesion. The precise rate of dysplasia-carcinoma progression is unknown, but it has been estimated to range from 5 to 7 years. IPMN is divided according to duct type; branch-, main-, or mixed-duct type. A branch- and mixed-duct type is found in younger patients and has a lower malignant potential. They rarely progress towards malignancy. On the other hand, the main-duct type is associated with malignant etiology and poorer survival. (Garcea *et al*., 2008)

Pancreatic NETs have heterogenous microscopic findings, and immunohistochemical staining markers, such chromogranin A (CrA), synaptophysin, CD 56 (a neural cell adhesion molecule), and neuron-specific enolase, can usually confirm the neuroendocrine origin. The malignant nature of pancreatic NETs has been defined by assessing the local invasion of the tumor, and metastases to lymph nodes and distant organs. Proliferative indices (Ki-67, monoclonal antibody developed against the Ki-67 antigen (MIB)) and the mitotic index are important prognostic factors in pancreatic NETs *(Table 2)*. Insulinomas are malignant in 5-15%, whereas the other pancreatic NETs are malignant in 50-90%. In the latter, metastases usually develop initially in regional lymph-nodes, later in the liver, and subsequently, in distant sites such as bone (Öberg & Eriksson, 2005).

Table 2. Criteria for assessing the prognosis of pancreatic NETs based on World Health Organization (WHO) criteria (according to Klöppel *et al*., 2007)

Biological behavior	Metastases	Invasion*	Histological differentiation	Tumor size (cm)	Angioinvasion	Ki-67 index (%)	Hormonal syndrome
Benign	-	-	Well differentiated	≤1	-	<2	-/+**
Benign or low-grade malignant	-	-	Well differentiated	>2	-/+	<2	-/+***
Low-grade malignant	+	+	Well differentiated	>3	+	>2	+***
High-grade malignant	+	+	Poorly differentiated	Any	+	>20	-

* invasion of adjacent organs (e.g. duodenum, stomach)
** insulinomas
*** insulinomas and other functioning tumors (e.g. glucagonomas)

2.3.2 Classification

Adenocarcinoma. In Western countries the International Union against Cancer (UICC) classification is used in pancreatic adenocarcinoma. Classification of anatomic extent includes T, N, and M categories *(Table 3)*.

Table 3. TNM classification according to UICC (according to Sobin, 2008)

TNM clinical classification for pancreatic adenocarcinoma	
T –	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T_{is}	Carcinoma in situ
T1	Tumor limited to pancreas, 2 cm or less in diameter
T2	Tumor limited to pancreas, more than 2 cm in diameter
T3	Tumor extends into any of the following: duodenum, bile duct, peripancreatic tissue
T4	Tumor extends into any of the following: stomach, spleen, colon, adjacent large vessels
N –	Regional lymph-nodes
NX	Regional lymph-nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
	N1a Metastasis in a single regional lymph node
	N1b Metastasis in multiple regional lymph nodes
M –	Distant metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Cystic neoplasms. Many forms of classification of pancreatic cysts exist at present. One form of classification is based on the nature of the cyst wall lining (degenerative changes in solid tumors, no lining, mucinous epithelium-, serous-, squamous-, and acinar-cell-lined), and the other according to origin (epithelial-, exocrine-, unknown/mixed-, endocrine-, and mesenchymal origin).

Pancreatic NETs. Pancreatic NETs are divided clinically into functional and non-functional forms. Functional forms secrete biologically active peptides (gastrin, insulin, glucagon, vasoactive intestinal peptide (VIP), somatostatin, growth hormone releasing factor, adrenocorticotropic hormone, serotonin, prostaglandins) causing syndromes. Even over 70% of non-functional pancreatic NETs secretes substances, *e.g.* pancreatic polypeptide, neurotensin, ghrelin, neuron-specific enolase, Crs, each of which does not cause specific symptoms (Klöppel & Anlauf, 2005). In general, histologic classification of pancreatic NETs has failed to predict growth patterns for a given tumor. However, this classification will allow a more standardized comparison of results of different studies. A TNM classification for pancreatic NETs has also been proposed, which provides a more standardized assessment of patients and has prognostic clinical value (Rindi *et al.*, 2006) *(Table 4).*

Table 4. TNM classification of pancreatic NETs according to WHO classification

pTNM classification for pancreatic NETs	
T –	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to pancreas and size less than 2 cm
T2	Tumor limited to pancreas and size 2-4 cm in diameter
T3	Tumor limited to pancreas and size over 4 cm or invading duodenum or bile duct
T4	Tumor extends to the wall of adjacent large vessels, stomach, spleen, colon, adrenal gland
N –	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Presence of regional lymph node metastasis
M –	Distant metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

2.3.3 Epidemiology

Worldwide, *adenocarcinoma of the pancreas* causes more than a quarter of a million deaths annually and is the 13th most common cancer (Parkin *et al.*, 2005). In 2007, the prevalance in the Finnish population was 691 cases and the incidence 6.7 and 9.2 cases per 100,000, respectively, for females and males (Finnish Cancer Registry, 2007). Smoking, family history, and chronic pancreatitis are unequivocal risk factors for pancreatic adenocarcinoma. Smoking is consistently reported as an environmental risk factor accounting for approximately 25% of all pancreatic cancers (Lowenfels & Maisonneuve, 2006). Cigarette smoking doubles the risk of pancreatic cancer, the effect being related to its duration and intensity. Over the past 30 years, incidence rates of pancreatic cancer have been decreasing in males and remained stable in females in Nordic countries (Nagenthiraja *et al.*, 2007). This is worth noticing considering the changes in smoking habits which have occurred over the last decades. It emphasizes our lack of understanding of the aetiology of pancreatic cancer. At the same time as smoking

is decreasing in the population, obesity is increasing. Recently, it has been observed that an excess bodyweight is associated with increased risk of malignancies also including pancreatic cancer (Renehan *et al.*, 2008). A family history of pancreatic adenocarcinoma in a first-degree relative is associated with a 2.5-5.3-fold increased risk of pancreatic cancer (Fernandez *et al.*, 1994; Silverman *et al.*, 1999; Schenk *et al.*, 2001; Ghadirian *et al.*, 2002). The number of genetic disorders, such as hereditary pancreatitis, familial adenomatous polyposis, familial multiple mole melanoma, Peutz-Jeghers syndrome, hereditary nonpolyposis CRC, familial breast cancer, and cystic fibrosis, is associated with increased risk of pancreatic adenocarcinoma. In contrast, there is a little evidence of alcohol consumption being associated with pancreatic cancer (Michaud *et al.*, 2001). The data showing that the risk of pancreatic cancer is similar in patients with alcohol-related and non-alcohol-related CP argue against a role for the direct effects of alcohol as a cause (Karlson *et al.*, 1997). There are studies documenting a positive association with diabetes mellitus (Huxley *et al.*, 2005) and CP (Karlson *et al.*, 1997) in pancreatic adenocarcinoma, although the etiologic evidence is still unclear.

The reported incidence of *CP* in western countries ranges from 3.5-10:100,000 (Witt *et al.*, 2007). The incidence of *pancreatic cystic lesions* according to an autopsy study is high, up to 24% (Kimura *et al.*, 1995) and, according to a radiological series, up to 1% (Spinelli *et al.*, 2004). *Pancreatic NETs* account for only 1-3% of all neoplasms of the pancreas with a clinical detection rate of 1:100,000. Asymptomatic pancreatic NETs appear to be much more common according to large autopsy studies, occurring in 0.5-1.5% of autopsies, and are undiagnosed (Öberg & Eriksson, 2005). The relative frequency of pancreatic NETs varies in different series, but most studies suggest a relative order of: non-functional pancreatic endocrine tumors > insulinoma > gastrinoma > glucagonoma > VIPoma, somatostatinoma > others (Metz & Jensen, 2008). Inherited disorders like multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau disease, von Recklinghausen's disease, and tuberous sclerosis, have an increased incidence of pancreatic NETs. In patients with MEN1, 80-100% develops non-functional pancreatic NET, 50-60% gastrinomas, and 20% insulinomas.

2.3.4 Diagnosis

The main issue in the diagnosis of pancreatic tumors is whether it is benign, premalignant, or malignant, and if pre- or malignant, is it operable. In addition, some benign pancreatic tumors have functional activity, and therefore operation is required. The diagnosis is based on symptoms, in combination with biochemical and imaging findings.

2.3.4.1 Tumor markers, cyst fluid analysis, and biochemical diagnosis

In *pancreatic adenocarcinoma,* the sialylated Lewis blood group carbohydrate antigen 19-9 (Ca19-9), is expressed in more than 80% of pancreatic cancers (Gattani *et al.*, 1996), although it lacks specificity. Ca19-9 is often elevated in several other types of cancers, including hepatocellular cancer, gastric cancer, CRC, and ovarian cancer. Also patients who are Lewis^{a-b-} blood group (approximately 4% of the general population) do

not produce this antigen (Tempero *et al.*, 1987). In addition, only half of cancers less than 2 cm in diameter are associated with elevated Ca19-9 levels (Egawa *et al.*, 2004). It has been observed that Ca19-9 levels over 150 kU/l are associated with unresectability (Forsmark *et al.*, 1994;Schlieman *et al.*, 2003). However, biliary obstruction leading to jaundice also raises Ca19-9 levels, therefore in these patients, the cut-off has been increased to 300 kU/l (Kim *et al.*, 1999). A recent study by Halloran showed that Ca19-9 levels help to select patients with pancreatic malignancy for surgery or laparoscopic US (Halloran *et al.*, 2008). There are several novel tumor markers, like serum human chorion gonadotrophin β, Ca72-4 (Louhimo *et al.*, 2004) and syndecan-1 expression (Juuti *et al.*, 2005), which have been reported to be as strong and independent prognostic factors in pancreatic cancer.

In differential diagnosis of *cystic lesions*, cyst fluid analysis (viscosity, amylase, tumor markers) has proved to be beneficial (Sand & Nordback, 2005). In a meta-analysis of van der Waaij et al. they performed a pooled analysis of 450 patients from 12 studies who underwent cyst fluid analysis (van der Waaij *et al.*, 2005). A cyst fluid amylase concentration of less than 250 U/l was able to exclude pseudocyst with a sensitivity of 44% and a specificity of 98%. Further, a CEA less than 5 ng/ml suggested a benign etiology with an accuracy of 67%, whereas CEA levels over 800 ng/ml suggested a mucinous neoplasm (premaligant/malignant etiology) with an accuracy of 79%. In a study by Brugge et al. Ca19-9 less than 37 U/ml strongly suggested benign etiology with a specificity of 97% combined with a low sensitivity of only 19% (Brugge *et al.*, 2004). In addition, serum Ca19-9 has also been reported to have a high positive predictive value of 96% in differentiating malignant and benign pancreatic cystic lesions (Fernandez-del Castillo *et al.*, 2006). With regard to cytology, the same study showed a sensitivity, specificity, and accuracy of 35%, 83%, and 58%, respectively. It has also been observed that a combination of viscocity and CEA is the best marker of mucinous neoplasms. According to a study by Räty and co-authors, a novel marker, tumor-associated trypsin inhibitor, appears to be promising in the differential diagnosis of benign from malignant cystic pancreatic lesions (Räty *et al.*, 2004).

In pancreatic NETs, specific tumor markers, such as CrA, are described in detail on page 35. *Insulinomas* ectopically secrete insulin, resulting in inappropriate hyperinsulinemia, which causes hypoglycemic episodes. Biochemical diagnosis is based on 72-hour fast. A serum glucose level of less than 2.5 mmol/l with a concomitant insulin level greater than 6 mU/ml, combined with an increased C-peptide level greater than 0.33 nmol/l, establishes the diagnosis. *Gastrinomas* secrete gastrin, which causes hyperchlorhydria, thereby producing the Zollinger-Ellison syndrome. Fasting hypergastrinemia occurs in 97-99% of patients so this is usually the initial study arousing suspicion of gastrinoma (Metz & Jensen, 2008). Diagnosis of *glucagonoma* is based on an inappropriately increased serum glugacon level greater than 177 ng/l. The diagnosis of *VIPomas* requires specific symptoms (secretory diarrhea) associated with an increased VIP level greater than 50 pmol/l. *Somatostatinomas* produce somatostatin, although there is no reliable provocative test to confirm the presence of somatostatinoma in patients with typical

symptoms and no observable mass. Related to the role of pre- or perioperative fine-needle aspiration (FNA), a study by Saleh and co-workers showed that immunohistochemical staining was able to successfully distinguish NET from pancreatic adenocarcinoma in a small series of patients (Saleh *et al.*, 1996).

2.3.4.2 Non-invasive imaging

2.3.4.2.1 Multidetector row computed tomography (MDCT)

CT is the initial and most common imaging method used when abnormalities of the pancreas are suspected. Over the past two decades the use of helical CT has been replaced by MDCT. MDCT scanners have markedly improved the speed and quality of cross-sectional imaging. Intravenous contrast combined with faster scanners make it possible to acquire data over a large volume of tissue during different circulatory phases in the span of a single breath-hold. Following the administration of contrast, pancreatic tumor is relatively hypovascular (low attenuation), while normal pancreatic tissue increases in density. However, approximately 10% of pancreatic tumors are not seen by CT because they are isoattenuating to the surrounding parenchyma. In these cases, secondary signs need to be examined (ductal dilatation, ductal interruption, tail atrophy, abnormal contour of pancreas) (Prokesch *et al.*, 2002). CT-based criteria for resectable pancreatic cancer include: 1) the absence of tumor extension to the SMA, celiac axis, and common hepatic artery; 2) a patent superior mesenteric–portal vein confluence; 3) absence of any metastatic disease (liver, lung, peritoneum, or other distant sites) (Varadhachary *et al.*, 2005). The criteria for resectability are under continous reassessment and differ between institutions. Numerous studies have examined the efficacy of CT in preoperative staging of pancreatic cancer. Helical CT has a high negative predictive value (NPV) for cancer resectability ranging from 93 to 96% (Raptopoulos *et al.*, 1997; Lu *et al.*, 1997), and also good results have been observed later on using MDCT. In a meta-analysis of 68 CT and MRI studies, sensitivities of 84% for MRI and 91% for helical CT were observed in primary diagnosis of pancreatic cancer. The sensitivities of assessing resectability of the tumor were equal for both imaging methods (82% *vs.* 81%) (Bipat *et al.*, 2005). One of the common reasons for failed resection is the presence of vascular invasion. No prospective studies have been published using MDCT in assessing vascular involvement. The retrospective study by Vargas et al. reported NPV of 100% and accuracy of 99% in vascular invasion (Vargas *et al.*, 2004). *In M-staging of pancreatic cancer*, CT has limited value in the characterization of small liver lesions (Jones *et al.*, 1992) or peritoneal dissemination (Michl *et al.*, 2006).

In cystic lesions, the sensitivity of both CT and MRI is limited due to the fact that a substantial percentage of cystic pancreatic lesions have a nonspecific appearance on cross-sectional imaging (Visser *et al.*, 2007).

In pancreaticoduodenal NETs, at present high resolution CT is highly effective in the diagnosis of liver metastases (sensitivity up to 94%) but less effective in identifying primary tumors because the more common functional tumors are small. However, a recent study

using MDCT showed a sensitivity of 84% in primary diagnosis (Rappeport *et al.*, 2006). Non-functioning NETs are typically larger and their detection approaches 100%.

2.3.4.2.2 Magnetic resonance imaging (MRI)

MRI is typically used as a problem-solving tool, when a pancreatic mass is suspected, but not identified on MDCT. The use of MRI on the pancreas has undergone an important evolution due to the improved performance of gradient and phased-array coils, as well as in fast MRI techniques. Furthermore, the addition of extracellular contrast agents (gadolium chelates) and hormonal stimulation with secretin enables morphology and function to be combined in a single examination. MRI has increased tissue contrast resolution over CT, which is its primary imaging advantage. A pancreatic tumor almost invariably appears hypointense in contrast to bright pancreas on fat-suppressed T_1-weighted images and as isodense or mildly hyperintense in T_2-weighted images. Pancreatic adenocarcinoma appears hypointense due to hypovascularity of the tumor during the arterial phase of enhancement when the pancreas itself is maximally enhanced (hyperintense) after gadolium administration (Sahani *et al*., 2008). In *primary diagnosis of pancreatic cancer*, studies reveal that the sensitivity of MRI when a contrast agent is utilized is better than CT, although the majority of direct comparative studies were not performed using MDCT (Schima *et al.*, 2007). *In M-staging of pancreatic cancer*, Lopez-Hänninen and co-authors reported a positive predictive value (PPV) of 90% and NPV of 83% in assessing resectability (Lopez-Hänninen *et al.*, 2002). In cases of hepatic metastasis, MRI was able to improve specificity to 98% compared to MDCT (77%), although the sensitivity to lesions under 1 cm was similar (Mehmet *et al.*, 2006).

In diagnosis of CP, MRI has advantages including assessment of signal changes of the parenchyma with or without contrast agent in order to evaluate fibrosis, ductal anatomy, and structural changes (main pancreatic duct, side-branches). More recently, the possibilitity of quantifying the secretory response to secretin stimulation has improved the assessment of exocrine pancreatic reserve. The limitation of MRI in diagnosis of CP is lack of sensitivity in detecting calcification, as well as the cause of non-calcified filling defects. By magnetic resonance cholangiopancreaticography (MRCP) the structural changes in ducts could be evaluated; smooth and incomplete stenosis, irregular contour, pseudocysts, and filling defects due to calculi, protein plugs or debris, often reflect CP more than pancreatic cancer. Delayed enhancement after gadolium administration may be observed when an inflammatory mass is suspected (Matos *et al*., 2006).

As mentioned above, in diagnosis of *cystic lesions*, MRI has limited sensitivity and has no advantage over CT (Boellaard *et al.*, 2008). On the contrary, in diagnosis of IPMN, several reports have described the superiority of MRI and MRCP over endoscopic retrograde cholangiopancreaticography (ERCP) and helical CT in the evaluation of the malignant etiology of IPMN (Matos *et al.*, 2006).

In primary dignosis of *pancreatic NETs,* MRI has been reported to have a sensitivity of 85% in the detection of hepatic metastases (Dromain *et al.*, 2005). However, conventional

imaging for pancreatic NETs localizes only 10-60% of primary tumors (Modlin *et al.*, 2008). Due to rapid advances in CT, as well as in MRI technology, many of the prior comparative studies need to be reevaluated.

2.3.4.2.3 Ultrasonography (US)

The usefulness of transabdominal US in the diagnosis and staging of *pancreatic adenocarcinoma* is limited. Even prospective studies concerning US during the last decade are lacking. US as first-line imaging has sensitivities that vary between 57-83% (Haycox *et al.*, 1998). CeUS has been used as an alternative to a more expensive imaging modality. Based on studies by Rickes and co-authors, sensitivities were 87%, 85% and 95-100% for ceUS in *adenocarcinoma, pancreatitis and cystic lesions*, respectively (Rickes *et al.*, 2006). In cystic lesion, US has been found to be particularly valuable in showing internal septae, mural nodules, and solid areas within cysts.

Currently, in the case of *pancreatic NET*, US performed intraoperatively was superior in detecting radiographically occult insulinomas with sensitivity of 95% (Hiramoto *et al*., 2001).

2.3.4.2.4 Positron emission tomography (PET)

During the last fifteen years, several studies have been published concerning ^{18}F-FDG-PET *in diagnosis of primary pancreatic adenocarcinoma*. In the detection of primary tumor, the sensitivity of ^{18}F-FDG-PET is similar to that of CT scan, ranging from 65% to 100%, but the specificities seem to be higher *(Table 5)*. The early and delayed scanning has proved to be advantageous in different cancers (Kubota *et al.*, 2001). Optimation of scanning protocols in pancreatic adenocarcinoma has given controversial results. One study showed a significant increase in uptake at two-hour over one-hour image (Nishiyama *et al.*, 2005a), while another study showed a decreased uptake of ^{18}F-FDG at two-hour image in pancreatic cancer explained by the washout of tracer (Higashi *et al.*, 2002). Recent advances in PET/CT imaging have strengthened the value of ^{18}F-FDG-PET/CT *(Table 6)*. Further, the clinical significance of respiratory artifacts has been studied for an early PET/CT design (Osman *et al.*, 2003) and respiratory gating could also be valuable when the pancreas is imaged, although prospective studies are lacking. Hosten and co-authors reported a case study of a patient with adenocarcinoma in the head of the pancreas seen in retrospective fusion of PET and CT images (Hosten *et al.*, 2000). Later, the same group evaluated the clinical benefit of retrospective PET/CT image fusion in the diagnostic workup of pancreatic cancer (Lemke *et al.*, 2004). In their retrospective study, 104 patients with suspected pancreatic lesion underwent preoperative helical CT and ^{18}F-FDG-PET. The sensitivity of the CT and PET imaging was 77% and 84%, respectively, and with the retrospective fusion of these two imaging modalities, the sensitivity improved to the level of 89%. So far, only two prospective studies have been conducted to evaluate the value of combined PET/CT in the diagnosis of pancreatic malignancy. Heinrich and his study group demonstrated a PPV of 91% for PET/CT, but a NPV of only 64% for pancreatic cancer but still estimated that PET/CT was a cost-effective method in this patient group (Heinrich *et al.*, 2005). Recently,

Schick compared prospectively PET/CT, EUS, ERCP, and US in a series of 46 patients. PET/CT had a sensitivity of 89% and a specificity of 74% in the evaluation of solid pancreatic lesions of over 1 cm in diameter, which was not significantly different from conventional imaging methods (Schick *et al.*, 2008).

Table 5. Studies comparing the sensitivities and specificities of ^{18}F-FDG-PET and CT in the diagnosis of pancreatic tumors

Author, year	N	Design	Comparative imaging methods	PET Se (%)	PET Sp (%)	CT Se (%)	CT Sp (%)
1. Bares et al. 1993	15	prospective	CT, US, ERCP	92	100	95	50
2. Bares et al. 1994	40	prospective	CT, US (n=36) (retrospective)	89	85	100	23
3. Inokuma et al. 1995	46	prospective	CT, US, EUS (n=40)	94	82	89	73
4. Kato et al. 1995	24	prospective*	CT, MRI	93	78	not stated	not stated
5. Friess et al.1995	80	prospective	none	94	88		
6. Stollfuss et al. 1995	73	propective	CT	95	99	80	74
7. Ho et al. 1996	14	prospective	CT	100	67	25	100
8. Zimny et al. 1997	106	prospective	none	89	53		
9. Rajput et al. 1998	13	retrospective	CT, ERCP (n=8), EUS (n=5)	82	100	73	0**
10. Keogan et al. 1998	37	prospective	CT	88	83	75	83
11. Rose et al. 1998	65	retrospective	CT	92	85	65	62
12. Imdahl et al. 1999	48	prospective	CT (retrospective), US, ERCP (n=36)	96	100	50	44
13. Delbeke et al. 1999	65	prospective	CT	92	85	65	61
14. Diederichs et al. 2000	122	prospective***	CT (n=103), ERCP (n=101)	88	73	88	87
15. Sendler et al. 2000	42	prospective	CT, US	71	67	74	46
16. Nakamoto et al. 2000	47	prospective****	none	100 (delayed)	75 (delayed)		
17. Koyoma et al. 2001	86	not stated	CT, MRI (n=37)	82	81	91	62
18. Kasperk et al. 2001	103	prospective	CT, US, ERCP	92	58	85	89
19. Papos et al. 2002	22	not stated	CT, US, ERCP	100	88	100	50
20. Kalady et al. 2002	54	retrospective	CT	88	86	90	62
21. Lytras et al. 2005	112	retrospective	CT	73	60	89	65
22. Borbath et al. 2005	59	retrospective	MRI, EUS, laparoscopy	88	55	88 (MRI)	91 (MRI)
23. Maenura et al. 2006	42	prospective	none	87	67		
24. Bang et al. 2006	102	prospective	CT	97	78	80	44
25. Wakabayashi et al. 2008	53	retrospective*****	CT	93	-	89	-
26. Seo et al. 2008	56	retrospective*****	none	91	-		

Se; sensitivity
Sp; specificity

* included nine patients with CP
** included two patients with CP
*** patients with elevated plasma glucose (>130 mg/dl) or C-reactive protein >3 mg/L excluded
**** two PET scans (early and delayed)
***** included only patients with confirmed primary pancreatic adenocarcinoma

Table 6. Studies evaluating the usefulness of ^{18}F-FDG-PET/CT in the diagnosis of pancreatic adenocarcinoma

Author	N	Design	Comparative imaging methods	Se (%)	Sp (%)	PPV (%)	NPV (%)
1. Lemke et al. 2004	104	retrospective	none	89	64	81	76
2. Heinrich et al. 2005	59	prospective	CT	89	69	91	64
3. Schick et al. 2008	46	prospective	US, EUS, (ERCP)	89	74	83	82
4. Strobel et al. 2008	50	retrospective	ce PET/CT	100	56	66	100
5. Farma et al. 2008	82	retrospective	CT	89	88	97	68

Se; sensitivity
Sp; specificity
PPV; positive predictive value
NPV; negative predictive value

In N-staging of disease, PET as well as PET/CT has not proved to be beneficial. However, opposite result have also been published, in a recent study by Strobel using PET/CT in the diagnosis of pancreatic cancer (Strobel *et al.*, 2008). They showed that arterial infiltration was diagnosed in all five patients using cePET/CT. Another study reported PET/CT to be significantly less sensitive in the evaluation of local regional disease than EUS (Farma *et al.*, 2008).

In M-staging of disease, Nishiyama and co-authors reported a sensitivity of 82% in the detection of metastatic disease for ^{18}F-FDG-PET, while CT had a sensitivity of 64% (Nishiyama *et al.*, 2005b). However, the same study showed that ^{18}F-FDG-PET has a weakness in diagnosing a small liver lesion under 1 cm with a sensitivity of 50%. On the contrary, a recent study showed that cePET/CT had higher sensitivity and specificity in detecting liver metastasis (82% and 97%, respectively) than PET alone or non-cePET/CT (Strobel *et al.*, 2008). CePET/CT detected all seven patients with lung metastasis, while PET alone showed metastasis in only one patient.

Prediction of survival in pancreatic adenocarcinoma; Lyshchik and co-authors showed that combining staging information with ratios of ^{18}F-FDG uptake at one- and two-hour images after injection was predictive of patient survival (Lyshchik *et al.*, 2005). Sperti and co-authors confirmed the former finding (Nakata *et al.*, 2001) and reported in a study of 118 patients, that survival was significantly influenced by SUV, and was also an independent predictor of survival (Sperti *et al.*, 2003).

In the diagnosis of cystic lesions a recent study suggests, that ^{18}F-FDG-PET may offer a high degree of differentiation between malignant and benign cystic lesions with sensitivities and a PPV over 90% (Sperti *et al.*, 2005), although a lower sensitivity of 57% has also been reported (Mansour *et al.*, 2006). Studies have also shown promising results of ^{18}F-FDG-PET in the diagnosis of IPMN (Sperti *et al.*, 2007; Baiocchi *et al.*, 2008). The evidence of ^{18}F-FDG-PET in cystic lesions is still lacking, especially its role in clinically important premalignant cystic lesions, and no prospective studies using combined PET/CT machine have been done so far. The study by Tann and co-authors compared CT, PET and retrospective fusion of combined images in thirty patients with cystic lesions of the pancreas (Tann *et al.*, 2007). Sensitivities of CT, PET, and combined images of PET and CT were 67-71%, 57%, and 86%, respectively.

As noted earlier, patients with *CP* have an increased risk of developing pancreatic cancer and, currently, no imaging study can reliably differentiate a malignant tumor from CP. A study by van Kouwen and co-authors reported that ^{18}F-FDG-PET can differentiate between neoplastic and inflammatory tumors with a sensitivity of 91% and a specificity of 87% (van Kouwen *et al.*, 2005).

Limitations. Imaging of the pancreas using ^{18}F-FDG-PET has several limitations. Uptake of the ^{18}F-FDG is not specific for cancer, being seen also in inflammatory and granulomatous processes, as well as in normal tissues. As is well known, inflammatory

conditions such as pancreatitis (van Kouwen *et al.*, 2005) form the main limitation in ^{18}F-FDG-PET imaging of pancreatic tumors. Secondly, hyperglycemia (Zimny *et al.*, 1998; Delbeke *et al.*, 1999) where endogenous glucose competes with the ^{18}F-FDG lowers the sensitivity. Some of these limitations could be avoided using integrated PET/CT. Further, an optimal scanning protocol could include delayed imaging, and possible respiratory gating, as well as glucose, and C-reactive protein (CRP) measurement before imaging.

In most *pancreatic NETs,* the use of ^{18}F-FDG is limited because of the low glucose turnover. ^{18}F-FDG-PET has been useful in cases of high-proliferative activity and low differentiation (Sundin *et al.*, 2007). Pancreatic β-cells can take up amine precursors and convert these into amines by aminoaciddecarboxylase (AADC) (Ericson *et al.*, 1977; Borelli *et al.*, 1997; de Lonlay *et al.*, 2006). Based on this, aminoacid precursor tracers are useful in PET imaging. The most used aminoacid precursor tracers in the imaging of pancreatic NETs are ^{11}C-5-hydroxytryptophan (^{11}C-5-HTP) (Örlefors *et al.*, 2005; Koopmans *et al.*, 2008a), and ^{18}F-DOPA (Otonkoski *et al.*, 2006; Koopmans *et al.*, 2008a). Because NETs express somatostatin receptors (SR), they have been tradionally studied using somatostatin receptor scintigrapy (SRS). The study using somatostatin (SST) analog, ^{68}Ga-DOTA-D-Phe^{1}-Tyr^{3}-octreotide (^{8}Ga-DOTA-TOC) as a tracer included 23 patients with pancreatic NETs, and it showed that ^{68}Ga-DOTA-TOC was significantly more sensitive than SRS (overall sensitivity 97% *vs*. 55%) (Gabriel *et al.*, 2007). In addition, the new method showed all pancreatic lesions, while single photon emission computed tomography missed two patients and CT four patients. As shown in *Table 8*, page 38, several aminoacid precursor tracers have been tested in the diagnosis of pancreatic NET, but most studies included only few patients. No prospective studies have been conducted using integrated PET/CT, but it is likely that such scanning will play an increasingly important role in the future for imaging pancreatic NETs. In addition, the routine use of carbidopa premedication in the diagnosis of pancreatic NETs needs to be further evaluated.

2.3.4.3 Invasive imaging

2.3.4.3.1 Endoscopic retrograde cholangiopancreaticography (ERCP)

During the last decades, ERCP has been important in the workup of patients with pancreatic malignancy. The major advantage of ERCP is that diagnostic and therapeutic procedures can be carried out at the same time. Brushing biopsies can be obtained and stent insertion can be performed simultaneously. In addition, it obtains high resolution images of the pancreatic duct and is considered as a gold standard for evaluating the pancreatic duct (Kwon & Scheiman, 2006). ERCP allows the accurate delineation of the site of biliary obstruction and aids in excluding obstruction at multiple levels. ERCP allowed correct differentiation of malignant from benign lesions in 76% of the patients according a prospective study (Domagk *et al.*, 2004), and it is useful in detecting tumors, if there is main ductal involvement. Especially in the diagnosis of *IPMN,* ERCP is considered a standard procedure. It reveals any dilatation of the main pancreatic duct

or branches with filling defects due to the presence of either mural nodules or mucin. The diagnostic accuracy can be further improved using the balloon-catheter technique, according to one study depending on main- or branch-duct type neoplasms, up to 84% and 82%, respectively.

ERCP is regarded as the gold standard for *the detection of CP*. Typical alterations of pancreatic ducts are; dilatation, stenoses, and abnormalities of the side-branches.

2.3.4.3.2 Endoscopic US and fine-needle aspiration (FNA)

Recently, the benefits of EUS for the diagnosis and staging of pancreatic lesions have been well proven. Aside from tumor detection, EUS-guided FNA (EUS-FNA) may be indicated when tissue sampling is required. FNA is appropriate for cytological evaluation (needle; less than 1 mm in diameter, 20-25 Gauge), whereas 14-19 Gauge needles (core biopsies) are used to obtain tissue cores for histopathological analysis. FNA is often preferred when sampling is deeply located, in sites adjacent to major vessels, or in situations in which the needle is to be passed through the bowel wall. DeWitt and co-authors showed as high sensitivity as 98% for EUS in a series of 104 patients (DeWitt *et al.*, 2004). The role of EUS-guided FNA is still evolving. Several studies have shown high sensitivity in the range 75-90%, and specificity in the range 82-100% with a mean accuracy of 85% for diagnosis of pancreatic lesions (Boujaoude, 2007). Benign pathology in EUS-FNA biopsies does not always exclude the malignancy. EUS has several limitations; invasiveness of the technique including risks of bleeding and perforation, operator dependency, and lack of assessment of distant metastasis (Sahani *et al.*, 2008). Later, studies have shown EUS to be more sensitive in primary pancreatic tumor detection than ^{18}F-FDG-PET (93-98% *vs.* 87%) (Mertz *et al.*, 2000;Borbath *et al.*, 2005). However, both of these studies were conducted before the ^{18}F-FDG-PET/CT era.

In the detection of pancreatic cystic lesions, the demonstration of a solid component, invasion outside the pancreatic parenchyma, or pancreatic duct obstruction is suggestive of malignancy. However, in the absence of these features the ability of EUS to diagnose malignancy is limited with an overall sensitivity, specificity, and accuracy of 56%, 45%, and 51%, respectively (Brugge *et al.*, 2004).

The role of EUS in *diagnosing early stage CP* is not well defined. According to a recent review article (Rizk & Gerke, 2007), EUS was accurate in ruling out CP if no pancreatic abnormalities exist, and in diagnosing CP, if multiple criteria (*i.e.* hyperechoic foci, heterogeneity, cysts, calcification, ductal dilatation) are present. These criteria are highly sensitive (up to 85%), but they lack specificity in early stages (<60%).

In detection of pancreatic NETs, EUS has shown a high sensitivity of 93% and a specificity of 95% (Anderson *et al.*, 2000). EUS combined with FNA is reported to have a poor diagnostic accuracy of 46% for pancreatic NETs (McLean & Fairclough, 2005). FNA is rarely needed with functional pancreatic NETs because diagnosis is made by biochemical testing.

In addition to EUS guidance, FNA biopsies can be taken using US or CT guidance percutaneously. CT- and US-guided FNAs of pancreatic lesions have both been reported with an accuracy ranging from 61% to 98%, but a NPV of only 58% was observed (Hartwig *et al.*, 2009). Percutaneus FNA has been proposed for detecting malignancies when the lesion is large and located in the body or tail of the pancreas, in cases where pancreatic lesion is unresectable on imaging methods, when the patient is unfit for surgery, or neoadjuvant chemoradiation is planned. According to a recent review, preoperative tissue diagnosis of potentially resectable pancreatic tumors is not generally advisable, as malignancy cannot be ruled out with adequate reliability (Hartwig *et al.*, 2009).

2.3.4.3.3 Staging laparoscopy

In order to minimize the number of patients with imaging occult disease that undergo unnecessary laparotomy, laparoscopy was incorporated early in staging of pancreatic cancer. A review article showed that laparoscopy identified 10-36% of the patients with unresectable disease who were spared a laparotomy (Stefanidis *et al.*, 2006). The added value of staging laparoscopy has been better sensitivity in diagnosing peritoneal carcinosis and small liver lesions; still, it does not affect the management of the majority of patients examined. The review concluded that selective use of staging laparoscopy may therefore be more appropriate. Predictors identified in this review included large tumor size (>3 cm), tumor location in the body or tail of the pancreas, or Ca19-9 level >150 U/ml. In patients with locally advanced pancreatic cancer without distant disease who are considered for chemoradiation, laparoscopy may effectively identify imaging-occult Stage 4 disease, and thus prevent the morbidity and cost associated with unnecessary treatments. However, prospective studies are not available to validate preoperative predictors of those patients, who benefit most from staging laparoscopy and the main controversy today is whether it should be used routinely or selectively.

2.4 Neuroendocrine tumors (NETs)

2.4.1 Pathology

NETs originate from the diffuse neuroendocrine system. The function of cells of this system is to regulate neighbouring cells by the excretion of biologically active amines and hormones. In the GI-tract and pancreas, 15 neuroendocrine cell types producing different hormones but all expressing the general neuroendocrine marker synaptophysin can be distinguished. Especially the presence of CrA, is widely used to identify GI NETs (Klöppel & Anlauf, 2005). Tradionally, they are separated into benign or malignant neoplasms. Most NETs are well-differentiated tumors that are characterized by a solid trabecular or glandular structure, tumor cell monomorphism with absent or low cytological atypia, and a low mitotic activity (< 2 mitoses/10 high-power field) and proliferative status (Ki-67 < 2%). Only in the presence of metastasis and/or invasive growth of the tumor is defined as a well-differentiated NE carcinoma. Poorly differentiated NE carcinomas are characterized by a predominantly solid structure with abundant necrosis, cellular atypia

with high mitotic index, and proliferative status (Ki-67>15%). A third of the entire tumor cell population consists of mixed exocrine-endocrine carcinomas, which are epithelial tumors with predominant exocrine and endocrine component mixed (Öberg *et al.*, 2004). A recent standard WHO classification has proposed GI NETs be assigned to one of three categories (well-differentiated tumor, well-differentiated carcinoma, and poorly differentiated carcinoma) based on histology, size, and proliferative indices (Klöppel *et al.*, 2007) *(Table 7)*. Prognostic factors include tumor size, angioinvasion, mitotic activity, and Ki-67/MIB proliferative indexes.

Table 7. Classification of NETs of the GI-tract based on WHO criteria (according to Klöppel *et al*., 2007)

Biological behavior	Metastases	Invasion of muscularis propria	Histological differentiation	Tumor size (cm)	Angioinvasion	Ki-67 index (%)	Hormonal syndrome
Benign	-	-	Well differentiated endocrine tumor	≤1*	-	<2	-*
Benign or low-grade malignant	-	-	Well differentiated endocrine tumor	≤2	-/+	<2	-
Low-grade malignant	+	+**	Well differentiated endocrine carcinoma	>2	+	>2	+
High-grade malignant	+	+	Poorly differentiated endocrine carcinoma	Any	+	>15	-

* Exception: malignant duodenal gastrinomas are usually smaller than 1 cm and confined to submucosa
** Exception: benign NETs of the appendix usually invade the muscularis propria

2.4.2 Classification

The classification of NETs has been under continuous modification. First, Williams and Sandler attempted a systemic classification of gastroenteropancreatic (GEP) NETs in 1960. They subdivided NETs (then called 'carcinoid' tumors) according to the section of the embryonal primitive gut (fore-, mid-, and hindgut). In 1980, the WHO suggested a classification system in which carcinoid tumors were separated from pancreatic tumors, Merkel cell carcinomas, paragangliomas, and others. Because of the lack of histopathological and prognostically relevant information, Capella and co-authors created a new classification, which considered size and metastases of the tumor, and histopathological features, as well as clinical features (including the presence of hormone hypersecretion syndrome). Based on this, in 2000, the WHO published a new classification *(Table 7)* as mentioned earlier. However a widely accepted classification system presented in 2006 by Rindi and co-authors taking into consideration both a staging system and a grading system is even more useful (Rindi *et al.*, 2006). The latter

characterizes the proliferative potential of NETs using either a mitotic count or the Ki-67 labeling index. A more detailed classification of pancreatic NETs is shown in *Table 2* and *Table 4.*

2.4.3 Epidemiology

The incidence of NETs has increased during the last 30 years. A recent study based on the Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute (US) registries reported the annual incidence of NETs from 1973 to 2004 increasing from 1.09/100,000 to 5.25/100,000 (Yao *et al.*, 2008). Another recent study showed that NET incidence was observed to be 3.24/100,000 in a Norwegian population, which is similar to the US Caucasian population (Hauso *et al.*, 2008). Ileal and appendiceal NETs are the most common, accounting for 45% of all NETs in the GI-tract. While NETs in the colon are rare, NETs of the rectum account for 20% of the GI-tract NETs. The incidence of gastric NETs is increasing due to increased application of endoscopy and it may become the most common GI-tract NET in the future. Further, also the incidence of pancreatic NETs is increasing (Klöppel *et al.*, 2007).

2.4.4 Diagnosis

2.4.4.1 Biochemical diagnosis

Diagnosis of NETs is based on clinical presentation, hormone assays, and pathology. In the diagnosis of NETs the demonstration of elevated levels of peptides and biogenic amines in the blood is essential. The most widely used marker is plasma CrA. CrA is an acidic soluble protein found in large secretory granules of NET cells. It has an overall diagnostic sensitivity of 60-100% in patients with metastatic disease, but less than 50% in patients with localized and early disease (Zatelli *et al.*, 2007). Further, CrA levels reflect tumor burden and it has been used to assess recurrences, tumor growth, and changes in tumor size (Campana *et al.*, 2007). Other specific markers are plasma neuron-specific enolase (increased in 83-100%), pancreatic polypeptide, pancreastatin, and in the more malignant phenotype, human chorionic gonadotropin (increased in 25-40%) (Öberg *et al.*, 2004; Modlin *et al.*, 2008; Metz & Jensen, 2008).

2.4.4.2 Anatomical imaging

At present, the primary tumor is not localized in 20-50% of GEP NETs. Conventional imaging, such as CT, MRI, and US detect only less than 50% of NETs in small gut and pancreas. Better sensitivity is observed in bronchial and thymic tumors. Approximately 80-90% of liver metastases larger than 1-2 cm are detected by conventional imaging (Öberg *et al.*, 2004). EUS is used in the diagnosis of primary tumors, as well as in local tumor invasion and regional lymph-node metastases with a sensitivity and specificity of more than 80% (Öberg *et al.*, 2004).

2.4.4.3 Functional imaging

2.4.4.3.1 Somatostatin receptor scintigraphy (SRS) and metaiodobenzylguanidine (MIBG) scintigraphy

Nowadays, SRS and MIBG scintigraphy are routine in patients with suspicion of a NET, and their sensitivity exceeds that of CT and MRI (Krenning *et al.*, 1993;van der Harst *et al.*, 2001). Currently, *SRS imaging* is the method of choice for the staging of NETs (Kumbasar *et al.*, 2004). Somatostatin (SST) is a small regulatory peptide, which is widely distributed in the human body. NETs frequently express a high density of SST receptors (SR), which is exploited by imaging techniques using SST analogues. Based on the high receptor expression, SR imaging using ^{111}In-octreotide provides important information on the tumor localization of many NETs. SRS is based on the expression of SR in endocrine tumors and, therefore, the density of these receptors determines the efficacy of this imaging method. Octreotide analogues bind with high affinity to SST2 and with varying affinity to the SST5, SST3 and SST4 receptors. Due to this, SRS has low sensitivity in localizing small tumors lacking the SST2 receptor, which is the case in 20-50% of NETs (Reubi *et al.*, 1994). SRS is widely available, and yields the best results in paragangliomas and GI NETs, being least suitable in medullary thyroid cancer (MTC). SRS is particular useful for showing liver metastases with a sensitivity of almost 90% (Gibril & Jensen, 2004). Besides the staging of disease, SRS is used to assess the efficacy of treatment with SST analogue.

Further, the labeled catecholamine analogue, MIBG, is another well-established tracer for scintigraphy visualization. *MIBG scintigraphy* has become the imaging method of choice for neuroblastoma and pheochromocytoma, but its sensitivity to all NETs is inferior to that of SRS. According to a recent review, up to 30% of NETs had no accumulation of MIBG (Rufini *et al.*, 2006), and MIBG scintigraphy seems to have limited sensitivity for the diagnosis of metastasized disease due to decreased expression of norepinehrine transporters by less-differentiated cells. The sensitivity of MIBG scintigraphy was 57% in metastatic pheochromocytoma, and 92-96% in nonmetastatic disease, based on the findings from a series of 75 patients (van der Harst *et al.*, 2001).

2.4.4.3.2 PET; Aminoacid precursor and somatostatin receptor (SR) tracers

Aminoacid precursor tracers. NETs have the capacity to take up and decarboxylate amine precursors, based on the amine precursor uptake and decarboxylation (APUD) concept introduced by Pearse (Pearse, 1969). Several study groups have published results of patients with NET using aminoacid precursor tracers in PET scanning *(Table 8)*. First, *^{11}C-5HTP*, aminoacid precursor, has been successfully used in the diagnosis of NETs. The study by Örlefors and co-workers reported that ^{11}C-5-HTP-PET could detect more tumor lesions than SRS and CT in 58% of the study patients (Örlefors *et al.*, 2005). Since the pioneering study of Ahlström in 1995 using carbon-11 labeled -DOPA (Ahlström *et al.*, 1995), ^{18}F-DOPA, has been used for diagnosis of carcinoid tumors (Hoegerle *et al.*, 2001a;Becherer *et al.*, 2004;Koopmans *et al.*, 2008a), pheochromocytomas (Hoegerle *et al.*, 2002;Timmers *et al.*, 2007), MTCs (Hoegerle *et al.*, 2001b;Beuthien-Baumann *et al.*, 2007;Koopmans *et al.*, 2008b), and glomus tumors (Hoegerle *et al.*, 2003). During recent years, PET based

imaging with labeled amino acid precursors has become a success story in the localization and staging of NETs (Hoegerle *et al.*, 2001a;Becherer *et al.*, 2004;Koopmans *et al.*, 2006). A PET study by Sundin and co-workers demonstrated that AADC decarboxylates *in vivo* 5-HTP and DOPA to 5-HT (serotonin) and dopamine, respectively (Sundin *et al.*, 2000). In addition to the FDA metabolite, DOPA is also the origin of many other metabolites such as 3-O-methyl-fluorodopa (OMFD), 6-fluoro-L-3,4-dihydroxyphenylacetic acid (FDOPAC), 6-fluorohomovanillic acid (FHVA), as well as sulfated conjugates (Miletich *et al.*, 1993) *(Figure 3).* Referring to *Figure 2* on page 15, when the AADC pathway is blocked with carbidopa, the amount of metabolites changes (Neels *et al.*, 2008). So far, the accumulation of these other metabolites than FDA into various types of NETs is largely unknown. Although the results are promising, experience with these PET tracers is still limited. It is foreseeable that in the future the first step in imaging of NETs will be with the use of aminoacid tracers, such as ^{18}F-DOPA, on a PET/CT machine.

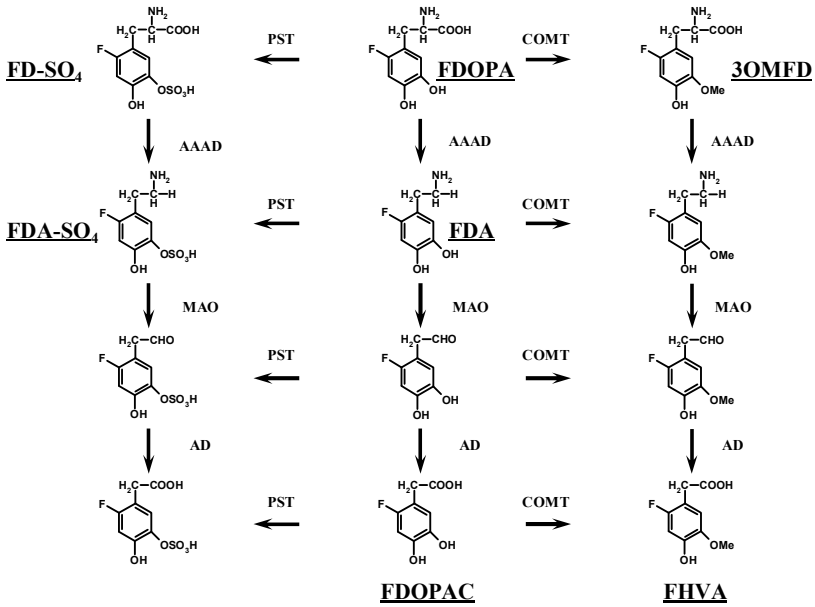


Figure 3. *Different metabolites of ^{18}F-DOPA. FDOPA; 6-fluoro-L-DOPA, FDA; 6-fluorodopamine, 3OMFD; 3-O-methyl-fluorodopa, FDOPAC; 1.3.4-dihydroxy-6-fluorophenylacetic acid, FHVA; 6-fluorohomovanillic acid, AAAD; aminoacid decarboxylase, COMT; catechol-O-methyl-transferase, MAO; monoamine oxidase, PST; phenolsulfotransferase, and AD; alhehyde dehydrogenase (Haaparanta-Solin, 2006. © Reprinted with permission.)*

SR tracers. Based on the high density expression of SRs in NETs, currently SR PET imaging has become the method of choice for staging of disease (Plockinger *et al.*, 2004). When chelators such as DOTA are coupled to SST analogues, these molecules can thereafter be labeled with positron-emitting isotopes such as ^{68}Ga. Thereafter the labeled SST analogues can be used for PET imaging. Thus far, the tracers ^{68}Ga-DOTA-TOC and ^{68}Ga- DOTA -1-Nal^3-octreotide (^{68}Ga-DOTA-NOC) have been studied most and the results for these tracers are promising (Hofmann *et al.*, 2001;Gabriel *et al.*, 2007;Fanti

et al., 2008;Ambrosini *et al.*, 2008). The study by Gabriel and co-authors showed a sensitivity of 97% and a specificity of 92% for ^{68}Ga-DOTA-TOC (Gabriel *et al.*, 2007). Since their mechanism is receptor-based, they provide a good visualization of well-differentiated NET and data on receptor status, which are important in the assessment of disease and in the planning of targeted radionuclide therapy. Moreover, the synthesis of ^{68}Ga-DOTA peptides is easier compared to ^{18}F-DOPA because of the advantage of in-house prepation (commercial generator) of ^{68}Ga without the need for a cyclotron.

Table 8. Different aminoacid precursors used in PET scanning in patients with NET

Author, year	N	NET type	Tracer	Design	Comparative imaging methods	PET Se (%)	PET Sp (%)
1. Ahlström et al. 1995	22	pancreatic NET	^{11}C-DOPA	prospective	^{11}C-HTP (n=6), CT	77	100
2. Anderson et al. 2000	8	different types (pancreatic NET n=3)	^{64}Cu-TETA-Octreotide		SRS	75	100
3. Pacak et al. 2001	28	pheochromocytoma	^{18}F-dopamine	not stated		100	not stated
4. Hoergerle et al. 2001	11	MTC	^{18}F-DOPA	prospective	^{18}F-FDG-PET, SRS, CT/MRI	63	100
5. Hoergerle et al. 2001	14	pheochromocytoma	^{18}F-DOPA	prospective	MRI, MIBG scintigraphy	100	100
6. Hoergerle et al. 2001	17	different types	^{18}F-DOPA	prospective	^{18}F-FDG PET, SRS, CT/MRI	65	not stated
7. Hoergerle et al. 2003	10	glomus tumors	^{18}F-DOPA	prospective	SPECT, MRI	100	100
8. Becherer et al. 2004	23	different types (pancreatic NET n=6)	^{18}F-DOPA	prospective	CT, SRS	20-100*	81-100**
9. Örlefors et al. 2005	42	different types	^{15}C-HTP	prospective	SRS, CT	95	100
10. Örlefors et al 2006	6	different NET (pancreatic NET n=7)	^{15}C-HTP with / without carbidopa	prospective		100/100***	
11. Koopmans et al. 2006	53	different types (advanced)	^{18}F-DOPA	prospective	SRS, CT	100	not stated
12. Montravers et al. 2006	30	carcinoid/ non-carsinoid	^{18}F-DOPA	retrospective	SRS	93/25	75/100
13. Timmers et al. 2007	11	pheochromocytoma	^{18}F-DOPA with/ without carbidopa	prospective	CT, MRI	47/50	not stated
14. Beuthien-Baumann et al. 2007	15	MTC	^{18}F-DOPA/ ^{18}F-OMFD	retrospective	^{18}F-FDG-PET	100****	not stated
15. Gabriel et al. 2007	84	different types (insulinoma n=23)	^{68}Ga-DOTA-Tyr^{3}-Octreotide	prospective	MDCT	97	92
16. Koopmans et al. 2008	21	MTC	^{18}F-DOPA	prospective	^{18}F-FDG-PET, SRS, CT/MRI	62 (patient-based)/ 71 (lesion-based)	not stated
17. Koopmans et al. 2008	47	carsinoid tumor (n=24) pancreatic islet cell tumors (n=23)	^{18}F-DOPA/ ^{15}C-HTP	prospective	SRS, CT	96/100 (carsinoid) 89/100 (islet cell tumor)	not stated
18. Ilias et al. 2008	53	pheochromocytoma	^{18}F-dopamine	prospective	CT/MRI, SRS, MIBG scintigraphy	90	not stated
19. Kayani et al. 2008	38	different types (pancreatic NET n=9)	^{68}Ga-DOTA-TATE	prospective	^{18}F-FDG-PET/CT	82	not stated
20. Ambrosini et al. 2008	13	GEP (pancreatic NET n=8)	^{68}Ga-DOTA-NOC/ ^{18}F-DOPA	prospective	CT, US	100/69	not stated
21. Timmers et al. 2009	99	pheochromocytoma	^{18}F-dopamine	prospective	CT/MRI, MIBG scintigraphy (n=77)	92	90

Se; sensitivity
Sp; specificity

* 20% in lungs, 100% in skeletel, mediastinal lesions
** 81% in liver, 100% pancreas, lymph nodes, mediastinal lesions
*** a significant increase in SUV after carbidopa administration
**** only two out of seven patients have histological verification

3 OBJECTIVES OF THE STUDY

The purpose of the present study was

1) To compare the accuracy of ^{18}F-FDG-PET/CT, MDCT and MRI in the diagnosis, staging and assessment for surgery in patients with suspected pancreatic malignancy ***(I)***

2) To study blood flow and metabolism in malignant and benign pancreatic lesions and to determine their prognostic value ***(II)***

3) To study the potential of ^{18}F-DOPA-PET in identifying and localizing the insulin secreting tumors or ß-cell hyperplasia of the pancreas in adults ***(III)***

4) To evaluate the effect of carbidopa pretreatment prior to ^{18}F-DOPA-PET/CT imaging in patients with primary hyperinsulinemic hypoglycemia (PHH) ***(IV)***

5) To evaluate the clinical value of ^{18}F-DOPA-PET/(CT) in primary diagnosis, staging, and restaging in patients with different types of NETs ***(V)***

4 SUBJECTS AND STUDY DESIGN

4.1 Study patients and design

This study was carried out to study the role of PET/(CT) in GI-malignancies, specifically, pancreatic tumors and NETs. Three tracers (^{18}F-FDG, ^{15}O-H_2O, ^{18}F-DOPA) were used in PET/(CT) imaging, and the findings of PET/(CT) scans were compared to conventional imaging *(Table 9)*.

Table 9. Patient groups in different studies (number of patients shown in parenthesis)

	Study I	*Study II*	*Study III*	*Study IV*	*Study V*
Indication	Pancreatic tumor	Pancreatic tumor	Pancreatic NET	Pancreatic NET	NET; primary diagnosis, staging, restaging
Design	Prospective	Prospective	Prospective	Prospective	Retrospective
Number of study patients	38	26*	10 study patients 7 control patients	3	82 (93 PET studies)
Tracer	^{18}F-FDG	^{18}F-FDG ^{15}O-H_2O	^{18}F-DOPA	^{18}F-DOPA	^{18}F-DOPA
Carbidopa pretreatment	-	-	no	yes (3) no (3)	yes (19) no (74)
PET scanner	PET/CT	PET/CT	PET	PET/CT	PET (26) PET/CT (67)
Other imaging methods	MDCT (38) MRI (38)		MDCT (10) MRI (7) SRS (2) EUS/IOUS (4)	MDCT (3) MRI (2) EUS (2)	MDCT (75) MRI (23) SRS/MIBG (5)

* Patients of *study II* were also included in *study I*

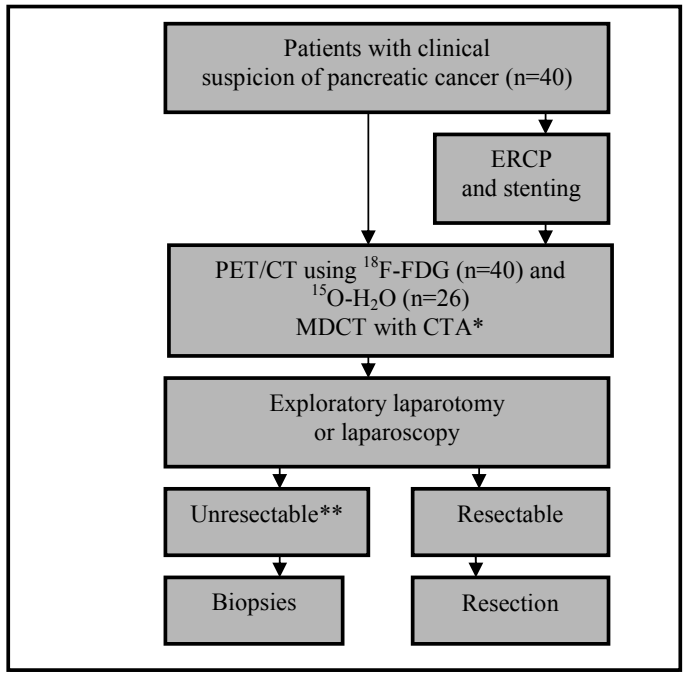
Studies I-IV. Both the study protocol and the informed consent form were approved by the ethics committee of the Hospital District of Southwest Finland. All patients gave written informed consent before entering the study. *Study V* was retrospective and data collection was approved by the joint ethical Committee of Turku University Hospital.

4.1.1 (I-II)

Principle. Study I was carried out to compare prospectively ^{18}F-FDG-PET/CT to MDCT and MRI in the evaluation of 38 consecutive patients with suspected pancreatic malignancy between September 2006 and October 2007. Twenty-six of the patients in *study I* also participated in *study II*, where pancreatic blood flow (BF) was measured using ^{15}O-H_2O-PET/CT and metabolism using ^{18}F-FDG-PET/CT, in different pancreatic lesions, to determine the prognostic value of these parameters.

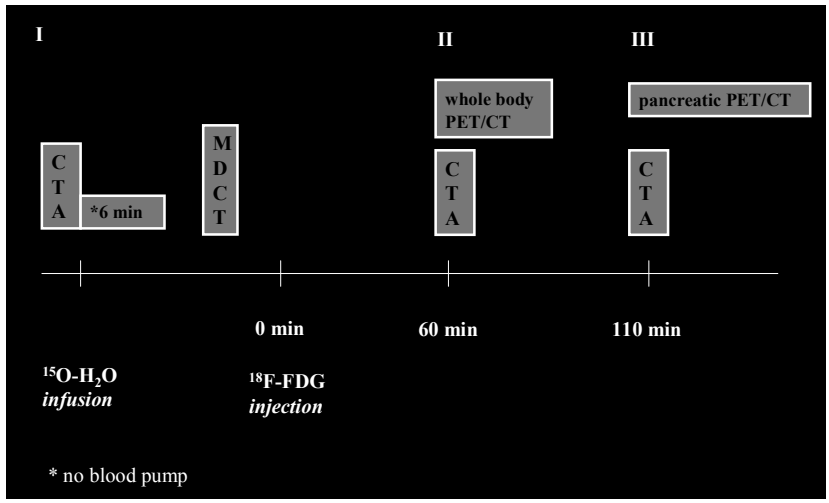
Study design (Figures 4 and 5). A total of 40 patients was enrolled in this study and 38 patients were included in the final analysis. All the patients underwent both comparative MDCT and MRI imaging. The therapeutic work-up was performed according to the usual procedures of our institution. Results of imaging methods were compared to

operative and histopathological findings or follow-up. In *study II,* ^{15}O-H_2O-PET/CT was conducted in order to assess BF, and ^{18}F-FDG-PET/CT to assess the metabolism of different pancreatic lesions.



* CTA; computed tomography angiography
** indication for unresectability; 1. distant metastasis, 2. invasion into the large vessels (including SMA, celiac axis, common hepatic artery and superior mesenteric-portal vein confluence)

Figure 4. Design of *Studies I* and *II*



min; minutes
CTA; computed tomography angiography

Figure 5. Flow chart of imaging protocol (*Studies I* and *II*)

4.1.2 (III-IV)

Principle. Study III was set up to determine the potential of ^{18}F-DOPA-PET in identifying and localizing the insulin secreting tumors or ß-cell hyperplasia of the pancreas in adults, and to compare the technique with the established conventional imaging methods. *Study IV* was carried out to study the effect of carbidopa premedication on ^{18}F-DOPA-PET/CT imaging in patients with insulinoma.

Study design. Study III included ten consecutive patients with confirmed PHH and presumed insulin-secreting tumor, and they were prospectively imaged using ^{18}F-DOPA-PET. All patients were operated on and histological verification was available in each case. Semi-quantative PET results using SUV were compared to uptake values of seven consecutive patients with nonpancreatic NET. In *study IV*, we imaged three patients with PHH using ^{18}F-DOPA-PET/CT with and without carbidopa premedication.

4.1.3 (V)

Principle. Study V was set up to determine the potential of ^{18}F-DOPA-PET in primary diagnosis, staging and, restaging of different types of NETs.

Study design. In this retrospective study 82 patients were imaged with PET/CT and PET using ^{18}F-DOPA. A total of 93 PET images was analyzed. The diagnostic accuracy of the PET/(CT) was assessed by comparing the histopathological reports and clinical follow-up. Indication for PET/(CT) in most cases was negative or inconclusive findings in conventional imaging methods.

5 METHODS

5.1 Positron emission tomography *(III, V)* -computed tomography *(I-V)*

5.1.1 Production of positron-emitting tracer

5.1.1.1 ^{18}F-FDG ***(I, II)***

^{18}F-FDG (half-life=110 minutes) was synthesized by the modified method of Hemacher (Hamacher *et al.*, 1986). The radioactivity of synthesis was 76 gigabecquerel (GBq)/ µmol, and the radiochemical purity exceeded 95%.

5.1.1.2 ^{15}O-H_2O ***(II)***

A low-energy deuteron accelerator Cyclone 3 (Ion Beam Application Inc., Louvain-La-Neuve, Belgium) was used for production of ^{15}O (half-life=123 seconds). To synthesize radiowater for BF imaging, a diffusion membrane technique in a constantly working water module was applied (Radio Water Generator, Hidex Oy, Finland). H_2O was produced using the dialysis technique in a continuously working water module (Sipilä *et al.*, 2001). Sterility and pyrogenity tests were performed to verify the purity of the product. The radiochemical purity of the ^{15}O-H_2O was approximately 97%.

5.1.1.3 ^{18}F-DOPA ***(III-V)***

^{18}F-DOPA (half-life=110 minutes) was synthesized according to the method of Chirakal (Chirakal *et al.*, 1986) with some modifications by Bergman (Bergman *et al*., 1994). The specific radioactivity was 44 MBq/µmol, and the radiochemical purity approximately 95%.

5.1.2 PET/(CT) image acquisition and processing

Studies I-II

PET/CT studies were performed at the Turku PET Center. The imaging device was a Discovery VCT PET-CT (General Electric Medical Systems, Milwaukee, WI, USA). After six-hour fasting, approximately 370 MBq of ^{18}F-FDG was injected intravenously to each patient. Static PET/CT imaging covering the upper torso from eyebrows to mid-thighs was started approximately 60 minutes after ^{18}F-FDG injection (3-minute emission scan/position). Delayed PET emission images of the upper abdomen were acquired at approximately 110 minutes after administration of ^{18}F-FDG. Transaxial, coronal, and sagittal sections were obtained for visual analysis. Any abnormal focal ^{18}F-FDG activity was considered as positive for tumor. To perform the semiquantitative analysis, the maximum and mean SUVs were calculated in the suspected neoplastic focus. ^{18}F-FDG activity concentration values were corrected for radioactive decay and SUV were calculated (SUV=Activity Concentration / (Injected Dose / Body Mass)). Retention

index (RI) using early and delayed SUVs was calculated (RI=100X(SUV_{2h}-SUV_{1h})/SUV_{1h}). In *studies I* and *II*, the resulting values were normalized to plasma glucose levels according to the formula SUVX(plasma glucose/5) (Boellaard *et al.*, 2008)**.** For definite assessment of a pancreatic tumor, both the SUV and visual aspects were considered. The radiation dose of low-dose CT and ^{18}F-FDG injection was approximately 15 millisievert (mSv).

In *study II*, the methods of measuring BF with ^{15}O-H_2O are based on the principle of inert gas exchange between blood and tissues (Kety and Smith, 1945), and BF images were calculated using the linearized one-tissue compartment model (Blomqvist, 1984). Lawson-Hanson non-negative least squares were used to calculate general linear least squares functions. The input time-activity curves (TACs) for ^{15}O-H_2O scans were obtained directly from transaxial PET images using a threshold method to locate the aorta. Suitable planes were selected visually with the help of PET and CT images. The diameter of the aorta in these planes was measured using the CT image, and the value was used in the threshold process as well as the correction of partial volume and spill-over effects during extraction (Liukko K.E *et al*., 2007). After extraction of the pancreatic TAC from the image series and comparison to arterial TAC, no delay was observed in the ascending part of the TAC, and no correction was performed. Images were analysed on computer using a non-commercial research imaging software (Vinci, Max-Planck-Institut für Neurologische Forschung, Cologne, Germany). Perfusion and SUV of ^{18}F-FDG for different tissues were obtained by positioning a round 3-plane region of interest (ROI) with a diameter of 1 cm (0.77 cm^3) on the area of the lesion with the highest ^{18}F-FDG uptake, and copying it onto the corresponding region in the perfusion image using the CT image as anatomical reference. This was facilitated by the good co-registration of PET and CT images from the PET/CT scanner. To calculate metabolism/blood flow ratio (SUV/BF), ^{18}F-FDG SUVs normalized to plasma glucose were divided by the blood flow values to obtain the SUV/BF ratio. Effective radiation dose per injection of ^{15}O-H_2O was 1.2 mSv.

Studies III-V

Patients fasted for at least six hours before the PET or PET/CT scan. If the patient was under medication that prevents pancreatic insulin release (diazoxide, somatostatin analogues or cortisone), the medication was withdrawn for the study day (24 hours). Plasma glucose level was monitored and a glucose (G5%-G10%, 40-100 ml/h) infusion was given, if needed, to keep plasma glucose between 4.0-5.0 mmol/l. The average administered dose of ^{18}F-DOPA was approximately 234 MBq. Scanning began 60 minutes after injection. Patients underwent a whole body PET scan from the level of the eyes to the mid-thigh with a GE Advanced PET scanner operated in 2D mode. The GE Advance PET scanner consists of 18 rings of bismuth germinate detectors yielding 35 transverse slices spaced at 4.25 mm intervals. The imaging field of view is 55 cm in diameter and the axial length is 15.2 cm. To obtain images for visual and semi-quantitative analysis the data were corrected for deadtime, decay, and photon attenuation, and reconstructed in

a 128 x 128 matrix. The final in-plane resolution in the segmented attenuation correction and iterative-reconstructed and Hann-filtered (4.6 mm) image was 5 mm full-width half-maximum (FWHM) when scanned with GE Advance. After May 2005 scans were acquired on a Discovery VCT PET-CT (General Electric Medical Systems, Milwaukee, WI, USA) operated in 3D mode. A fully 3D reconstruction algorithm (VUE Point) was used when scanning with PET-CT. Images were reconstructed using two iterations and 28 subsets with a 6.0 mm FWHM postfilter. In combined PET-CT, a CT-based scan was used for attenuation correction purposes and to help in anatomical localization of ^{18}F-DOPA uptake. Immediately after the CT, an emission PET scan was acquired in 3-dimensional mode over the same anatomical regions starting at the level of the mid-thigh. The decarboxylase inhibitor, carbidopa, was given as a premedication in all patients in *study IV* and in 19 patients in *study V*.

In *study III*, PET images were analyzed visually and semi-quantitatively by calculating mean and maximum SUVs in the ROIs drawn separately on the pancreatic head, body, and tail. Axial, coronal, and sagittal views were evaluated, with the pancreas invariably having a sufficiently high uptake of ^{18}F-DOPA to distinguish it from the liver, duodenum, and kidneys. Variable uptake was seen in the gallbladder and biliary duct. Pancreatic tissue uptake of PET images was always correlated side by side with anatomical reference images of CT or MRI. Interpretation was based on consensus of two specialists with significant experience in PET imaging, and there was no disagreement.

In *study V*, PET images were analyzed visually and semi-quantitatively by calculating mean and maximum SUVs in the ROI. ROIs were placed around the regions of increased ^{18}F-DOPA uptake for SUV_{max} and SUV_{mean} determination. Any focal tracer accumulation exceeding normal regional tracer uptake was interpreted as a pathological finding. Whenever PET/CT was available, a clear uptake in the area where CT suggested bone fracture or degenerative bone lesions was not regarded as a positive finding.

5.2 Multidetector row computed tomography (MDCT) *(I, III, V)*

In *studies I* and *II*, diagnostic abdominal MDCT with pancreas protocol was performed as part of clinical routine. At the same time, CTA was done. MDCT examination was performed with a multisection scanner with four- or 16-section capability (GE medical Systems, Milwaukee, Wis). Non-ceMDCT of the upper abdomen is performed with 5-mm section thickness and 5-mm spacing. An intravenous contrast agent was administered and imaging was started in three phases half-automatically. The first two phases were imaged in a thin-sliced section (64 X 0.625 mm) of the upper abdomen (arteriography and parenchymic imaging) and the third, venous phase imaging of the whole abdomen. Radiation dose was approximately 15-20 mSv.

In *study III*, all patients were examined with CT. Seven out of ten patients were imaged on a four-row CT scanner (Siemens Volume Zoom, Erlangen, Germany), and three patients were imaged on a one-row CT scanner (Siemens Somatom Plus, Erlangen, Germany). In

all examinations the reconstructed final transverse slice thickness was either 5 or 6 mm. Four patients were imaged without contrast injection and after contrast administration in both the arterial and venous phase. Six patients were imaged without contrast and post-contrast venous phase.

Due to the retrospective nature of *study V*, CT was performed in different radiology clinics, and consequently no uniform protocol could be described. CT was performed on 75 patients.

5.3 Magnetic resonance imaging (MRI) *(I-III)*

In *studies I* and *II*, MRI of pancreas and MRCP were performed using a 1.5 Tesla system (Intera, Philips Co Ltd, Netherlands) using a phased-array surface coil. T_1-weighted coronal and axial fast field (dual) echo images were obtained. Gadolium-enhanced dynamic T_1-weighted imaging was performed in three phases (arterial, parenchymal, and venous) concentrating on the pancreatic parenchyma. The last phase was obtained in the axial plane. Axial fat saturated T_2-weighted MRI and MRCP was performed using a single-shot fast spin-echo sequence before contrast agent administration.

In *study III*, MRI imaging was performed at 1.5 Tesla (Vision or Symphony, Siemens Medical System, Erlangen, Germany) on six patients and at 1.5 Tesla (Genesis Signa, GE Medical Systems, Milwaukee, USA) on one patient. Five patients were imaged on Symphony with the following pulse sequences: transverse T_2-weighted images with and without fat saturation, and transverse T_1-weighted images with slice thickness of 5 mm, in addition to axial T_1-weighted images with and without administration of contrast agent, gadopentetate dimeglumine (Magnevist, Schering AG, Berlin, Germany). The T_1-weighted sequence was performed after intravenous administration of Magnevist followed by a saline flush in pre-contrast, arterial, venous, and steady state phases. One patient was imaged with Vision with the following pulse sequences: transverse and coronal T_2-weighted images with slice thickness of 5 mm, transverse T_2-weighted images with slice thickness of 6 mm, and T_1-weighted images with fat saturation with and without Magnevist. One patient was imaged with Genesis Signa with the following pulse sequences: transverse T_2-weighted images with and without fat saturation, transverse T_1-weighted phase images, coronal T_2-weighted images with fat saturation, and transverse T_1-weighted GR images with fat saturation. This last sequence was performed with and without administration of Magnevist in pre-contrast, arterial, venous, and steady state phases.

In the retrospective *study V*, MRI was performed on 23 patients with different imaging protocols.

5.4 Biochemical status

Studies I and *II*. All patients had blood samples taken including complete blood count, CRP, Ca19-9, CEA, and liver values (alkaline phosphatase, alanin transferase, total

bilirubin, international normalized ratio) and amylase. Extra serum samples were collected from each patient.

Studies III-V. Endocrine status of the study patients was collected based on the type of NET, shown in more detail in articles III-V. In *study V*, in the primary diagnosis and staging group, only patients with biochemical confirmation of disease were included. The restaging group also included patients with negative biochemistry (n=17).

5.5 Statistics

Statistical analyses were performed using SAS/STAT statistical analysis program package, version 8.2 (SAS Institute Inc., Cary, NC, USA) in *studies I, II, IV* and *V* and SPSS statistical software (version13.0; SPSS Inc, IL, USA) in *study III*. Specificity and sensitivity of different imaging methods were calculated using a 2X2 contingency table. A Mc Nemar's test was performed to compare different imaging methods (*studies I, III, V*) and κ coefficient was determined to quantify agreement of imaging mathods (*studies III, V*). In *study I*, for the receiver operating characteristics (ROC) analysis, sensitivities and specificities for different cutoff points were calculated. Both in *study I* and *study II*, the survival analyses were carried out using Kaplan-Meier estimates and the association of SUV_{max}, SUV/BF ratio and survival was assessed by log-rank test. $P<0.05$ was considered statistically significant. Student's unpaired t-test was used for normally distributed parameters, while correlations for different groups separately were calculated using Pearson correlation. The Wilcoxon signed rank test was used to evaluate the number of regions and lesions diagnosed by different imaging methods in *study V*. The 95 % confidence interval was calculated for the absolute mean difference between groups. P values of less than 0.05 were considered statistically significant. Results are expressed as mean±standard deviation.

6 RESULTS

6.1 PET/CT using ^{18}F-FDG and ^{15}O-H_2O in primary diagnosis and staging of pancreatic tumors *(I, II)*

6.1.1 Primary diagnosis

6.1.1.1 Glucose uptake in pancreatic tumors (I)

Out of 38 study patients, pancreatic adenocarcinoma was diagnosed in 17, NET in three, mass-forming pancreatitis in four, cystic lesion in six, and fibrosis in two. Six patients had a finding of normal pancreas. The diagnostic accuracy of ^{18}F-FDG-PET/CT for primary pancreatic malignancy was 90% compared to 77% and 79% for MDCT and MRI, respectively. Patients were divided into two groups depending on indication; 1. pancreatic tumor seen in US or/and CT in referring center, and 2. patients with jaundice and suspected malignant biliary stricture seen in ERCP.

In the group of 17 patients with suspicion of pancreatic tumor in US or CT in the referring center, the PPV and NPV of ^{18}F-FDG-PET/CT to differentiate between benign and malignant tumor were 100% and 90%, respectively *(Table 10)*. The specificity was higher in ^{18}F-FDG-PET/CT (100%) than in MDCT (80%) or MRI (90%). On the other hand, the sensitivity of ^{18}F-FDG-PET/CT was lower than that of MDCT or MRI (86% *vs.* 100%)**.** In this group, a lesion pathologically verified as a low-grade NET led to a false negative finding in ^{18}F-FDG-PET/CT.

Table 10. Ability of ^{18}F-FDG-PET/CT to differentiate benign and malignant tumor seen in MDCT (n=12) and/or US (n=10) in referring center (n=17)

	Malignant			
^{18}F-FDG-PET/CT	+	-		
+	6	0	100% (6/6)	PPV
-	1	10	90% (10/11)	NPV
	86% (6/7)	100% (10/10)		
	sensitivity	specificity		

Twenty-one patients with jaundice underwent ERCP and in all cases the stricture was suspected to be malignant. ^{18}F-FDG-PET/CT was able to distinguish between a benign and a malignant stricture with a sensitivity of 85%, and with a PPV of 92% *(Table 11)*. The corresponding sensitivities of MDCT and MRI were 77% and 86%, respectively.

Table 11. Ability of ^{18}F-FDG-PET/CT to differentiate benign and malignant biliary stricture (n=21) *(© Reprinted with permission of the copyright holders.)*

	Malignant			
^{18}F-FDG-PET/CT	+	-		
+	11	1	92% (11/12)	PPV
-	2	7	78% (7/9)	NPV
	85% (11/13) sensitivity	88% (7/8) specificity		

Distributions of SUVs in the normal pancreas, benign, and malignant pancreatic lesions are shown in box-plots *(Figure 6)*. Average SUV_{max1h} was significantly higher in malignant lesions (4.9±2.8) compared to normal pancreas (2.0±0.6, P=0.003) and benign lesions (2.3±0.8, P=0.009). When delayed SUV_{max2h} was used, the significant difference between benign and malignant lesions remained; although at the same level as in SUV_{max1h} *(Figure 6)*.Delayed imaging did not add anything to diagnosis. Glucose-corrected SUV_{max}s and SUV_{mean}s were analyzed and a strong correlation was observed without any significant difference between the compared groups.

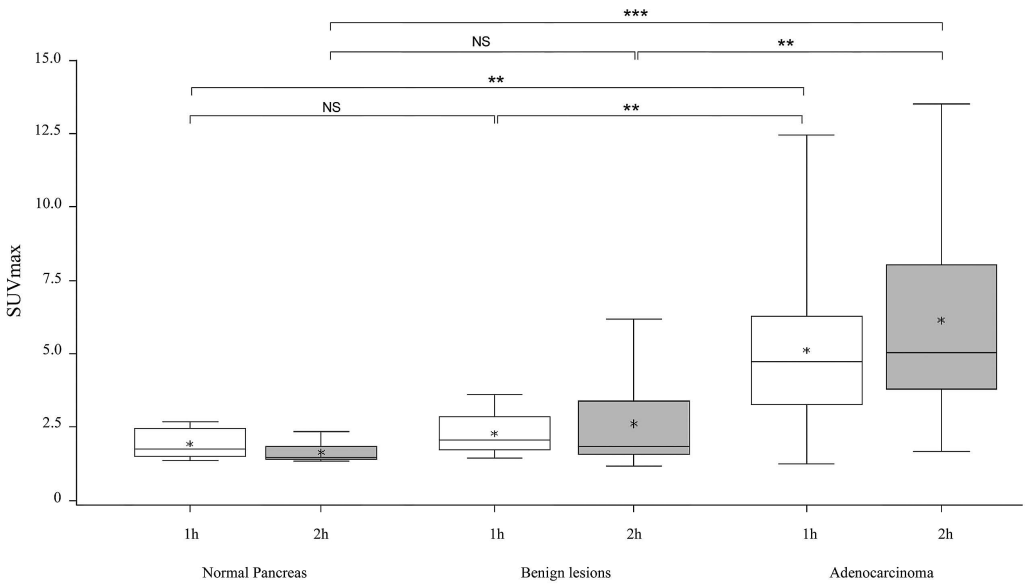


Figure 6. Box-plot images of early (1h) and delayed (2h) SUV_{max}s in patients with normal pancreas, benign lesion, and adenocarcinoma (three patients with pancreatic NET were excluded) *(© Reprinted with permission of the copyright holders.)*

6.1.1.2 Pancreatic flow (II)

In a series of 26 patients, BF patterns varied between groups of normal pancreatic tissue, benign, and malignant lesions. The average BF was 113.8±48.2 ml/min/dl in patients with normal pancreas. Instead, significantly lower BF was observed in patients with a benign or a malignant lesion of the pancreas (59.0±26.7 ml/min/dl and 45.7±18.5 ml/min/dl, respectively). The BFs of a benign and a malignant lesion were not significantly different. In addition, the lesions in the head of the pancreas also decreased BF of the non-tumoral part of the pancreas. *(Figure 7)*

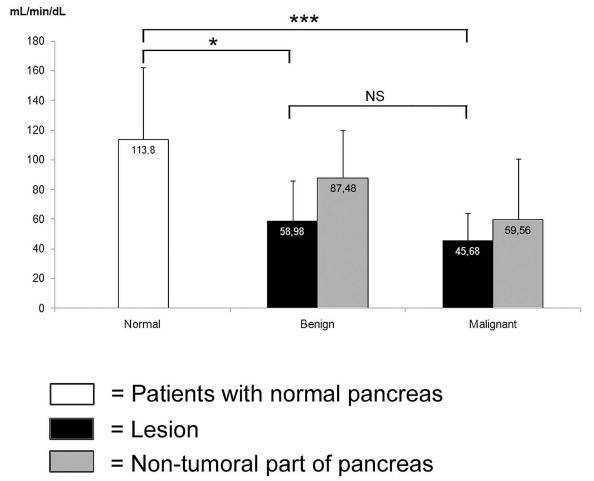


Figure 7. Blood flow of normal pancreas and different types of pancreatic lesions *(© Reprinted with permission of the copyright holders.)*

6.1.1.3 Association between metabolism (SUV) and blood flow (BF) (II)

Because the pattern of glucose uptake and perfusion were opposite in patients with pancreatic adenocarcinoma, we tested whether the ratio of SUV and BF could be useful for the assessment of type of tumor. SUV/BF ratio was significantly different in normal pancreas and benign lesions compared to malignant lesions, but the ratio was not significantly different between normal pancreas and benign lesions *(Figure 8)*. *Figure 9* shows is an example of the SUV/BF image, which is calculated by realignment of tumor in both images and reslicing. To obtain the resulting ratio image, the individual ^{18}F-FDG SUV_{max} voxel values were divided by the BF voxel values of the same anatomical position in the BF image.

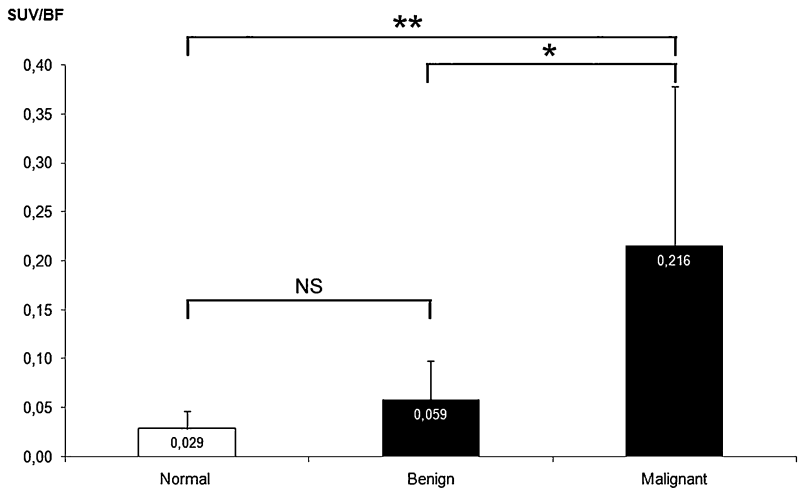


Figure 8. Metabolism (SUV) and blood flow (BF) ratio of normal pancreas, benign, and malignant lesion *(© Reprinted with permission of the copyright holders.)*

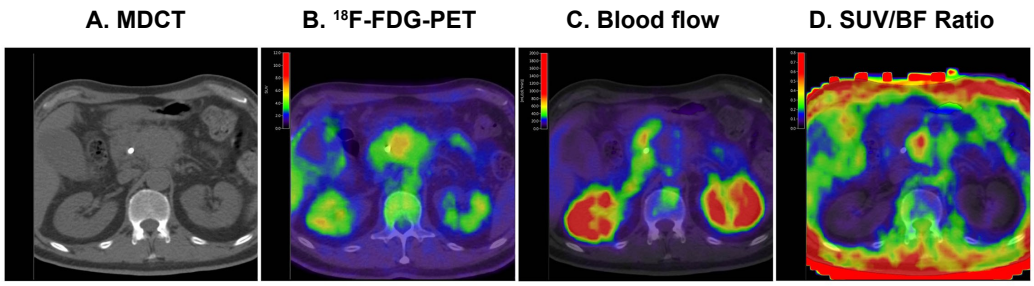


Figure 9. A 64-year old male with a history of abdominal pain and significant weight loss developed jaundice. MDCT showed a tumor in the head of the pancreas (A), and ^{18}F-FDG uptake was observed in PET (B). Reduced BF of the tumor was detected compared to the non-tumoral part of the pancreas in ^{15}O-H_2O-PET/CT (C). Further, SUV/BF ratio was high, 0.58, as a sign of aggressive disease (D). At operation, radical resection was not possible and the biopsy of the tumor revealed adenocarcinoma gradus 2. The patient died three months after diagnosis.

Furthermore, when the SUV_{max} was plotted against the BF values of the same lesion, a clustering of values according to the lesion pathology was observed. However, there was no significant correlation between ^{18}F-FDG SUV_{max} and BF in any of the three groups. Corresponding SUV_{max} and SUV_{mean} were calculated and the results were similar.

6.1.2 ^{18}F-FDG-PET/CT in staging (I)

N-staging: In 17 patients with advanced pancreatic adenocarcinoma, all three imaging methods (MDCT, MRI, and ^{18}F-FDG-PET/CT) had a sensitivity of 30% for N-staging. Clinical/pathological N-stage changed in five out of eight patients after ^{18}F-FDG-PET/CT or MDCT, and in six patients after MRI.

M-staging: ^{18}F-FDG-PET/CT had significantly superior sensitivity (88%) in M-staging of disease compared to MDCT and MRI (38%). Overall clinical/pathological M-stage changed in one out of 14 patients after ^{18}F-FDG-PET/CT compared to four patients after MDCT and MRI. *Figure 10* shows an example of a patient with additional liver metastasis seen in ^{18}F-FDG-PET/CT.

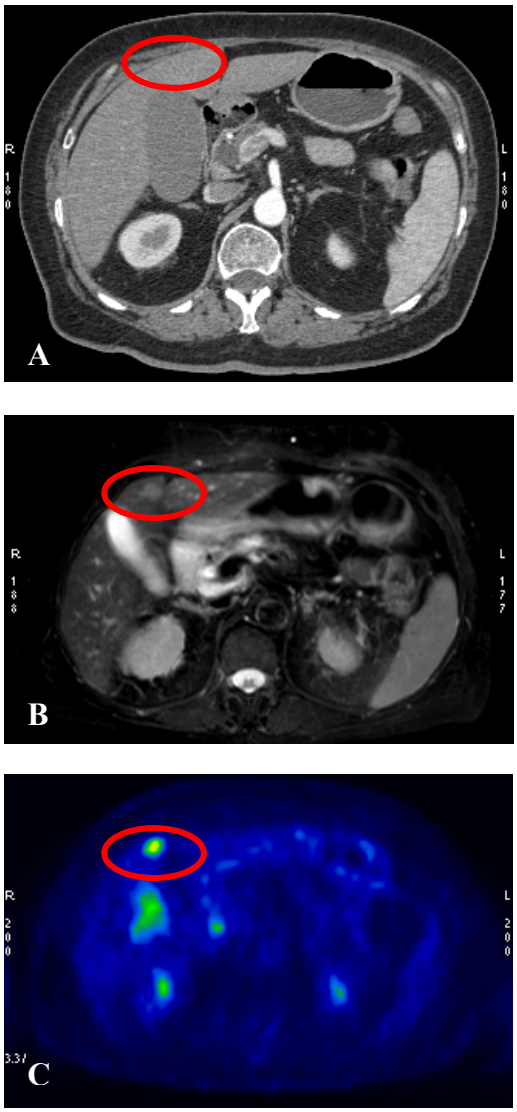


Figure 10. Representation of a patient with additional liver metastasis seen in segment IV. A. contrast enhanced MDCT image with normal finding, B. in T_2 fat-saturated MRI image (diagnosed as liver cyst preoperatively), and C. a corresponding ^{18}F-FDG-PET/CT image.

6.1.3 Impact on patients' management (I)

The clinical management of 10 out of 38 patients (26%) was altered after ^{18}F-FDG-PET/CT compared to findings of MRI, and in eleven patients (29%) when compared to results of MDCT. Six patients' (16%) operations would have been avoided if ^{18}F-FDG-PET/CT findings had been relied on. Three of these patients had additional liver metastases seen in ^{18}F-FDG-PET/CT and three patients had benign disease (1 CP, 2 SCA). In addition, in two patients with biliary stricture, MDCT suspected a tumor in the head of the pancreas, while ^{18}F-FDG-PET/CT was negative. Neither of these patients was operated on and no malignancy has been observed in follow-up.

6.1.4 Survival (I-II)

In *study I*, the association between SUV_{max} and the overall survival was calculated in patients with pancreatic adenocarcinoma, with the mean follow-up time at the close-out date being 15.8±3.4 months. In this group, one patient had RO (complete) resection, while two patients had R1 (a distance of the tumor from the resection margin of less than 1 mm) and R2 (incomplete; remaining macroscopic tumor tissue) resection. In 14 patients, resection was not possible. All seventeen patients had systemic chemotherapy with gemcitabine lasting from two weeks to 12 months. Kaplan-Meier analysis was performed taking account of the small sample size limiting the interpretation of the results. Median SUV_{max} (4.27) was used as cut-off value. Kaplan-Meier survival analysis showed significantly poorer survival in patients with high SUV_{max} (>4.27) than in patients with low SUV_{max} (<4.27) (P=0.029) *(Figure 11)*.

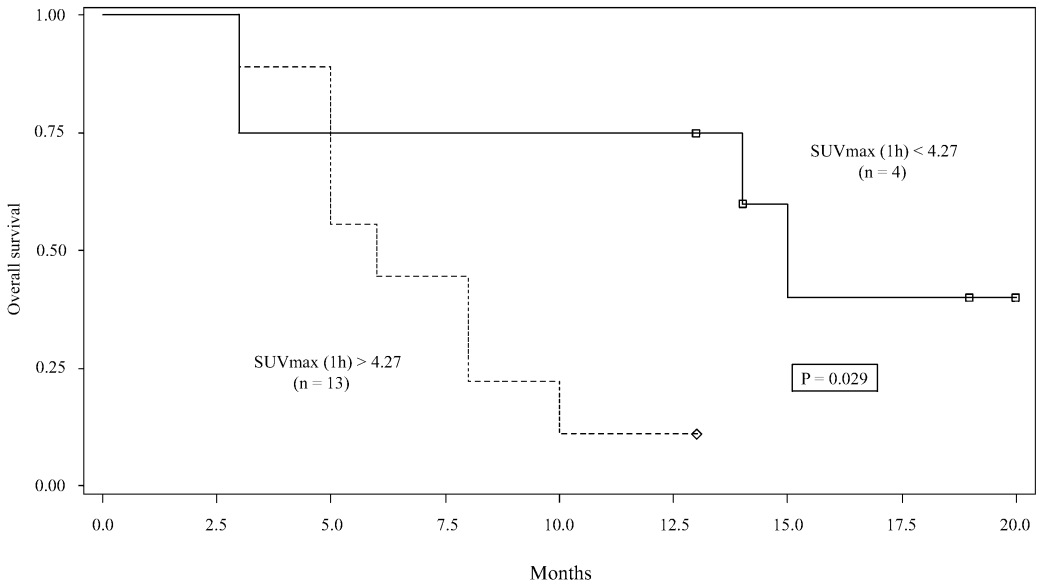


Figure 11. Kaplan-Meier survival analysis of all patients with pancreatic adenocarcinoma (n=17) according to SUV_{max} of primary tumor (*Study I*)

In *study II*, eleven patients with pancreatic malignancy were followed for at least 13 months after the diagnosis, and five of these patients were alive at the time of analysis. One patient died soon after ^{18}F-FDG-PET/CT imaging due to postoperative complications. The remaining ten patients were divided into two groups using survival at 12 months after diagnosis as cut-off. The SUV_{max} and BF between the groups living less or longer than 12 months were not significantly different (10.6±5.7 *vs.* 6.7±2.7, P=0.202 and 34.2±14.3 ml/min/dl *vs.* 55.6±18.7 ml/min/dl, P=0.077, respectively). By contrast, when the SUV/BF ratio was compared between these two groups, a high SUV/BF was associated with poorer prognosis (0.3±1.6 *vs.* 0.1±0.5; P=0.024). Similarly, when Kaplan-Meier analysis was performed, taking account of the small number of patients, for all three measurements (^{18}F-FDG SUV_{max}, BF, and SUV/BF ratio) using the respective median values as cut-off, only the SUV/BF ratio showed borderline significance in log-rank test (P=0.056) (*Figure 12)*.

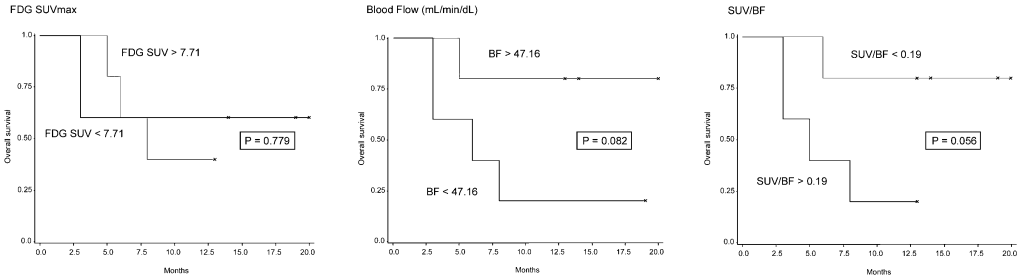


Figure 12. Kaplan-Meier survival analysis of 10 patients with pancreatic cancer using ^{18}F-FDG SUV_{max}, BF, and SUV/BF ratio (*Study II*)

6.2 ^{18}F-DOPA-PET/(CT) in diagnosis of pancreaticoduodenal NET *(I, III-V)*

Studies I, III-V. The overall series of studies included 26 patients with functional and three patients with non-functional pancreaticoduodenal NET *(Table 12)*. In *studies III-V*, ten patients had a solitary benign insulinoma, and one malignant insulinoma with metastasis. Furthermore, three patients had histological verification of focal ß-cell hyperplasia. Eight patients did not have a finding of pancreatic NET. By visual inspection of ^{18}F-DOPA-PET images, it was possible in 16 out of 18 patients (89%) to localize the pancreatic lesion, subsequently confirmed by histological analysis. All patients with ß-cell hyperplasia showed increased focal uptake of ^{18}F-DOPA in the affected areas *(Figure 13)*. As compared to CT or MRI, ^{18}F-DOPA-PET was more sensitive in localizing diseased pancreatic tissue. Additionally, ^{18}F-DOPA- PET was also more accurate than EUS and SRS. *(Table 12)*

Table 12. Accuracy of different imaging methods in patients with pancreatic NET both primary diagnosis and suspicion of recurrence (*Studies I, III-V*)

Pancreaticoduodenal NET	^{18}F-DOPA-PET Ac %	^{18}F-FDG-PET Ac %	CT Ac %	MRI Ac %	IOUS/EUS Ac %	SRS Ac %
functional* n=26	85 (22/26)	ND	44 (11/25)	50 (6/12)	43 (3/7)	50 (4/8)
non-functional** n=3	100 (1/1)	33 (1/3)	100 (3/3)	100 (3/3)	ND	ND

* including: suspicion of insulinoma n=5, suspicion of residive insulinoma n=3, insulinoma n=11, β-cell hyperplasia n=3, vipoma n=1, residive gastrinoma n=1, hepatic metastasis of formerly operated pancreatic NET n=1, multiple pancreatic NET (MEN1 syndrome) n=1

** including: low-grade NET n=2 and high-grade NET n=1

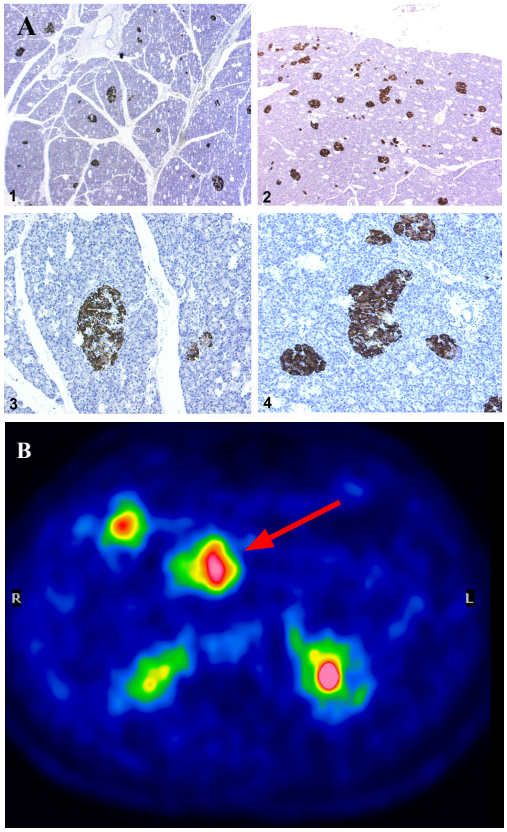


Figure 13. A. The histology of patient #1 (*Study III*) with β-cell hyperplasia. Histological analysis of the pancreas was otherwise normal (**1, 3**) except for a focal islet excess seen in the head of the pancreas (**2, 4**). Original magnification 200 and 400. The histology agreed with the focal ^{18}F-DOPA uptake in the functional PET imaging (**B**). *(© Reprinted with permission of the copyright holders.)*

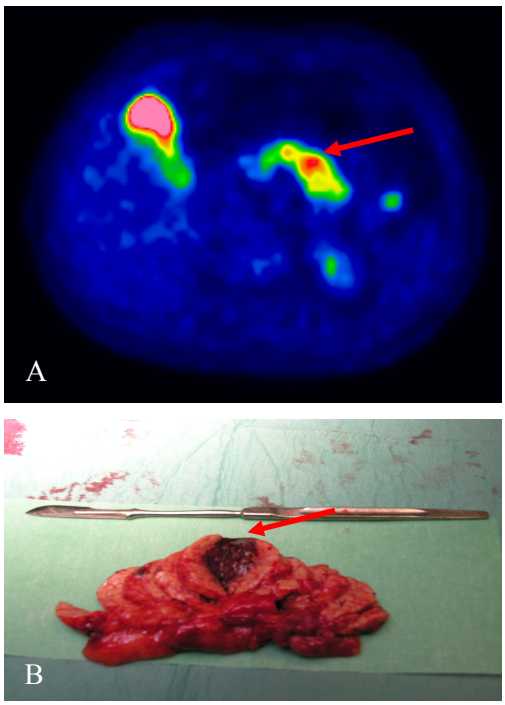


Figure 14. A. Focal ^{18}F-DOPA uptake in the body of the pancreas without carbidopa premedication. **B.** Subtotal pancreatic resection was done and histological analysis showed low-grade malignant insulinoma Ki-67 9% (Patient #1, *Study IV*)

Study IV. This prospective study tested the effect of carbidopa on pancreatic ^{18}F-DOPA uptake in patients with suspected islet cell tumor. All patients had strong biochemical proof of an insulinoma. Three patients were imaged and two patients had well-differentiated insulinoma *(Figure 14)*, and one patient had histological verification of β-cell hyperplasia. Prevention of ^{18}F-DOPA decarboxylation by carbidopa prohibited accumulation of radioactivity into the disease focus in two out of three patients. In one patient with insulinoma both PET scans showed the lesion.

6.3 ^{18}F-DOPA-PET/(CT) in primary diagnosis, staging, and restaging of abdominal NET *(V)*

In *study V*, 93 ^{18}F-DOPA-PET/(CT) scans were analyzed in patients with NETs and overall accuracy of ^{18}F-DOPA-PET/(CT) was 90%. For primary diagnosis and staging of clinically suspected NET, the ^{18}F-DOPA-PET/(CT) has an accuracy of 88% (n=32), and 92% for restaging of disease (n=61). The indications for ^{18}F-DOPA-PET/(CT) imaging of restaging included suspicion of recurrence (n=51), and follow-up studies (n=10). In this group, ^{18}F-DOPA-PET/(CT) detected advanced stage of disease in 31 patients, while in four patients, the PET scan failed to detect metastasis either partly (n=2) or completely (n=2). In these patients with advanced stage of disease, ^{18}F-DOPA-PET/(CT) detected significantly more affected regions and lesions compared to the combined results of CT and MRI. Additionally, ^{18}F-DOPA-PET/(CT) detected a mean value of 0.9 regions and 1.9 lesions more than SRS and MIBG scintigraphy (n=15) *(Table 13)*.

Table 13. Number of affected regions and lesions detected in ^{18}F-DOPA-PET/(CT) compared to combined CT/MRI (A) and SRS/MIBG (B) in patients with advanced stage of NET

	^{18}F-DOPA-PET/(CT) N=31	CT/MRI N=31	
region*	2.7	1.1	P<0.0001
lesion	5.0	1.7	P<0.0001

A

	^{18}F-DOPA-PET/(CT) N=15	SRS/MIBG N=15	
region*	3.0	2.1	P=0.076
lesion	5.5	3.6	P=0.075

B

* different body region (i.e. lung, head-neck region, mediastinum, abdomen, bone)

6.3.1 Other GI-tract NETs and pheochromocytoma (V)

Study V included 26 patients with GI-tract NET. Most of the patients (n=24) had ^{18}F-DOPA-PET/(CT) imaging for restaging of disease. In the restaging group, ten patients had suspicion of recurrence, and 14 patients restaging for treatment planning or follow-up. In the restaging group, the primary tumor originated from the appendix in eight, from the small intestine in five, from the esophagus in two, was of gastric origin in one, and of colorectal origin in two. The rest of the patient had a primary tumor of unknown

origin. In restaging, the sensitivity and specificity were 86% and 100%, respectively. The serum CrA levels were significantly increased in 71% of the patients (73.7±211.1 nmol/l). In GI-NETs, neither biochemical proof of disease nor presence of symptoms was associated with the sensitivity of ^{18}F-DOPA-PET/(CT).

Twenty-five patients with suspicion of primary or recurrent pheochromocytoma were imaged using ^{18}F-DOPA-PET/(CT). In primary diagnosis of disease (n=16), all patients had biochemical proof of disease with elevated urinary metanephrine levels (11.1±15.3 μmol/day). ^{18}F-DOPA-PET/(CT) had an accuracy of 100%, and five patients had a finding of pheochromocytoma. In the restaging group, eight patients had suspicion of recurrence and one patient had a follow-up study. In restaging of pheochromocytoma the accuracy was 89%. In three patients with suspicion of residive extra-adrenal pheochromocytoma, ^{18}F-DOPA-PET/(CT) achieved an accuracy of 100%.

6.3.2 Impact on patients' management (V)

In 44 patients ^{18}F-DOPA-PET/(CT) scans gave additional information compared to conventional imaging methods, and in an additional 11 patients, ^{18}F-DOPA-PET/CT gave information for clinical diagnosis without comparative conventional imaging, thus the clinical management was changed in 55/93 (59%) cases. In addition, ^{18}F-DOPA-PET/(CT) confirmed the diagnosis in 29 obscure cases with inconclusive findings in conventional imaging. In 35 patients with biochemical proof of disease and negative conventional imaging, ^{18}F-DOPA-PET/(CT) had a PPV of 92% and a NPV of 95%.

7 DISCUSSION

In recent years, PET has gained acceptance as a promising modality for oncological imaging. In the field of GI-malignancies, the method has been applied in the diagnosis of esophageal and colorectal cancer, as well as lymphoma. Promising results have also been gained in the diagnosis of pancreatic cancer and NETs, although the role of PET is still evolving. The use of PET has been extensively studied since the 1990's in pancreatic cancer and NETs, but controversial results have been obtained in the clinical trials.

In the present series of studies, different PET tracers were used in the diagnosis and staging of pancreatic tumors and NETs. Metabolisms of pancreatic tumors were studied using tracer ^{18}F-FDG *(I)* and BF of these tumors using ^{15}O-H_2O *(II)*. In *studies III-V* aminoacid precursor tracer, ^{18}F-DOPA, was used in PET/(CT) imaging to assess the role of this method in different types of NETs, especially among pancreatic NETs *(III-IV)*.

7.1 The role of PET in pancreatic tumors *(I-V)*

7.1.1 Diagnosis of primary pancreatic tumor

Differential diagnosis of pancreatic diseases remains a difficult problem in clinical practice. The purpose of *studies I* and *II* was to study the role of ^{18}F-FDG-PET/CT in primary diagnosis of pancreatic tumors, as well as ^{15}O-H_2O-PET/CT in assessing BF of different types of pancreatic lesions. *Studies III* and *IV* were designed to study insulinoma and β-cell hyperplasia using ^{18}F-DOPA-PET/(CT) with and without carbidopa premedication. *Study V* was a retrospective analysis of ^{18}F-DOPA-PET/(CT) in the diagnosis of different types of NETs, and included 13 patients with suspicion of primary or residive pancreatic NET.

7.1.1.1 Pancreatic adenocarcinoma (I, II)

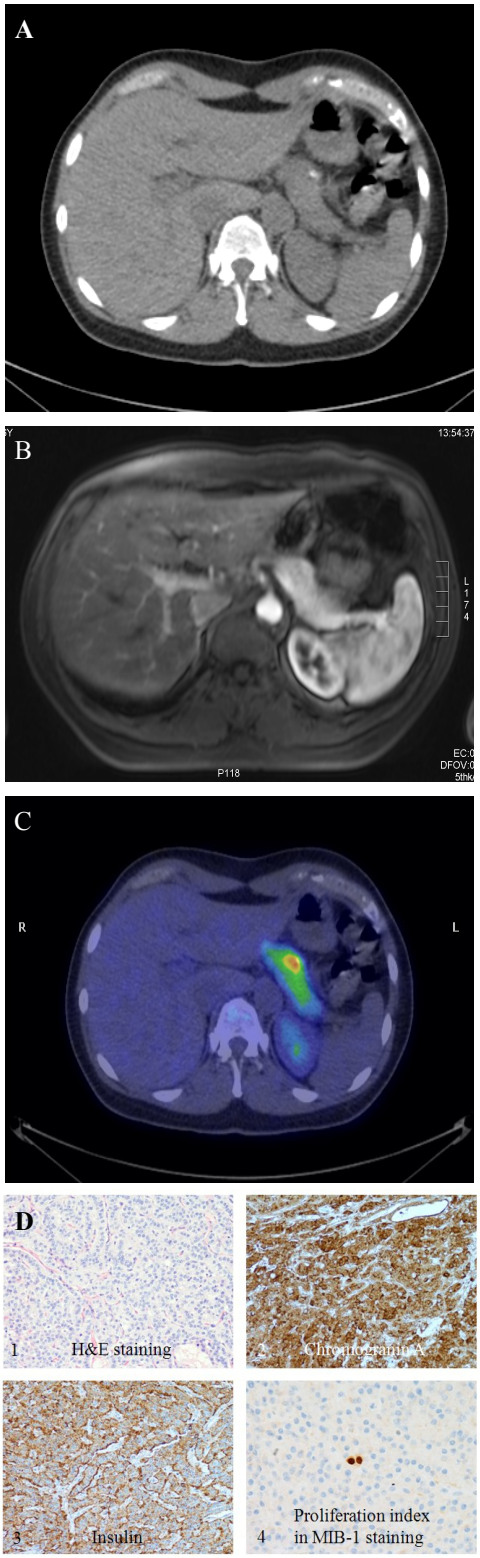
The main finding was that ^{18}F-FDG-PET/CT had significantly higher accuracy compared to MDCT and MRI in a group of 38 patients (90% *vs*. 77% and 79%) *(Study I)*. Especially in 21 patients with suspected malignant biliary stricture, ^{18}F-FDG-PET/CT was able to differentiate a malignant and a benign biliary stricture with a high PPV of 92%. So far, only two prospective studies have been conducted using combined PET/CT in the diagnosis of pancreatic cancer with encouraging results (Heinrich *et al.*, 2005;Schick *et al.*, 2008). In addition to the improvements in the PET/CT technique, both CT and MRI have also undergone significant technical developments. Related to this, the strength of our study was that we used the most dedicated scanners not only in PET/CT but also in MDCT and MRI. Concerning patients with jaundice and biliary stricture, the results of our study are in good agreement with former studies. Study by Wakabyashi reported a sensitivity of 86% for ^{18}F-FDG-PET in 30 patients with biliary stricture (Wakabayashi *et al.*, 2005). Later, the same group reported that delayed scanning could be advantageous

in the diagnosis of biliary stricture for those patients with negative or equivalent early imaging achieving a sensitivity of 86% for delayed scanning (Nishiyama *et al.*, 2007). Former studies have shown the advantage of delayed scanning in the differentiation of malignant and benign lesions (Nakamoto *et al.*, 2000;Lyshchik *et al.*, 2005). In our study delayed imaging did not provide any significant benefit in the diagnosis of pancreatic lesions. Furthermore, *study I* included three patients with non-functional pancreatic NET, and it is well-known that ^{18}F-FDG-PET/CT is poor in detecting low-grade NETs (Adams *et al.*, 1998). Accumulation of ^{18}F-FDG in tumors is an index of increased glucose uptake reflecting tumor aggressiveness, and, therefore ^{18}F-FDG-PET/CT is more sensitive in detecting high-grade NETs. In accordance with previous studies, in *study I,* only one out of the three NETs was detected using ^{18}F-FDG-PET/CT, and histology in that case confirmed a high-grade NET with a proliferation index Ki-67 of 25% *(Table 12)*.

For the first time, the differences in BF and its relationship to metabolic activity both in pathological pancreatic lesions and in the normal pancreas were evaluated using combined ^{15}O-H_2O- and ^{18}F-FDG-PET/CT imaging *(Study II)*. The study showed that both benign and malignant pancreatic lesions had decreased perfusion compared to normal pancreatic tissue. No significant difference between the BF of benign and malignant lesion was observed. However, the SUV/BF ratio seemed to differentiate benign findings from malignant tumors. Studies on the relationship between the metabolism of tumors and their BF have provided rather variable results; both a positive correlation (Zasadny *et al.*, 2003) and a negative correlation (Hirasawa *et al.*, 2007). *Study II* did not demonstrate any correlation between these two parameters, and this finding was in agreement with a study by Hoekstra et al. (Hoekstra *et al.*, 2002).

7.1.1.2 Pancreatic NETs (III-V)

Study IV reported the novel finding that the use of carbidopa premedication in ^{18}F-DOPA-PET/CT could mask a finding of insulinoma or β-cell hyperplasia. Prevention of ^{18}F-DOPA decarboxylation using carbidopa totally prohibited accumulation of radioactivity into the disease focus in two out of three patiens. This report was the first to describe this important phenomenon. In accordance with this finding, de Lonley reported in a study of DOPA decarboxylase in infants with congenital diffuse and focal hyperinsulinism, that in one child with diffuse form, ^{18}F-DOPA uptake disappeared completely after carbidopa administration (de Lonlay *et al.*, 2006). The explanation behind this phenomenon could be that carbidopa decreases the production of FDA and may potentially cause false negative findings if the visualization of the tumor is related to the storage of FDA in vesicles. Furthermore, vesicular monoamine transporter type 2 (VMAT2) is expressed at dopamine nerve terminals in the central nervous system and β-cells but is absent in the exocrine pancreas and many abdominal tissues (Souza *et al.*, 2006). It is assumed that FDA is required for the imaging of β-cells and insulinomas, while uptake of radioactivity is related to the storage of FDA into vesicles. Therefore, the routine use of carbidopa premedication before ^{18}F-DOPA should be avoided when there is a suspicion of an insulinoma or β-cell hyperplasia in adults or in infants. A suggested imaging protocol for patients with suspicion of insulinoma is presented as a case report in *Figure 15.*



*A 46-year-old female with a 10-year history of episodes of fatique, dizziness, and seizures after exercise. The symptoms relieved after eating. The fasting glucose level was 2.3 mmol/l with a concomitant insulin level of 5.8 mU/l, and C-peptide level 0.66 nmol/l. Biochemical tests and symptoms revealed an insulinoma. Neither MDCT (**A**) nor MRI (**B**) was able to detect a pancreatic tumor. The patient also underwent EUS without any significant findings in the pancreas. Therefore, the patient was referred to ^{18}F-DOPA-PET/CT. ^{18}F-DOPA-PET/CT without carbidopa premedication showed an increased ^{18}F-DOPA uptake in the tail of the pancreas (**C**). Patient was operated on and the tail of the pancreas was resected laparoscopically. Histolological analysis showed typical findings of well-differentiated insulinoma (WHO1) with a size of 6 mm (**D**) (1. hematoxylin-eosin -, 2. chromogranin A -, 3. insulin -, 4. MIB-1 stains). Postoperatively, patient has remained entirely asymptomatic.*

Figure15. Imaging protocol of insulinoma presented as a case report

In patients with insulinoma or β-cell hyperplasia, ^{18}F-DOPA-PET was a significantly more sensitive imaging method to identify the disease focus compared to CT or MRI. It has been shown recently by us (Otonkoski *et al.*, 2006) and others (Ribeiro *et al.*, 2005;de Lonlay *et al.*, 2006) that ^{18}F-DOPA-PET is a useful non-invasive diagnostic method in infants with PHH. *Study III* was the first to study prospectively ^{18}F-DOPA-PET in adult patients with PHH. This study showed focal accumulation of ^{18}F-DOPA in the pancreas of nine out of ten patients, and the focal lesion was confirmed histologically as an insulinoma or ß-cell hyperplasia in all ten patients. In line with infant studies, experience with adult patients indicates that the functional imaging with ^{18}F-DOPA-PET might help to optimize surgical treatment of focal ß-cell hyperplasia. So far, ß-cell hyperplasia is a rare and poorly characterized disease, and the existence of focal ß-cell hyperplasia in adults has been questioned. Recently, there has been a rising interest in ß-cell hyperplasia as a cause of PHH in adults (Jabri & Bayard, 2004;Tsujino *et al.*, 2005;Anlauf *et al.*, 2005;Service *et al.*, 2005). A novel finding was reported by Service et al. when six cases of ß-cell hyperplasia were found in patients after gastric-bypass surgery as treatment for severe obesity (Service *et al.*, 2005). The use of bariatric surgery for treating severe obesity has increased dramatically over the past decade, and related to this, the number of patients with ß-cell hyperplasia is also growing. Accurate localization of islet cell tumors provides important support for the surgery. Concerning the importance of biochemical proof of disease before ^{18}F-DOPA-PET imaging, the retrospective *study V* showed lower diagnostic accuracy than *study III* in a group of patients with pancreatic NETs (63% *vs.* 90%, respectively). This is explained by the fact that patients with suspicion of insulinoma had rather weak biochemical proof of disease in *study V* because the patients with histologically verified insulinoma and β-cell hyperplasia reported in *study III* were excluded. It is very important to have a strong biochemical proof of functional pancreatic NET to obtain the greatest benefit from ^{18}F-DOPA-PET/CT.

7.1.2 Staging of pancreatic adenocarcinoma (I)

T- and N-staging: In *study I*, in 12 patients out of 17 with malignant disease, clinical T-stage could be assessed, and it was altered in nine patiens after ^{18}F-FDG-PET/CT (8 underestimated, 1 overestimated). ^{18}F-FDG-PET/CT had no additional value compared to MDCT or MRI in T-staging of pancreatic adenocarcinoma. Clinical N-stage was changed in five out of eight patients after ^{18}F-FDG-PET/CT. Related to this, ^{18}F-FDG-PET/CT was not able to assess the clinically important resectability of the tumor due to low sensitivity in detection of the local spreading of disease. The high signal intensity of the primary tumor hides the active lymph nodes near by. In line with this, there are no previous data supporting the usefulness of ^{18}F-FDG-PET in detecting local spread of pancreatic cancer because of the lack of detailed anatomical information (sensitivities 46-71%) (Bares *et al.*, 1994;Diederichs *et al.*, 2000;Wakabayashi *et al.*, 2008). However, it seems that when PET was combined with CT, the ability to show local spreading of disease was still very poor (sensitivity 21-68%) (Lemke *et al.*, 2004;Heinrich *et al.*,

2005). A recent retrospective study by Farma and co-workers reported that by combining different imaging methods (CT, EUS, ^{18}F-FDG-PET/CT) it was possible to increase the detection rate of local disease to 53% compared to 4% when using only ^{18}F-FDG-PET/CT (Farma *et al.*, 2008).

M-staging: In *study I*, ^{18}F-FDG-PET/CT missed the presence of liver metastasis in one out of seven patiens, while both MDCT and MRI missed four of these metastatic liver lesions. In support of our results, several studies (Jadvar & Fischman, 2001;Nishiyama *et al.*, 2005b;Wakabayashi *et al.*, 2008) have shown that ^{18}F-FDG-PET has a complementary role in M-staging. ^{18}F-FDG-PET leads to a more accurate preoperative diagnosis and avoids unnecessary non-curative operations with sensitivities ranging from 70 to 82% and specificities from 95 to 98% (Diederichs *et al.*, 2000;Nishiyama *et al.*, 2005b). With respect to the results of *study I* and previous findings, ^{18}F-FDG-PET/CT is a very useful method when assessing distant disease.

7.1.3 Impact of PET/CT on patients' management (I)

In *study I*, in 10 out of 38 patients, the result of a preoperative ^{18}F-FDG-PET/CT scan would have significantly influenced patients' treatment protocol. The greatest advantage using an additional ^{18}F-FDG-PET/CT was gained in the group of patients with biliary stricture with unknown etiology and inconclusive findings in conventional imaging. In four out of 21 patients with biliary stricture, the additional use of ^{18}F-FDG-PET/CT affected the treatment planning by confirming the adenocarcinoma (n=2) not seen in MDCT or MRI, or by confirming benign etiology (n=2) with a false positive finding in MDCT and MRI. Another group with additional benefit of ^{18}F-FDG-PET/CT imaging was in patients with distant spreading of disease. Strengthening our results, Heinrich et al. also evaluated the impact of ^{18}F-FDG-PET/CT on patients' management, with the finding that five out 59 study patients avoided operation because of metastasis diagnosed by ^{18}F-FDG-PET/CT. In addition, the sum of $1,066 per patient was finally saved by the additional use of ^{18}F-FDG-PET/CT (Heinrich *et al.*, 2005). Based on former studies, 11-16% of the study patients' management was changed by using ^{18}F-FDG-PET/CT (Heinrich *et al.*, 2005;Farma *et al.*, 2008). In terms of the clinical relevance of *study II,* combined ^{15}O-H_2O- and ^{18}F-FDG-PET/CT imaging seems to be a reliable method in the differential diagnosis of pancreatic lesion related to the finding that the SUV/BF ratio was significantly different between these groups. Furthermore, ^{15}O-H_2O-PET/CT could also be utilized in assessing the effect of oncological treatments. However, these findings needs to be studied further. In this respect, tumor BF and metabolism seem to be among the most relevant clinical parameters (Hoekstra *et al.*, 2002;Miles & Williams, 2008).

In *study I*, in 17 patients with pancreatic adenocarcinoma, Kaplan-Meier survival analysis showed poorer survival with high SUV_{max} (cut-off value >4.27). A similar trend was noticed in *study II* when the SUV/BF ratio was calculated in a subgroup of 11 patients with the finding that a higher ratio predicted poorer survival. This result in *study II* could explain in part the resistance of pancreatic cancer to oncological treatments,

such as antiangiogenic therapy (Kindler HL, 2007). Due to the small number of patients conclusions regarding survival should be drawn with caution. In accordance with our finding, former studies have shown a correlation between high SUV in pancreatic tumor and poor survival (Nakata *et al.*, 2001;Sperti *et al.*, 2003). This finding strengthens the idea that repeated ^{18}F-FDG-PET/CT during oncological treatments could be used in assessing the effect of the therapy.

7.2 The role of ^{18}F-DOPA-PET in other forms of abdominal NETs *(V)*

7.2.1 In the primary diagnosis and staging (V)

On the basis of *study V*, ^{18}F-DOPA PET is a very powerful tool for the primary diagnosis of NETs with an accuracy of 88%. We have used ^{18}F-DOPA for almost a decade as a tracer in PET imaging of NETs. Our experiences are in accordance with previous studies. However, all larger previous studies (Hoegerle *et al.*, 2001a;Becherer *et al.*, 2004;Montravers *et al.*, 2006;Koopmans *et al.*, 2006) included mostly patients with advanced NETs. To our knowledge, the current study is the first to assess ^{18}F-DOPA-PET in primary diagnosis of NETs in various organs, and the largest in the diagnosis of pheochromocytoma using ^{18}F-DOPA-PET. Results of this study, especially the high sensitivity of 100% for 25 patients with suspected pheochromocytoma, are in concordance with previous findings. However only one study has been conducted on the primary diagnosis of pheochromocytoma using ^{18}F-DOPA-PET with a reported sensitivity of up to 100% (Hoegerle *et al.*, 2002). Recently, Montravers and co-workers concluded, in their study of 33 patients, that ^{18}F-DOPA-PET seems to be significantly more accurate in well-differentiated than in poorly-differentiated NETs with an accuracy of 89% and 36%, respectively (Montravers *et al.*, 2006). The results of *study V* support this finding; five out of six patients with false negative finding in ^{18}F-DOPA-PET imaging had advanced neuroendocrine carcinoma.

7.2.2 In restaging (V)

In *study V,* the ability of ^{18}F-DOPA-PET/(CT) in the restaging of NETs was analyzed. The current data showed an accuracy of 92% in a group of 61 patients. Furthermore, in patients with a formerly known NET and increasing tumor markers, ^{18}F-DOPA-PET was a highly sensitive first-line imaging method in detecting a recurrent NET. Previously, it has been shown by others that ^{18}F-DOPA-PET is more sensitive than conventional imaging in detecting skeletal lesions (Becherer *et al.*, 2004), and it also found more tumor lesions per region compared with combined SRS and CT (96% *vs.* 65%) (Koopmans *et al.*, 2006) in patients with advanced stage of NETs. The finding of this study is in agreement with these previous studies, since ^{18}F-DOPA-PET detected significantly more tumor regions and lesions than combined CT/MRI imaging ($p<0.0001$) *(Table 13)*.

7.2.3 Impact of patients' management (V)

In *study V*, the main goal was to analyze the clinical value of ^{18}F-DOPA-PET/(CT) in patients with suspicion of primary NET and positive biochemistry as well as restaging of disease. Overall, the clinical treatments of 55 of the 93 study patients were affected. The greatest added value of ^{18}F-DOPA-PET/(CT) was in the group of patients with biochemical proof of disease and inconclusive findings in conventional imaging. In 35 patients with biochemical proof of disease and negative conventional imaging, ^{18}F-DOPA-PET/(CT) achieved both high PPV and NPV (92% and 95%, respectively). Most studies so far have focused on patients with a known NET and extensive metastatic disease. The current study further expands previous studies by assessing the clinical application of ^{18}F-DOPA-PET in patients with only a suspected NET with specific symptoms and positive biochemistry. Previous studies with advanced NET have shown excellent detection properties of ^{18}F-DOPA-PET for liver, bone, and abdominal regions (Becherer *et al.*, 2004;Koopmans *et al.*, 2006). Related to more accurate lesion and region detection, the diagnosis of extrahepatic disease may lead to cancellation of planned liver surgery or other debulking procedures, which are becoming more common for NETs. In addition, more precise determination of the amount and type of tumor burden has an impact on medical treatment choices and may also affect patients' prognosis.

7.3 Methodological considerations, limitations, and strengths of PET in pancreatic tumors and NETs

From the methological point of view imaging of the pancreas using the PET technique is many-sided, and there are several general limitations. First of all, hyperglycemia related to diabetes lowers the sensitivity of ^{18}F-FDG-PET imaging (Diederichs *et al.*, 1998). In *study I,* plasma glucose was measured but we did not use the glucose correction of SUV in the final analysis due to the similar results without glucose correction and the similar level of glucose values between groups (patients with normal pancreas, benign or malignant lesion). In addition, nowadays, clinical ^{18}F-FDG-PET/CT protocol does not include routine glucose corrections. However, those patients selected for *study II* (26 out of 38 patients with additional ^{15}O-H_2O-PET/CT imaging) had significantly different glucose values between patients with benign and malignant lesions, and therefore glucose correction was used to avoid bias.

Secondly, inflammation due to pancreatitis could cause false positive findings in ^{18}F-FDG-PET/CT imaging because inflammatory foci in the pancreas also accumulate ^{18}F-FDG (Friess *et al.*, 1995;Shreve, 1998;Diederichs *et al.*, 1998;Yokoyama *et al.*, 2005). Further, the role of ^{18}F-FDG-PET in AIP is still evolving. Recently, encouraging results have been reported on the differential diagnosis of pancreatic adenocarcinoma and AIP using ^{18}F-FDG-PET with a typical finding of multiple, diffuse and heterogenous ^{18}F-FDG accumulation in patients with AIP (Ozaki *et al.*, 2008). In *study I,* all four patients with mass-forming CP had a negative PET scan. On the other hand, one patient with cystic

lesions due to CP was false positive and one adenocarcinoma was misdiagnosed as a CP.

Thirdly, biliary stenting or other benign inflammatory conditions may have ^{18}F-FDG uptake in PET imaging (Anderson *et al.*, 2004). In our series of patients with jaundice, cholestasis was treated by endoscopic stenting before ^{18}F-FDG-PET/CT scanning, and the placed stent did not cause any problems in interpretation due to the corresponding anatomical CT image. The role of preoperative biliary stenting is under discussion and there is no general consensus. Some studies have shown a positive intraoperative bile culture to be associated with higher mortality and morbidity rates following pancreaticoduodenectomy (Sewnath *et al.*, 2002;Jagannath *et al.*, 2005).

Finally, movement of the pancreas due to respiration is observed to produce artifacts in the area of the diaphragm, and can be decreased by half if optimized breath-holding protocols are used (Beyer *et al.*, 2003). A new gating technique to account for respiratory motion during the PET/CT scan could improve the diagnostic accuracy of pancreatic imaging, although prospective studies have not yet been done.

In *study II*, tumor perfusion was conducted using ^{15}O-H_2O-PET/CT, which has several benefits compared to other methods. First, ^{15}O-H_2O-PET/CT is currently the most quantitative and best validated method to measure perfusion with applications in several tissue and tumor types, even though this method is feasible only in a few centers. An additional advantage of PET imaging is the possibility to concurrently measure metabolic activity using tracer ^{18}F-FDG. In *study II*, the dynamic ^{15}O-H_2O-PET scan was combined with a static ^{18}F-FDG-PET scan. The dynamic ^{18}F-FDG-PET data and calculation of the glucose extraction index would potentially provide more information.Unfortunately, due to lack of longer scanning time, and limited patient compliance this was not possible in this study protocol.

A methodological improvement of ^{18}F-DOPA-PET imaging is the use of the AADC inhibitor, carbidopa, as a premedication. In neurological ^{18}F-DOPA-PET studies, carbidopa has been used for decades to decrease metabolism of ^{18}F-DOPA in the periphery. This increases the cerebral accumulation of labeled amino acids and largely reduces extraction of radioactive metabolites into urine (Örlefors *et al.*, 2006). Carbidopa increases plasma levels of DOPA and OMFD (Hoffman *et al.*, 1992), reduces urinary radioactivity concentration, and thereby improves the visualization of NETs (Örlefors *et al.*, 2006). Several studies have shown that the image quality improves markedly following pretreatment with carbidopa, based on equivalent metabolic pathways (Brown *et al.*, 1998;Koopmans *et al.*, 2006). The high radioactivity in the urinary system might also cause reconstruction artifacts in abdominal scans. Therefore, carbidopa pretreatment has become the standard protocol in PET imaging of NET also in our institute. There is also some evidence that increased formation of OMFD by blocking decarboxylation with carbidopa might have a distinctive role in the imaging of NETs (Bergmann *et al.*, 2004). ^{18}F-fluorine-labeled OMFD has also been tested as a PET tracer for NETs, but

the results are controversial (Bergmann *et al.*, 2004;Beuthien-Baumann *et al.*, 2007). As discussed above, the effect of carbidopa is different when the pancreas is imaged *(Study IV)*.

The studies of this thesis have several limitations. First of all, *studies I and II* included a heterogenous group of patients and only few patients with a finding of cystic lesions and mass-forming CP. A larger number of patients having cystic lesions or CPs would have been interesting and challenging to image using ^{18}F-FDG-PET/CT. Thus, conclusions should not be drawn even though ^{18}F-FDG-PET/CT seems to be a reliable method also in these diseases. Increasing the number of study patients could have improved the power of the statistical analysis, but it is unlikely that the major conclusions of these studies would have changed. Furthermore, due to the small number of patients, the study did not assess the role of ^{18}F-FDG-PET/CT in the diagnosis of premalignant lesions of the pancreas, which would have been a very important aspect from the clinical point of view. In addition, only three out of 17 patients with pancreatic adenocarcinoma had radical resection, and no venous resection was done in our institution. These facts make the reliablity of the T- and N-staging assessment controversial. Another limitation is that in *studies III* and *V*, conventional imaging studies were not performed systematically in all patients, and *study V* was conducted retrospectively. Furthermore, the main limitation of *study V* was the lack of a pathological reference standard, but obtaining a biopsy specimen for histological verification from all participants with negative tests and several lesions was not feasible.

Apart from the aforementioned limitations, the current studies offered several benefits. *Studies I* and *II* were prospectively performed in highly standardized conditions using a combined PET/CT imaging modality and the results compared to dedicated MDCT and MRI. In *study I,* the interpretation of different imaging methods was done blindly. *Studies III* and *IV* were also conducted prospectively, and the small sample size was due to the rarity of pancreatic NETs. Furthermore, since May 2006, carbidopa has been used in our institute as a premedication among NET patients to improve visualization of the tumor, and in *study V,* carbidopa was given to 19 patients.

7.4 Future aspects

The introduction of inline PET/CT scanners and tumor-specific tracers offers a great potential for the PET/CT technique to become standard usage in the primary diagnosis of pancreatic lesions and different types of NETs, in addition to the staging of these diseases.

On the basis of the encouraging results, combined ^{18}F-FDG-PET/CT together with contrast-enhanced MDCT is promising as an ‘all-in-one’ imaging technique for the detection of primary tumor, and for showing the distant metastases of pancreatic cancer. Optimized scanning protocols including control of blood glucose and motion of organs in the upper abdomen can further improve the diagnostic sensitivity of ^{18}F-FDG-PET/

CT, and might enable more accurate detection of early-stage pancreatic cancer, although larger studies are needed to confirm the results of this study. As new therapeutic agents targeting angiogenic mechanisms of pancreatic tumors are being introduced, it is becoming obvious that careful classification and selection of patients prior to treatment is necessary for these therapeutic strategies to be successful (Nalluri *et al.*, 2008). Since some parameters related to BF have been shown to correlate with microvascular density (Folkman, 2002), the use of drugs targeting angiogenesis could be optimized by pre-treatment measurement of BF, which could be measured reliably by the ^{15}O-H_2O-PET/CT technique. Both BF and vascularisation of tumors vary strongly, and therefore poor selection of patients might also explain why many clinical trials have failed to demonstrate any significant benefit of anti-angiogenic therapies in the case of pancreatic malignancy (Kindler HL, 2007). Further studies are needed to evaluate the role of combined ^{15}O-H_2O- and ^{18}F-FDG-PET/CT in assessing the effect of oncological treatments.

New tracer developments are continuously taking place in oncological imaging but there is no strong evidence of new PET tracers in pancreatic cancer. ^{18}F-fluorothymidine has been proposed as a promising new positron-emitting radiopharmaceutical, based on assessment of the proportion of cells undergoing active proliferation. Unfortunately, preliminary results in pancreatic cancer are poor with a sensitivity of only 40% (Quon *et al*., 2008). In the diagnosis of NETs, several promising tracers have been investigated. Receptor-based tracers such as SST analog can now be labeled with positron-emitting isotopes. Thus far, the published results are promising (Gabriel *et al.*, 2007), but only one study has been conducted to compare a receptor-based tracer, ^{68}Ga-DOTA-NOC, to ^{18}F-DOPA showing advantages over ^{18}F-DOPA (Ambrosini *et al.*, 2008). A comparison of the metabolic and the receptor-based approach would be interesting to give more information on inter- and intra-patient heterogeneity of receptor expression, and on metabolic activity within tumor lesions. Further studies are needed to resolve which types of NETs are better visualized by receptor-based tracers and which by metabolic tracers such as ^{18}F-DOPA or ^{11}C-5-HTP. Thus, comparisons between metabolic and receptor-based imaging methods for the detection of NETs are needed in the near future. New targeted drug therapies for NETs are being developed but, up to now, no nuclear medicine techniques have been tested for their value for in the treatment monitoring of NETs.

8 CONCLUSIONS

On the basis of the present investigations, the following conclusions can be drawn

1. *Study I* evaluated the impact of ^{18}FDG-PET/CT, MDCT, and MRI in the primary diagnosis and staging of pancreatic cancer. The clinical management was altered in one fourth of patients using additional ^{18}F-FDG-PET/CT. MRI did not have any additional value compared to MDCT. Based on this study, ^{18}F-FDG-PET/CT, combined with diagnostic MDCT, is an efficient first-line imaging tool in the differentiation of primary pancreatic tumors and the detecting of distant metastasis in pancreatic cancer, but ^{18}F-FDG-PET/CT could not assess the local resectability of the tumor.

2. *Study II* presents data on BF and metabolism in the normal pancreas and pancreatic lesions, measured using ^{15}O-H_2O- and ^{18}F-FDG-PET/CT. BF of a malignant lesion is significantly reduced compared to the normal pancreas. In contrast, BF of a benign and a malignant lesion does not differ. On the other hand, the SUV/BF ratio is significantly higher in malignant lesions than in benign lesions or in patients with a normal pancreas. Furthermore, it seems that in malignant lesions the SUV/BF ratio could predict survival.

3. *Study III* patients with PHH were imaged using ^{18}F-DOPA-PET/(CT). ^{18}F-DOPA-PET/(CT) detected the disease focus in the pancreas in nine out of ten patients as subsequently confirmed by histology. Based on this study, ^{18}F-DOPA-PET/(CT) is a useful method in the diagnosis of insulinoma and β-cell hyperplasia in adult patients.

4. *Study IV* demonstrates the novel finding that prevention of ^{18}F-DOPA decorboxylation by means of carbidopa totally prohibited accumulation of radioactivity into the disease focus in two out of three patients with PHH. Therefore, carbidopa premedication should not be used in ^{18}F-DOPA-PET/CT imaging when islet cell tumor of the pancreas is suspected.

5. In *study V,* ninety-three ^{18}F-DOPA-PET/(CT) scans in patients with NET were evaluated. The diagnostic accuracy was assessed by comparing histopathological reports (n=30) and clinical follow-up (n=63). In patients having ^{18}F-DOPA-PET/(CT) for the primary diagnosis, the accuracy was 88%, and for restaging 92%. This study indicates that ^{18}F-DOPA-PET/(CT) is a sensitive first-line imaging method in both the primary diagnosis and the restaging of NET.

9 ACKNOWLEDGEMENTS

This work was carried out at the Department of Surgery and Turku PET Centre in Turku University during the years 2006-2009.

I express my sincere appreciation to Professor of Surgery Pauli Puolakkainen for all his support, excellent advice and essential help during this project. It has been an honor to work with you. I am indebted to Professor Jaakko Hartiala, head of the Clinical Physiology and Nuclear Medicine Department, Professor Juhani Knuuti, director of the PET centre, and to my chief, Docent Timo Savunen, head of the Surgical Department, for providing all the facilities and for support during this project. Professor Emeritus Juha Niinikoski and Professor Peter Roberts are acknowledged for being so supportive towards my studies.

My endless gratitude is due to my supervisors Professor Pirjo Nuutila and Docent Jari Ovaska for excellent guidance during this project. Thank you, Pirjo, for believing in me. Your perfect blend of effectiveness, responsibility, support and encouragement have guided me through the years and made all this possible. Thank you, Jari, for giving me a great opportunity to work in your clinic of gastroenterological surgery. Your advice in both clinical and scientific work has been valuable. I have been very fortunate to work with you and I admire your straightforward attitude.

I gratefully acknowledge the reviewers, Professor Stefano Fanti and Docent Juhani Sand, for their invaluable comments that greatly improved the quality of this thesis.

I wish to thank all my excellent co-authors. I am indebted to Professor Heikki Minn and Docent Marko Seppänen, the co-authors of all these studies, for being important persons during my first steps in science. Professor Matti Välimäki and Docent Timo Sane are warmly thanked for excellent help in revision of the manuscripts. I would like to thank Docent Risto Gullichsen, not only for being a co-author but also for being one of the most important teachers during my career in surgery. Special thanks are extended to Gaber Komar, MD for his great contribution to this thesis. Docent Kalle Alanen, Ronald Borra MD, PhD, Kirsti Dean, MD, Sami Kajander, MD, Kaisa Liukko, MD, and Irina Rinta-Kiikka, MD, PhD are thanked for their priceless help in analyzing the PANCA results. Jörgen Bergman, MSc, PhD, Professor Riitta Parkkola, Anna Salonen, MD and Professor Olof Solin are thanked for their help in DOPA studies. Pirkko Korsoff, MD, Laura Nummijärvi, MD, Docent Pasi Salmela, Docent Jorma Salmi, and Juha Saltevo, MD, PhD are all acknowledged for their help in collecting the NET patient data. Irina Lisinen, MSc, is sincerely thanked for her valuable help with the statistical analysis. I want to thank Jacqueline Välimäki, MA, for her excellent help in the linguistic revision of this thesis.

I thank all my colleagues in the department of GI-surgery. I express my sincere thanks to Docent Juha Grönroos for his support and important advice during this process. Mika Helmiö, MD, Heikki Huhtinen, MD, PhD, Simo Laine, MD, PhD, Maija Lavonius, MD, PhD, Erkki Pekkala, MD, PhD, Docent Arto Rantala, Paulina Salminen, MD, PhD, Heikki Sarparanta, MD, and Pirita Varpe, MD are sincerely thanked for their supportive attitude. Furthermore, my thanks go to residents Jussi Aalto, MD, Ville Falenius, MD, Susanna Moisander, MD, Hanna Vihervaara, MD, and former work-mates Marja Hilska, MD, PhD, Matti Hämäläinen, MD, Jukka Karvonen, MD, PhD, and Sven Lill, MD are all thanked. I consider myself privileged to have had the opportunity to work with you and you have all played an important role in my short career in surgery.

I would like to express my warm thanks to the members of the CardMet and Oncological research Team: Marco Bucci, Han Chunlei, Patricia Iozzo, Jarna Hannukainen, Katja Havu-Auren, Ilkka Heinonen, Miikka Honka, Erika Hoppela, Kari Kalliokoski, Mikko Kankaanpää, Anna Karmi, Jukka Kemppainen, Jan Kiss, Nina Koivuviita, Nobu Kudomi, Marko Laaksonen, Iina Laitinen, Riikka Lautamäki, Hanna-Riikka Lehto, Heidi Leppänen, Markus Lindroos, Alexander Naum, Sergey Nesterov, Janne Orava, Helena Tuunanen, Heikki Ukkonen, Antti Viljanen, and Kirsi Virtanen.

I thank all my other co-workers in the Turku PET Centre especially Vesa Oikonen, Hannu Sipilä, Mika Teräs, Tuula Tolvanen, and Terhi Tuokkola in addition to the researchers in other teams. Rami Mikkola and Marko Tättäläinen are sincerely thanked for their help in IT issues. I also thank secretaries Mirja Jyrkinen and Sinikka Lehtola for their valuable help.

I thank the personnel at the Turku PET Centre. Radiographers Minna Aatsinki, Heidi Betlehem, Sari Hermonen, Anne-Mari Jokinen, Tarja Keskitalo, Annika Larvanko, Leena Lehtimäki, Hannele Lehtinen, Kalevi Mölsä, Outi Numminen and Marjo Tähti are especially thanked for their help and flexibility during imaging protocols. Also Medical laboratory technologists Riitta Fabritius, Heidi Lappalainen, Eija Nirhamo, Emilia Puhakka, Leena Tokoi, Sanna Suominen, Kirsi Tammi and research nurse Heli Ylikoski are warmly acknowledged.

I am deeply grateful to the personnel in the department of Surgery. In particular, I would like to thank the staffs of dept 216 and dept 227 for their help with the PANCA study patients. Anne Mäkinen and Tuula Siren are acknowledged for help in secretarial matters.

I thank all the patients who participated in the study.

My warm thanks go to my dear friends in Lahti, Tampere, and Turku. I value your friendship more than you know. Especially I want to thank Anu, Hanna, Petra, and Synnöve for sharing all the great moments during the last decade, and Nina, Erika, and Jarkko, for helping to make me feel at home, outside work, here in Turku.

My deepest thanks go to my family. My parents, Terttu and Jorma, are thanked for their constant support and unconditional love. You have always guided me in the right direction in my life and supported me in my academic career. I thank my brother Jarno, his wife Minna, and their beautiful children, Jerry and Matilda, for their understanding and love. My mother-in-law Aira is warmly thanked for her friendly and supportive attitude towards me.

With all my heart I thank Ari and Otto just for everything that has been and is to come. Ari, your cool guidance and your strong belief that extremely well-organized free time is necessary for successful scientific work surprisingly became reality. Thank you, Otto, for the inspiring kicks motivating me to stick to my timetable and complete this thesis ahead of schedule. The two of you make everything worthwhile.

These studies were financially supported by an EVO grant, the Finnish Cancer Foundation, the National Graduate School of Clinical Investigation, the Gastrointestinal Disorders Research Foundation, the Finnish Medical Society Duodecim, the Turku Medical Society Duodecim, the Ida Montin Foundation, and the Maud Kuistila Foundation, all of which are gratefully acknowledged.

Turku, September 2009

10 REFERENCES

Abdel-Nabi, H., Doerr, R. J., Lamonica, D. M., Cronin, V. R., Galantowicz, P. J., Carbone, G. M., & Spaulding, M. B. (1998). Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings. *Radiology* **206**, 755-760.

Adams, S., Baum, R., Rink, T., Schumm-Drager, P. M., Usadel, K. H., & Hor, G. (1998). Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. *Eur.J.Nucl.Med.* **25**, 79-83.

Ahlström, H., Eriksson, B., Bergström, M., Bjurling, P., Langström, B., & Öberg, K. (1995). Pancreatic neuroendocrine tumors: diagnosis with PET. *Radiology* **195**, 333-337.

Ambrosini, V., Tomassetti, P., Castellucci, P., Campana, D., Montini, G., Rubello, D., Nanni, C., Rizzello, A., Franchi, R., & Fanti, S. (2008). Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours. *Eur.J.Nucl.Med.Mol.Imaging* **35**, 1431-1438.

Anderson, C. D., Rice, M. H., Pinson, C. W., Chapman, W. C., Chari, R. S., & Delbeke, D. (2004). Fluorodeoxyglucose PET imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma. *J.Gastrointest.Surg.* **8**, 90-97.

Anderson, M. A., Carpenter, S., Thompson, N. W., Nostrant, T. T., Elta, G. H., & Scheiman, J. M. (2000). Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. *Am.J.Gastroenterol.* **95**, 2271-2277.

Anlauf, M., Wieben, D., Perren, A., Sipos, B., Komminoth, P., Raffel, A., Kruse, M. L., Fottner, C., Knoefel, W. T., Monig, H., Heitz, P. U., & Klöppel, G. (2005). Persistent hyperinsulinemic hypoglycemia in 15 adults with diffuse nesidioblastosis: diagnostic criteria, incidence, and characterization of beta-cell changes. *Am.J.Surg.Pathol.* **29**, 524-533.

Baiocchi, G. L., Portolani, N., Bertagna, F., Gheza, F., Pizzocaro, C., Giubbini, R., & Giulini, S. M. (2008). Possible additional value of 18FDG-PET in managing pancreas intraductal papillary mucinous neoplasms: preliminary results. *J.Exp.Clin.Cancer Res.* **27**, 10.

Bar-Shalom, R., Guralnik, L., Tsalic, M., Leiderman, M., Frenkel, A., Gaitini, D., Ben Nun, A., Keidar, Z., & Israel, O. (2005). The additional value of PET/CT over PET in FDG imaging of oesophageal cancer. *Eur.J.Nucl.Med.Mol.Imaging* **32**, 918-924.

Bares, R., Klever, P., Hauptmann, S., Hellwig, D., Fass, J., Cremerius, U., Schumpelick, V., Mittermayer, C., & Bull, U. (1994). F-18 fluorodeoxyglucose PET in vivo evaluation of pancreatic glucose metabolism for detection of pancreatic cancer. *Radiology* **192**, 79-86.

Becherer, A., Szabo, M., Karanikas, G., Wunderbaldinger, P., Angelberger, P., Raderer, M., Kurtaran, A., Dudczak, R., & Kletter, K. (2004). Imaging of advanced neuroendocrine tumors with (18)F-FDOPA PET. *J.Nucl.Med.* **45**, 1161-1167.

Bergman J, Haaparanta M, Lehikoinen P, & Solin O. (1994) Electrophilic synthesis of 6-18Ffuoro-L-dopa starting from aqueous-18Ffluoride. *J Labelled Comp Radiopharm* **35**, 476-477.

Bergmann, R., Pietzsch, J., Fuechtner, F., Pawelke, B., Beuthien-Baumann, B., Johannsen, B., & Kotzerke, J. (2004). 3-O-methyl-6-18F-fluoro-L-dopa, a new tumor imaging agent: investigation of transport mechanism in vitro. *J.Nucl.Med.* **45**, 2116-2122.

Beuthien-Baumann, B., Strumpf, A., Zessin, J., Bredow, J., & Kotzerke, J. (2007). Diagnostic impact of PET with (18)F-FDG, (18)F-DOPA and 3-O-methyl-6-[(18) F]fluoro-DOPA in recurrent or metastatic medullary thyroid carcinoma. *Eur.J.Nucl.Med.Mol.Imaging* **34**, 1604-1609.

Beyer, T., Antoch, G., Blodgett, T., Freudenberg, L. F., Akhurst, T., & Mueller, S. (2003). Dual-modality PET/CT imaging: the effect of respiratory motion on combined image quality in clinical oncology. *Eur.J.Nucl.Med.Mol.Imaging* **30**, 588-596.

Beyer, T., Townsend, D. W., Brun, T., Kinahan, P. E., Charron, M., Roddy, R., Jerin, J., Young, J., Byars, L., & Nutt, R. (2000). A combined PET/CT scanner for clinical oncology. *J.Nucl.Med.* **41**, 1369-1379.

Bipat, S., Phoa, S. S., van Delden, O. M., Bossuyt, P. M., Gouma, D. J., Lameris, J. S., & Stoker, J. (2005). Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a meta-analysis. *J.Comput.Assist.Tomogr.* **29**, 438-445.

Block, M. I., Patterson, G. A., Sundaresan, R. S., Bailey, M. S., Flanagan, F. L., Dehdashti, F., Siegel, B. A., & Cooper, J. D. (1997). Improvement in staging of esophageal cancer with the addition of positron emission tomography. *Ann.Thorac.Surg.* **64**, 770-776.

Blomqvist, G. (1984). On the construction of functional maps in positron emission tomography. *J.Cereb.Blood Flow Metab* **4**, 629-632.

Boellaard, R., Oyen, W. J., Hoekstra, C. J., Hoekstra, O. S., Visser, E. P., Willemsen, A. T., Arends, B., Verzijlbergen, F. J., Zijlstra, J., Paans, A. M., Comans, E. F., & Pruim, J. (2008). The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. *Eur.J.Nucl.Med.Mol. Imaging* **35**, 2320-2333.

Bomanji, J. B., Costa, D. C., & Ell, P. J. (2001). Clinical role of positron emission tomography in oncology. *Lancet Oncol.* **2**, 157-164.

Borbath, I., Van Beers, B. E., Lonneux, M., Schoonbroodt, D., Geubel, A., Gigot, J. F., & Deprez, P. H. (2005). Preoperative assessment of pancreatic tumors using magnetic resonance imaging, endoscopic

ultrasonography, positron emission tomography and laparoscopy. *Pancreatology.* **5**, 553-561.

Borelli, M. I., Villar, M. J., Orezzoli, A., & Gagliardino, J. J. (1997). Presence of DOPA decarboxylase and its localisation in adult rat pancreatic islet cells. *Diabetes Metab* **23**, 161-163.

Boujaoude, J. (2007). Role of endoscopic ultrasound in diagnosis and therapy of pancreatic adenocarcinoma. *World J.Gastroenterol.* **13**, 3662-3666.

Brown, W. D., Oakes, T. R., DeJesus, O. T., Taylor, M. D., Roberts, A. D., Nickles, R. J., & Holden, J. E. (1998). Fluorine-18-fluoro-L-DOPA dosimetry with carbidopa pretreatment. *J.Nucl.Med.* **39**, 1884-1891.

Brugge, W. R., Lewandrowski, K., Lee-Lewandrowski, E., Centeno, B. A., Szydlo, T., Regan, S., del Castillo, C. F., & Warshaw, A. L. (2004). Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* **126**, 1330-1336.

Campana, D., Nori, F., Piscitelli, L., Morselli-Labate, A. M., Pezzilli, R., Corinaldesi, R., & Tomassetti, P. (2007). Chromogranin A: is it a useful marker of neuroendocrine tumors? *J.Clin.Oncol.* **25**, 1967-1973.

Chatterton, B. E., Ho, S., I, Baldey, A., Lenzo, N., Patrikeos, A., Kelley, B., Wong, D., Ramshaw, J. E., & Scott, A. M. (2009). Positron emission tomography changes management and prognostic stratification in patients with oesophageal cancer: results of a multicentre prospective study. *Eur.J.Nucl.Med.Mol. Imaging* **36**, 354-361.

Chirakal, R., Firnau, G., & Garnett, E. S. (1986). High yield synthesis of 6-[18F]fluoro-L-dopa. *J.Nucl.Med.* **27**, 417-421.

Choi, J. Y., Lee, K. H., Shim, Y. M., Lee, K. S., Kim, J. J., Kim, S. E., & Kim, B. T. (2000). Improved detection of individual nodal involvement in squamous cell carcinoma of the esophagus by FDG PET. *J.Nucl.Med.* **41**, 808-815.

Chowdhury, F. U., Bradley, K. M., & Gleeson, F. V. (2008). The role of 18F-FDG PET/CT in the evaluation of oesophageal carcinoma. *Clin.Radiol.* **63**, 1297-1309.

Cohade, C., Osman, M., Leal, J., & Wahl, R. L. (2003). Direct comparison of (18)F-FDG PET and PET/CT in patients with colorectal carcinoma. *J.Nucl.Med.* **44**, 1797-1803.

de Lonlay, P., Simon-Carre, A., Ribeiro, M. J., Boddaert, N., Giurgea, I., Laborde, K., Bellanne-Chantelot, C., Verkarre, V., Polak, M., Rahier, J., Syrota, A., Seidenwurm, D., Nihoul-Fekete, C., Robert, J. J., Brunelle, F., & Jaubert, F. (2006). Congenital hyperinsulinism: pancreatic [18F]fluoro-L-dihydroxyphenylalanine (DOPA) positron emission tomography and immunohistochemistry study of DOPA decarboxylase and insulin secretion. *J.Clin.Endocrinol. Metab* **91**, 933-940.

Delbeke, D., Rose, D. M., Chapman, W. C., Pinson, C. W., Wright, J. K., Beauchamp, R. D., Shyr, Y., & Leach, S. D. (1999). Optimal interpretation of FDG PET in the diagnosis, staging and management of pancreatic carcinoma. *J.Nucl.Med.* **40**, 1784-1791.

DeWitt, J., Devereaux, B., Chriswell, M., McGreevy, K., Howard, T., Imperiale, T. F., Ciaccia, D., Lane, K. A., Maglinte, D., Kopecky, K., LeBlanc, J., McHenry, L., Madura, J., Aisen, A., Cramer, H., Cummings, O., & Sherman, S. (2004). Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. *Ann.Intern.Med.* **141**, 753-763.

Diederichs, C. G., Staib, L., Glatting, G., Beger, H. G., & Reske, S. N. (1998). FDG PET: elevated plasma glucose reduces both uptake and detection rate of pancreatic malignancies. *J.Nucl.Med.* **39**, 1030-1033.

Domagk, D., Wessling, J., Reimer, P., Hertel, L., Poremba, C., Senninger, N., Heinecke, A., Domschke, W., & Menzel, J. (2004). Endoscopic retrograde cholangiopancreatography, intraductal ultrasonography, and magnetic resonance cholangiopancreatography in bile duct strictures: a prospective comparison of imaging diagnostics with histopathological correlation. *Am.J.Gastroenterol.* **99**, 1684-1689.

Dromain, C., de Baere, T., Lumbroso, J., Caillet, H., Laplanche, A., Boige, V., Ducreux, M., Duvillard, P., Elias, D., Schlumberger, M., Sigal, R., & Baudin, E. (2005). Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. *J.Clin.Oncol.* **23**, 70-78.

Egawa, S., Takeda, K., Fukuyama, S., Motoi, F., Sunamura, M., & Matsuno, S. (2004). Clinicopathological aspects of small pancreatic cancer. *Pancreas* **28**, 235-240.

Elström, R., Guan, L., Baker, G., Nakhoda, K., Vergilio, J. A., Zhuang, H., Pitsilos, S., Bagg, A., Downs, L., Mehrotra, A., Kim, S., Alavi, A., & Schuster, S. J. (2003). Utility of FDG-PET scanning in lymphoma by WHO classification. *Blood* **101**, 3875-3876.

Ericson, L. E., Hakanson, R., & Lundquist, I. (1977). Accumulation of dopamine in mouse pancreatic B-cells following injection of L-DOPA. Localization to secretory granules and inhibition of insulin secretion. *Diabetologia* **13**, 117-124.

Fanti, S., Ambrosini, V., Tomassetti, P., Castellucci, P., Montini, G., Allegri, V., Grassetto, G., Rubello, D., Nanni, C., & Franchi, R. (2008). Evaluation of unusual neuroendocrine tumours by means of 68Ga-DOTA-NOC PET. *Biomed.Pharmacother.* **62**, 667-671.

Farma, J. M., Santillan, A. A., Melis, M., Walters, J., Belinc, D., Chen, D. T., Eikman, E. A., & Malafa, M. (2008). PET/CT Fusion Scan Enhances CT Staging in Patients with Pancreatic Neoplasms. *Ann.Surg.Oncol* **15**, 2465-2471.

Fernandez, E., La Vecchia, C., D'Avanzo, B., Negri, E., & Franceschi, S. (1994). Family history and the risk of liver, gallbladder, and pancreatic cancer. *Cancer Epidemiol.Biomarkers Prev.* **3**, 209-212.

Fernandez-del Castillo, C., Alsfasser, G., Targarona, J., Brugge, W. R., & Warshaw, A. L. (2006). Serum CA 19-9 in the management of cystic lesions of the pancreas. *Pancreas* **32**, 220.

Finnish Cancer Registry. URL: http://www.cancer.fi/statistics/

Flamen, P., Lerut, A., Van Cutsem, E., Cambier, J. P., Maes, A., De Wever, W., Peeters, M., De Leyn, P., Van Raemdonck, D., & Mortelmans, L. (2000). The utility of positron emission tomography for the diagnosis and staging of recurrent esophageal cancer. *J.Thorac. Cardiovasc.Surg.* **120**, 1085-1092.

Flamen, P., Stroobants, S., Van Cutsem, E., Dupont, P., Bormans, G., De Vadder, N., Penninckx, F., Van Hoe, L., & Mortelmans, L. (1999). Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. *J.Clin.Oncol.* **17**, 894-901.

Folkman, J. (2002). Role of angiogenesis in tumor growth and metastasis. *Semin.Oncol.* **29**, 15-18.

Forsmark, C. E., Lambiase, L., & Vogel, S. B. (1994). Diagnosis of pancreatic cancer and prediction of unresectability using the tumor-associated antigen CA19-9. *Pancreas* **9**, 731-734.

Freudenberg, L. S., Antoch, G., Schutt, P., Beyer, T., Jentzen, W., Muller, S. P., Gorges, R., Nowrousian, M. R., Bockisch, A., & Debatin, J. F. (2004). FDG-PET/CT in re-staging of patients with lymphoma. *Eur.J.Nucl. Med.Mol.Imaging* **31**, 325-329.

Friess, H., Langhans, J., Ebert, M., Beger, H. G., Stollfuss, J., Reske, S. N., & Buchler, M. W. (1995). Diagnosis of pancreatic cancer by 2[18F]-fluoro-2-deoxy-D-glucose positron emission tomography. *Gut* **36**, 771-777.

Gabriel, M., Decristoforo, C., Kendler, D., Dobrozemsky, G., Heute, D., Uprimny, C., Kovacs, P., Von Guggenberg, E., Bale, R., & Virgolini, I. J. (2007). 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J.Nucl.Med.* **48**, 508-518.

Gan, S. I., Rajan, E., Adler, D. G., Baron, T. H., Anderson, M. A., Cash, B. D., Davila, R. E., Dominitz, J. A., Harrison, M. E., III, Ikenberry, S. O., Lichtenstein, D., Qureshi, W., Shen, B., Zuckerman, M., Fanelli, R. D., Lee, K. K., & Van Guilder, T. (2007). Role of EUS. *Gastrointest.Endosc.* **66**, 425-434.

Garcea, G., Ong, S. L., Rajesh, A., Neal, C. P., Pollard, C. A., Berry, D. P., & Dennison, A. R. (2008). Cystic lesions of the pancreas. A diagnostic and management dilemma. *Pancreatology.* **8**, 236-251.

Gattani, A. M., Mandeli, J., & Bruckner, H. W. (1996). Tumor markers in patients with pancreatic carcinoma. *Cancer* **78**, 57-62.

Gazdar, A. F., Helman, L. J., Israel, M. A., Russell, E. K., Linnoila, R. I., Mulshine, J. L., Schuller, H. M., & Park, J. G. (1988). Expression of neuroendocrine cell markers L-dopa decarboxylase, chromogranin A, and dense core granules in human tumors of endocrine and nonendocrine origin. *Cancer Res.* **48**, 4078-4082.

Ghadirian, P., Liu, G., Gallinger, S., Schmocker, B., Paradis, A. J., Lal, G., Brunet, J. S., Foulkes, W. D., & Narod, S. A. (2002). Risk of pancreatic cancer among individuals with a family history of cancer of the pancreas. *Int.J.Cancer* **97**, 807-810.

Gibril, F. & Jensen, R. T. (2004). Diagnostic uses of radiolabelled somatostatin receptor analogues in gastroenteropancreatic endocrine tumours. *Dig.Liver Dis.* **36**, 106-S120.

Halloran, C. M., Ghaneh, P., Connor, S., Sutton, R., Neoptolemos, J. P., & Raraty, M. G. (2008). Carbohydrate antigen 19.9 accurately selects patients for laparoscopic assessment to determine resectability of pancreatic malignancy. *Br.J.Surg.* **95**, 453-459.

Hamacher, K., Coenen, H. H., & Stocklin, G. (1986). Efficient stereospecific synthesis of no-carrier-added 2-[18F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J.Nucl.Med.* **27**, 235-238.

Hartwig, W., Schneider, L., Diener, M. K., Bergmann, F., Buchler, M. W., & Werner, J. (2009). Preoperative tissue diagnosis for tumours of the pancreas. *Br.J.Surg.* **96**, 5-20.

Hauso, O., Gustafsson, B. I., Kidd, M., Waldum, H. L., Drozdov, I., Chan, A. K., & Modlin, I. M. (2008). Neuroendocrine tumor epidemiology: contrasting Norway and North America. *Cancer* **113**, 2655-2664.

Haycox, A., Lombard, M., Neoptolemos, J., & Walley, T. (1998). Review article: current treatment and optimal patient management in pancreatic cancer. *Aliment. Pharmacol.Ther.* **12**, 949-964.

Heeren, P. A., Jager, P. L., Bongaerts, F., van Dullemen, H., Sluiter, W., & Plukker, J. T. (2004). Detection of distant metastases in esophageal cancer with (18) F-FDG PET. *J.Nucl.Med.* **45**, 980-987.

Heinrich, S., Goerres, G. W., Schafer, M., Sagmeister, M., Bauerfeind, P., Pestalozzi, B. C., Hany, T. F., von Schulthess, G. K., & Clavien, P. A. (2005). Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. *Ann.Surg.* **242**, 235-243.

Heriot, A. G., Hicks, R. J., Drummond, E. G., Keck, J., Mackay, J., Chen, F., & Kalff, V. (2004). Does positron emission tomography change management in primary rectal cancer? A prospective assessment. *Dis.Colon Rectum* **47**, 451-458.

Hermanek, P. (1998). Pathology and biology of pancreatic ductal adenocarcinoma. *Langenbeck´s Arch Surg* **383**, 116-120.

Hermanek, P. (1999). Disseminated tumor cells versus micrometastasis: definitions and problems. *Anticancer Res.* **19**, 2771-2774.

Hernandez-Maraver, D., Hernandez-Navarro, F., Gomez-Leon, N., Coya, J., Rodriguez-Vigil, B., Madero, R., Pinilla, I., & Martin-Curto, L. M. (2006). Positron emission tomography/computed tomography: diagnostic accuracy in lymphoma. *Br.J.Haematol.* **135**, 293-302.

Higashi, T., Saga, T., Nakamoto, Y., Ishimori, T., Mamede, M. H., Wada, M., Doi, R., Hosotani, R., Imamura, M., & Konishi, J. (2002). Relationship between retention index in dual-phase (18)F-FDG PET, and hexokinase-II and glucose transporter-1 expression in pancreatic cancer. *J.Nucl.Med.* **43**, 173-180.

Hiramoto, J.S., Feldstein, V.A., LaBerge, J.M. & Norton J.A. (2001). Intraoperative Ultrasound and Preoperative Localization Detects All Occult Insulinomas. *Arch. Surg.* **136**, 1020-1026.

Hirasawa, H., Tsushima, Y., Hirasawa, S., Takei, H., Taketomi-Takahasi, A., Takano, A., Amanuma, M., & Endo, K. (2007). Perfusion CT of breast carcinoma: arterial perfusion of nonscirrhous carcinoma was higher than that of scirrhous carcinoma. *Acad.Radiol.* **14**, 547-552.

Hoegerle, S., Altehoefer, C., Ghanem, N., Koehler, G., Waller, C. F., Scheruebl, H., Moser, E., & Nitzsche, E. (2001a). Whole-body 18F dopa PET for detection of gastrointestinal carcinoid tumors. *Radiology* **220**, 373-380.

Hoegerle, S., Nitzsche, E., Altehoefer, C., Ghanem, N., Manz, T., Brink, I., Reincke, M., Moser, E., & Neumann, H. P. (2002). Pheochromocytomas: detection with 18F DOPA whole body PET--initial results. *Radiology* **222**, 507-512.

Hoegerle, S., Altehoefer, C., Ghanem, N., Brink, I., Moser, E., & Nitzsche, E. (2001b). 18F-DOPA positron emission tomography for tumour detection in patients with medullary thyroid carcinoma and elevated calcitonin levels. *Eur.J.Nucl.Med.* **28**, 64-71.

Hoegerle, S., Ghanem, N., Altehoefer, C., Schipper, J., Brink, I., Moser, E., & Neumann, H. P. (2003). 18F-DOPA positron emission tomography for the detection of glomus tumours. *Eur.J.Nucl.Med.Mol. Imaging* **30**, 689-694.

Hoekstra, C. J., Stroobants, S. G., Hoekstra, O. S., Smit, E. F., Vansteenkiste, J. F., & Lammertsma, A. A. (2002). Measurement of perfusion in stage IIIA-N2 non-small cell lung cancer using H(2)(15)O and positron emission tomography. *Clin.Cancer Res.* **8**, 2109-2115.

Hoffman, J. M., Melega, W. P., Hawk, T. C., Grafton, S. C., Luxen, A., Mahoney, D. K., Barrio, J. R., Huang, S. C., Mazziotta, J. C., & Phelps, M. E. (1992). The effects of carbidopa administration on 6-[18F]fluoro-L-dopa kinetics in positron emission tomography. *J.Nucl. Med.* **33**, 1472-1477.

Hofmann, M., Maecke, H., Borner, R., Weckesser, E., Schoffski, P., Oei, L., Schumacher, J., Henze, M., Heppeler, A., Meyer, J., & Knapp, H. (2001). Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. *Eur.J.Nucl.Med.* **28**, 1751-1757.

Hosch, S. B., Knoefel, W. T., Metz, S., Stoecklein, N., Niendorf, A., Broelsch, C. E., & Izbicki, J. R. (1997). Early lymphatic tumor cell dissemination in pancreatic cancer: frequency and prognostic significance. *Pancreas* **15**, 154-159.

Hosten, N., Lemke, A. J., Wiedenmann, B., Bohmig, M., & Rosewicz, S. (2000). Combined imaging techniques for pancreatic cancer. *Lancet* **356**, 909-910.

Huebner, R. H., Park, K. C., Shepherd, J. E., Schwimmer, J., Czernin, J., Phelps, M. E., & Gambhir, S. S. (2000). A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. *J.Nucl. Med.* **41**, 1177-1189.

Hustinx, R. (2004). PET imaging in assessing gastrointestinal tumors. *Radiol.Clin.North Am.* **42**, 1123-39, ix.

Huxley, R., Ansary-Moghaddam, A., Berrington, d. G., Barzi, F., & Woodward, M. (2005). Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br.J.Cancer* **92**, 2076-2083.

Jabri, A. L. & Bayard, C. (2004). Nesidioblastosis associated with hyperinsulinemic hypoglycemia in adults: review of the literature. *Eur.J.Intern.Med.* **15**, 407-410.

Jadvar, H. & Fischman, A. J. (2001). Evaluation of pancreatic carcinoma with FDG PET. *Abdom.Imaging* **26**, 254-259.

Jagannath, P., Dhir, V., Shrikhande, S., Shah, R. C., Mullerpatan, P., & Mohandas, K. M. (2005). Effect of preoperative biliary stenting on immediate outcome after pancreaticoduodenectomy. *Br.J.Surg.* **92**, 356-361.

Jerusalem, G., Beguin, Y., Najjar, F., Hustinx, R., Fassotte, M. F., Rigo, P., & Fillet, G. (2001). Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) for the staging of low-grade non-Hodgkin's lymphoma (NHL). *Ann.Oncol.* **12**, 825-830.

Jhanwar, Y. S. & Straus, D. J. (2006). The role of PET in lymphoma. *J.Nucl.Med.* **47**, 1326-1334.

Jones, E. C., Chezmar, J. L., Nelson, R. C., & Bernardino, M. E. (1992). The frequency and significance of small (less than or equal to 15 mm) hepatic lesions detected by CT. *AJR Am.J.Roentgenol.* **158**, 535-539.

Juuti, A., Nordling, S., Lundin, J., Louhimo, J., & Haglund, C. (2005). Syndecan-1 expression--a novel prognostic marker in pancreatic cancer. *Oncology* **68**, 97-106.

Kantorova, I., Lipska, L., Belohlavek, O., Visokai, V., Trubac, M., & Schneiderova, M. (2003). Routine (18) F-FDG PET preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making. *J.Nucl.Med.* **44**, 1784-1788.

Karlson, B. M., Ekbom, A., Josefsson, S., McLaughlin, J. K., Fraumeni, J. F., Jr., & Nyren, O. (1997). The risk of pancreatic cancer following pancreatitis: an association due to confounding? *Gastroenterology* **113**, 587-592.

Kato, H., Miyazaki, T., Nakajima, M., Takita, J., Kimura, H., Faried, A., Sohda, M., Fukai, Y., Masuda, N., Fukuchi, M., Manda, R., Ojima, H., Tsukada, K., Kuwano, H., Oriuchi, N., & Endo, K. (2005). The incremental effect of positron emission tomography on diagnostic accuracy in the initial staging of esophageal carcinoma. *Cancer* **103**, 148-156.

Kato, H., Kuwano, H., Nakajima, M., Miyazaki, T., Yoshikawa, M., Ojima, H., Tsukada, K., Oriuchi, N., Inoue, T., & Endo, K. (2002). Comparison between positron emission tomography and computed tomography in the use of the assessment of esophageal carcinoma. *Cancer* **94**, 921-928.

Kato, H., Miyazaki, T., Nakajima, M., Fukuchi, M., Manda, R., & Kuwano, H. (2004). Value of positron emission tomography in the diagnosis of recurrent oesophageal carcinoma. *Br.J.Surg.* **91**, 1004-1009.

Kim, H. J., Kim, M. H., Myung, S. J., Lim, B. C., Park, E. T., Yoo, K. S., Seo, D. W., Lee, S. K., & Min, Y. I. (1999). A new strategy for the application of CA19-9 in the differentiation of pancreaticobiliary cancer: analysis using a receiver operating characteristic curve. *Am.J.Gastroenterol.* **94**, 1941-1946.

Kimura, W., Nagai, H., Kuroda, A., Muto, T., & Esaki, Y. (1995). Analysis of small cystic lesions of the pancreas. *Int.J.Pancreatol.* **18**, 197-206.

Kindler HL. (2007). A double-blind, placebo-controlled, randomized phase III trial of gemsitabine (G) plus bevacizumab versus gemsitabine plus placebo (P) in patients with advanced pancreatic cancer (PC): a preliminary analysis of Cancer and Leukemia Group B (CALGB). ASCO Annual Meeting Proceedings. In: Niedzwiecki D, editor. 25 no.18S

Kinkel, K., Lu, Y., Both, M., Warren, R. S., & Thoeni, R. F. (2002). Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. *Radiology* **224**, 748-756.

Klöppel, G., Rindi, G., Anlauf, M., Perren, A., & Komminoth, P. (2007). Site-specific biology and pathology of gastroenteropancreatic neuroendocrine tumors. *Virchows Arch.* **451 Suppl 1**, 9-27.

Klöppel, G. & Anlauf, M. (2005). Epidemiology, tumour biology and histopathological classification of neuroendocrine tumours of the gastrointestinal tract. *Best.Pract.Res.Clin.Gastroenterol.* **19**, 507-517.

Kong, G., Jackson, C., Koh, D. M., Lewington, V., Sharma, B., Brown, G., Cunningham, D., & Cook, G. J. (2008). The use of 18F-FDG PET/CT in colorectal liver metastases--comparison with CT and liver MRI. *Eur.J.Nucl.Med.Mol.Imaging* **35**, 1323-1329.

Koopmans, K. P., de Vries, E. G., Kema, I. P., Elsinga, P. H., Neels, O. C., Sluiter, W. J., van der Horst-Schrivers AN, & Jager, P. L. (2006). Staging of carcinoid tumours with 18F-DOPA PET: a prospective, diagnostic accuracy study. *Lancet Oncol.* **7**, 728-734.

Koopmans, K. P., Neels, O. C., Kema, I. P., Elsinga, P. H., Sluiter, W. J., Vanghillewe, K., Brouwers, A. H., Jager, P. L., & de Vries, E. G. (2008a). Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. *J.Clin. Oncol.* **26**, 1489-1495.

Koopmans, K. P., de Groot, J. W., Plukker, J. T., de Vries, E. G., Kema, I. P., Sluiter, W. J., Jager, P. L., & Links, T. P. (2008b). 18F-dihydroxyphenylalanine PET in patients with biochemical evidence of medullary thyroid cancer: relation to tumor differentiation. *J.Nucl. Med.* **49**, 524-531.

Kostakoglu, L. & Goldsmith, S. J. (2003). 18F-FDG PET evaluation of the response to therapy for lymphoma and for breast, lung, and colorectal carcinoma. *J.Nucl. Med.* **44**, 224-239.

Krenning, E. P., Kwekkeboom, D. J., Bakker, W. H., Breeman, W. A., Kooij, P. P., Oei, H. Y., van Hagen, M., Postema, P. T., de Jong, M., Reubi, J. C., & . (1993). Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur.J.Nucl. Med.* **20**, 716-731.

Kubota, K., Itoh, M., Ozaki, K., Ono, S., Tashiro, M., Yamaguchi, K., Akaizawa, T., Yamada, K., & Fukuda, H. (2001). Advantage of delayed whole-body FDG-PET imaging for tumour detection. *Eur.J.Nucl.Med.* **28**, 696-703.

Kumbasar, B., Kamel, I. R., Tekes, A., Eng, J., Fishman, E. K., & Wahl, R. L. (2004). Imaging of neuroendocrine tumors: accuracy of helical CT versus SRS. *Abdom. Imaging* **29**, 696-702.

Kwee, T. C., Kwee, R. M., & Nievelstein, R. A. (2008). Imaging in staging of malignant lymphoma: a systematic review. *Blood* **111**, 504-516.

Kwon, R. S. & Scheiman, J. M. (2006). New advances in pancreatic imaging. *Curr.Opin.Gastroenterol.* **22**, 512-519.

la Fougere, C., Hundt, W., Brockel, N., Pfluger, T., Haug, A., Scher, B., Hacker, M., Hahn, K., Reiser, M., & Tiling, R. (2006). Value of PET/CT versus PET and CT performed as separate investigations in patients with Hodgkin's disease and non-Hodgkin's lymphoma. *Eur.J.Nucl.Med.Mol.Imaging* **33**, 1417-1425.

Larson, S. M., Schoder, H., & Yeung, H. (2004). Positron emission tomography/computerized tomography functional imaging of esophageal and colorectal cancer. *Cancer J.* **10**, 243-250.

Lemke, A. J., Niehues, S. M., Hosten, N., Amthauer, H., Boehmig, M., Stroszczynski, C., Rohlfing, T., Rosewicz, S., & Felix, R. (2004). Retrospective digital image fusion of multidetector CT and 18F-FDG PET: clinical value in pancreatic lesions--a prospective study with 104 patients. *J.Nucl.Med.* **45**, 1279-1286.

Liukko, K.E., Oikonen, V., Tolvanen T., Virtanen K.A., Viljanen A.P., Sipilä H.T., Nuutila P., Iozzo P. (2007). Non-Invasive Estimation of Subcutaneous and Visceral Adipose Tissue Blood Flow By Using 15OH2O PET with Image Derived Input Functions. *Open Med Imaging J.* **1**:7-13

Lopez-Hänninen E., Amthauer, H., Hosten, N., Ricke, J., Bohmig, M., Langrehr, J., Hintze, R., Neuhaus, P., Wiedenmann, B., Rosewicz, S., & Felix, R. (2002). Prospective evaluation of pancreatic tumors: accuracy of MR imaging with MR cholangiopancreatography and MR angiography. *Radiology* **224**, 34-41.

Louhimo, J., Alfthan, H., Stenman, U. H., & Haglund, C. (2004). Serum HCG beta and CA 72-4 are stronger prognostic factors than CEA, CA 19-9 and CA 242 in pancreatic cancer. *Oncology* **66**, 126-131.

Lowe, V. J., Fletcher, J. W., Gobar, L., Lawson, M., Kirchner, P., Valk, P., Karis, J., Hubner, K., Delbeke, D., Heiberg, E. V., Patz, E. F., & Coleman, R. E. (1998). Prospective investigation of positron emission tomography in lung nodules. *J.Clin.Oncol.* **16**, 1075-1084.

Lowenfels, A. B. & Maisonneuve, P. (2006). Epidemiology and risk factors for pancreatic cancer. *Best.Pract.Res. Clin.Gastroenterol.* **20**, 197-209.

Lu, D. S., Reber, H. A., Krasny, R. M., Kadell, B. M., & Sayre, J. (1997). Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. *AJR Am.J.Roentgenol.* **168**, 1439-1443.

Lyshchik, A., Higashi, T., Nakamoto, Y., Fujimoto, K., Doi, R., Imamura, M., & Saga, T. (2005). Dual-phase 18F-fluoro-2-deoxy-D-glucose positron emission tomography as a prognostic parameter in patients with pancreatic cancer. *Eur.J.Nucl.Med.Mol.Imaging* **32**, 389-397.

Mansour, J. C., Schwartz, L., Pandit-Taskar, N., D'Angelica, M., Fong, Y., Larson, S. M., Brennan, M. F., & Allen, P. J. (2006). The utility of F-18 fluorodeoxyglucose whole body PET imaging for determining malignancy in cystic lesions of the pancreas. *J.Gastrointest.Surg.* **10**, 1354-1360.

Matos, C., Bali, M. A., Delhaye, M., & Deviere, J. (2006). Magnetic resonance imaging in the detection of pancreatitis and pancreatic neoplasms. *Best.Pract.Res. Clin.Gastroenterol.* **20**, 157-178.

McLean, A. M. & Fairclough, P. D. (2005). Endoscopic ultrasound in the localisation of pancreatic islet cell tumours. *Best.Pract.Res.Clin.Endocrinol.Metab* **19**, 177-193.

Mehmet, E. S., Ichikawa, T., Sou, H., Saitou, R., Tsukamoto, T., Motosugi, U., & Araki, T. (2006). Pancreatic adenocarcinoma: MDCT versus MRI in the detection and assessment of locoregional extension. *J.Comput.Assist.Tomogr.* **30**, 583-590.

Mertz, H. R., Sechopoulos, P., Delbeke, D., & Leach, S. D. (2000). EUS, PET, and CT scanning for evaluation of pancreatic adenocarcinoma. *Gastrointest.Endosc.* **52**, 367-371.

Metz, D. C. & Jensen, R. T. (2008). Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* **135**, 1469-1492.

Michaud, D. S., Giovannucci, E., Willett, W. C., Colditz, G. A., & Fuchs, C. S. (2001). Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. *Cancer Epidemiol. Biomarkers Prev.* **10**, 429-437.

Michl, P., Pauls, S., & Gress, T. M. (2006). Evidence-based diagnosis and staging of pancreatic cancer. *Best. Pract.Res.Clin.Gastroenterol.* **20**, 227-251.

Miles, K. A. & Williams, R. E. (2008). Warburg revisited: imaging tumour blood flow and metabolism. *Cancer Imaging* **8**, 81-86.

Miletich, R. S., Comi, G., Bankiewicz, K., Plunkett, R., Adams, R., Di Chiro, G., & Kopin, I. J. (1993). 6-[18F]fluoro-L-dihydroxyphenylalanine metabolism and positron emission tomography after catechol-O-methyltransferase inhibition in normal and hemiparkinsonian monkeys. *Brain Res.* **626**, 1-13.

Modlin, I. M., Oberg, K., Chung, D. C., Jensen, R. T., de Herder, W. W., Thakker, R. V., Caplin, M., Delle, F. G., Kaltsas, G. A., Krenning, E. P., Moss, S. F., Nilsson, O., Rindi, G., Salazar, R., Ruszniewski, P., & Sundin, A. (2008). Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol.* **9**, 61-72.

Montravers, F., Grahek, D., Kerrou, K., Ruszniewski, P., de, B., V, Aide, N., Gutman, F., Grange, J. D., Lotz, J. P., & Talbot, J. N. (2006). Can fluorodihydroxyphenylalanine PET replace somatostatin receptor scintigraphy in patients with digestive endocrine tumors? *J.Nucl.Med.* **47**, 1455-1462.

Moog, F., Bangerter, M., Kotzerke, J., Guhlmann, A., Frickhofen, N., & Reske, S. N. (1998). 18-F-fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. *J.Clin.Oncol.* **16**, 603-609.

Moore, H. G., Akhurst, T., Larson, S. M., Minsky, B. D., Mazumdar, M., & Guillem, J. G. (2003). A case-controlled study of 18-fluorodeoxyglucose positron emission tomography in the detection of pelvic recurrence in previously irradiated rectal cancer patients. *J.Am.Coll.Surg.* **197**, 22-28.

Nagenthiraja, K., Ewertz, M., Engholm, G., & Storm, H. H. (2007). Incidence and mortality of pancreatic cancer in the Nordic countries 1971-2000. *Acta Oncol.* **46**, 1064-1069.

Nakamoto, Y., Higashi, T., Sakahara, H., Tamaki, N., Kogire, M., Doi, R., Hosotani, R., Imamura, M., & Konishi, J. (2000). Delayed (18)F-fluoro-2-deoxy-D-glucose positron emission tomography scan for differentiation between malignant and benign lesions in the pancreas. *Cancer* **89**, 2547-2554.

Nakata, B., Nishimura, S., Ishikawa, T., Ohira, M., Nishino, H., Kawabe, J., Ochi, H., & Hirakawa, K. (2001). Prognostic predictive value of 18F-fluorodeoxyglucose positron emission tomography for patients with pancreatic cancer. *Int.J.Oncol.* **19**, 53-58.

Nalluri, S. R., Chu, D., Keresztes, R., Zhu, X., & Wu, S. (2008). Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA* **300**, 2277-2285.

Neels, O. C., Koopmans, K. P., Jager, P. L., Vercauteren, L., van Waarde, A., Doorduin, J., Timmer-Bosscha, H., Brouwers, A. H., de Vries, E. G., Dierckx, R. A., Kema, I. P., & Elsinga, P. H. (2008). Manipulation of [11C]-5-hydroxytryptophan and 6-[18F]fluoro-3,4-dihydroxy-L-phenylalanine accumulation in neuroendocrine tumor cells. *Cancer Res.* **68**, 7183-7190.

Nishiyama, Y., Yamamoto, Y., Kimura, N., Miki, A., Sasakawa, Y., Wakabayashi, H., & Ohkawa, M. (2007). Comparison of early and delayed FDG PET for evaluation of biliary stricture. *Nucl.Med.Commun.* **28**, 914-919.

Nishiyama, Y., Yamamoto, Y., Monden, T., Sasakawa, Y., Tsutsui, K., Wakabayashi, H., & Ohkawa, M. (2005a). Evaluation of delayed additional FDG PET imaging in patients with pancreatic tumour. *Nucl.Med.Commun.* **26**, 895-901.

Nishiyama, Y., Yamamoto, Y., Yokoe, K., Monden, T., Sasakawa, Y., Tsutsui, K., Satoh, K., & Ohkawa, M. (2005b). Contribution of whole body FDG-PET to the detection of distant metastasis in pancreatic cancer. *Ann.Nucl.Med.* **19**, 491-497.

Osman, M. M., Cohade, C., Nakamoto, Y., Marshall, L. T., Leal, J. P., & Wahl, R. L. (2003). Clinically significant inaccurate localization of lesions with PET/CT: frequency in 300 patients. *J.Nucl.Med.* **44**, 240-243.

Otonkoski, T., Nänto-Salonen, K., Seppänen, M., Veijola, R., Huopio, H., Hussain, K., Tapanainen, P., Eskola, O., Parkkola, R., Ekström, K., Guiot, Y., Rahier, J., Laakso, M., Rintala, R., Nuutila, P., & Minn, H. (2006). Noninvasive Diagnosis of Focal Hyperinsulinism of Infancy With [18F]-DOPA Positron Emission Tomography. *Diabetes* **55**, 13-18.

Ozaki, Y., Oguchi, K., Hamano, H., Arakura, N., Muraki, T., Kiyosawa, K., Momose, M., Kadoya, M., Miyata, K., Aizawa, T., & Kawa, S. (2008). Differentiation of autoimmune pancreatitis from suspected pancreatic cancer by fluorine-18 fluorodeoxyglucose positron emission tomography. *J.Gastroenterol.* **43**, 144-151.

Park, I. J., Kim, H. C., Yu, C. S., Ryu, M. H., Chang, H. M., Kim, J. H., Ryu, J. S., Yeo, J. S., & Kim, J. C. (2006). Efficacy of PET/CT in the accurate evaluation of primary colorectal carcinoma. *Eur.J.Surg.Oncol.* **32**, 941-947.

Parkin, D. M., Bray, F., Ferlay, J., & Pisani, P. (2005). Global cancer statistics, 2002. *CA Cancer J.Clin.* **55**, 74-108.

Pearse, A. G. (1969). The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept. *J.Histochem.Cytochem.* **17**, 303-313.

Pfannenberg, A. C., Aschoff, P., Brechtel, K., Muller, M., Klein, M., Bares, R., Claussen, C. D., & Eschmann, S. M. (2007). Value of contrast-enhanced multiphase CT in combined PET/CT protocols for oncological imaging. *Br.J.Radiol.* **80**, 437-445.

Pfau, P. R., Perlman, S. B., Stanko, P., Frick, T. J., Gopal, D. V., Said, A., Zhang, Z., & Weigel, T. (2007). The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. *Gastrointest.Endosc.* **65**, 377-384.

Plockinger, U., Rindi, G., Arnold, R., Eriksson, B., Krenning, E. P., de Herder, W. W., Goede, A., Caplin, M., Oberg, K., Reubi, J. C., Nilsson, O., Delle, F. G., Ruszniewski, P., Ahlman, H., & Wiedenmann, B. (2004). Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology* **80**, 394-424.

Prokesch, R. W., Chow, L. C., Beaulieu, C. F., Bammer, R., & Jeffrey, R. B., Jr. (2002). Isoattenuating pancreatic adenocarcinoma at multi-detector row CT: secondary signs. *Radiology* **224**, 764-768.

Quon A., Chang S.T., Chin F., Kamaya A., Dick D.W., Loo B.W., Gambhir S.S., & Koong A.C. (2008). Initial evaluation of ^{18}F-fluorothymidine (FLT) PET/CT scanning for primary pancreatic cancer. *Eur. J. Nucl. Med. Mol. Imaging* **35**, 527-31.

Raanani, P., Shasha, Y., Perry, C., Metser, U., Naparstek, E., Apter, S., Nagler, A., Polliack, A., Ben Bassat, I., & Even-Sapir, E. (2006). Is CT scan still necessary for staging in Hodgkin and non-Hodgkin lymphoma patients in the PET/CT era? *Ann.Oncol.* **17**, 117-122.

Rappeport, E. D., Hansen, C. P., Kjaer, A., & Knigge, U. (2006). Multidetector computed tomography and neuroendocrine pancreaticoduodenal tumors. *Acta Radiol.* **47**, 248-256.

Raptopoulos, V., Steer, M. L., Sheiman, R. G., Vrachliotis, T. G., Gougoutas, C. A., & Movson, J. S. (1997). The use of helical CT and CT angiography to predict vascular involvement from pancreatic cancer: correlation with findings at surgery. *AJR Am.J.Roentgenol.* **168**, 971-977.

Räty, S., Sand, J., Alfthan, H., Haglund, C., & Nordback, I. (2004). Cyst fluid tumor-associated trypsin inhibitor may be helpful in the differentiation of cystic pancreatic lesions. *J.Gastrointest.Surg.* **8**, 569-574.

Renehan, A. G., Tyson, M., Egger, M., Heller, R. F., & Zwahlen, M. (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* **371**, 569-578.

Reske, S. N. & Kotzerke, J. (2001). FDG-PET for clinical use. Results of the 3rd German Interdisciplinary Consensus Conference, "Onko-PET III", 21 July and 19 September 2000. *Eur.J.Nucl.Med.* **28**, 1707-1723.

Reubi, J. C., Schaer, J. C., Waser, B., & Mengod, G. (1994). Expression and localization of somatostatin receptor SSTR1, SSTR2, and SSTR3 messenger RNAs in primary human tumors using in situ hybridization. *Cancer Res.* **54**, 3455-3459.

Rhodes, M. M., Delbeke, D., Whitlock, J. A., Martin, W., Kuttesch, J. F., Frangoul, H. A., & Shankar, S. (2006). Utility of FDG-PET/CT in follow-up of children treated for Hodgkin and non-Hodgkin lymphoma. *J.Pediatr. Hematol.Oncol.* **28**, 300-306.

Ribeiro, M. J., de Lonlay, P., Delzescaux, T., Boddaert, N., Jaubert, F., Bourgeois, S., Dolle, F., Nihoul-Fekete, C., Syrota, A., & Brunelle, F. (2005). Characterization of hyperinsulinism in infancy assessed with PET and 18F-fluoro-L-DOPA. *J.Nucl.Med.* **46**, 560-566.

Rickes, S., Monkemuller, K., & Malfertheiner, P. (2006). Contrast-enhanced ultrasound in the diagnosis of pancreatic tumors. *JOP.* **7**, 584-592.

Rindi, G., Klöppel, G., Alhman, H., Caplin, M., Couvelard, A., de Herder, W. W., Erikssson, B., Falchetti, A., Falconi, M., Komminoth, P., Korner, M., Lopes, J. M., McNicol, A. M., Nilsson, O., Perren, A., Scarpa, A., Scoazec, J. Y., & Wiedenmann, B. (2006). TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* **449**, 395-401.

Rizk, M. K. & Gerke, H. (2007). Utility of endoscopic ultrasound in pancreatitis: a review. *World J.Gastroenterol.* **13**, 6321-6326.

Ruers, T. J., Langenhoff, B. S., Neeleman, N., Jager, G. J., Strijk, S., Wobbes, T., Corstens, F. H., & Oyen, W. J. (2002). Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. *J.Clin.Oncol.* **20**, 388-395.

Rufini, V., Calcagni, M. L., & Baum, R. P. (2006). Imaging of neuroendocrine tumors. *Semin.Nucl.Med.* **36**, 228-247.

Sahani, D. V., Shah, Z. K., Catalano, O. A., Boland, G. W., & Brugge, W. R. (2008). Radiology of pancreatic adenocarcinoma: current status of imaging. *J.Gastroenterol.Hepatol.* **23**, 23-33.

Saleh, H. A., Masood, S., & Khatib, G. (1996). Percutaneous and intraoperative aspiration biopsy cytology of pancreatic neuroendocrine tumors: cytomorphologic study with an immunocytochemical contribution. *Acta Cytol.* **40**, 182-190.

Sand, J. & Nordback, I. (2005). The differentiation between pancreatic neoplastic cysts and pancreatic pseudocyst. *Scand.J.Surg.* **94**, 161-164.

Schaefer, N. G., Hany, T. F., Taverna, C., Seifert, B., Stumpe, K. D., von Schulthess, G. K., & Goerres, G. W. (2004). Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging--do we need contrast-enhanced CT? *Radiology* **232**, 823-829.

Schenk, M., Schwartz, A. G., O'Neal, E., Kinnard, M., Greenson, J. K., Fryzek, J. P., Ying, G. S., & Garabrant, D. H. (2001). Familial risk of pancreatic cancer. *J.Natl. Cancer Inst.* **93**, 640-644.

Schick, V., Franzius, C., Beyna, T., Oei, M. L., Schnekenburger, J., Weckesser, M., Domschke, W., Schober, O., Heindel, W., Pohle, T., & Juergens, K. U. (2008). Diagnostic impact of (18)F-FDG PET-CT evaluating solid pancreatic lesions versus endosonography, endoscopic retrograde cholangio-pancreatography with intraductal ultrasonography and abdominal ultrasound. *Eur.J.Nucl.Med.Mol.Imaging* **35**, 1775-1785.

Schima, W., Ba-Ssalamah, A., Kolblinger, C., Kulinna-Cosentini, C., Puespoek, A., & Gotzinger, P. (2007). Pancreatic adenocarcinoma. *Eur.Radiol.* **17**, 638-649.

Schlieman, M. G., Ho, H. S., & Bold, R. J. (2003). Utility of tumor markers in determining resectability of pancreatic cancer. *Arch.Surg.* **138**, 951-955.

Selzner, M., Hany, T. F., Wildbrett, P., McCormack, L., Kadry, Z., & Clavien, P. A. (2004). Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? *Ann.Surg.* **240**, 1027-1034.

Service, G. J., Thompson, G. B., Service, F. J., Andrews, J. C., Collazo-Clavell, M. L., & Lloyd, R. V. (2005). Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *N.Engl.J.Med.* **353**, 249-254.

Sewnath, M. E., Karsten, T. M., Prins, M. H., Rauws, E. J., Obertop, H., & Gouma, D. J. (2002). A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. *Ann.Surg.* **236**, 17-27.

Shin, S. S., Jeong, Y. Y., Min, J. J., Kim, H. R., Chung, T. W., & Kang, H. K. (2008). Preoperative staging of colorectal cancer: CT vs. integrated FDG PET/CT. *Abdom.Imaging* **33**, 270-277.

Shreve, P. D. (1998). Focal fluorine-18 fluorodeoxyglucose accumulation in inflammatory pancreatic disease. *Eur.J.Nucl.Med.* **25**, 259-264.

Silverman, D. T., Schiffman, M., Everhart, J., Goldstein, A., Lillemoe, K. D., Swanson, G. M., Schwartz, A. G., Brown, L. M., Greenberg, R. S., Schoenberg, J. B., Pottern, L. M., Hoover, R. N., & Fraumeni, J. F., Jr. (1999). Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br.J.Cancer* **80**, 1830-1837.

Sipilä, H., Clark, J. C., Peltola, O., & Teräs, M. (2001). An automatic [15O]H2O production system for heart and brain studies. *J Labelled Comp Rad* **44**, 1066-1068.

Souza, F., Simpson, N., Raffo, A., Saxena, C., Maffei, A., Hardy, M., Kilbourn, M., Goland, R., Leibel, R., Mann, J. J., Van Heertum, R., & Harris, P. E. (2006). Longitudinal noninvasive PET-based beta cell mass estimates in a spontaneous diabetes rat model. *J.Clin. Invest* **116**, 1506-1513.

Soyka, J. D., Veit-Haibach, P., Strobel, K., Breitenstein, S., Tschopp, A., Mende, K. A., Lago, M. P., & Hany, T. F. (2008). Staging pathways in recurrent colorectal carcinoma: is contrast-enhanced 18F-FDG PET/CT the diagnostic tool of choice? *J.Nucl.Med.* **49**, 354-361.

Sperti, C., Bissoli, S., Pasquali, C., Frison, L., Liessi, G., Chierichetti, F., & Pedrazzoli, S. (2007). 18-fluorodeoxyglucose positron emission tomography enhances computed tomography diagnosis of malignant intraductal papillary mucinous neoplasms of the pancreas. *Ann.Surg.* **246**, 932-937.

Sperti, C., Pasquali, C., Chierichetti, F., Ferronato, A., Decet, G., & Pedrazzoli, S. (2003). 18-Fluorodeoxyglucose positron emission tomography in predicting survival of patients with pancreatic carcinoma. *J.Gastrointest. Surg.* **7**, 953-959.

Sperti, C., Pasquali, C., Decet, G., Chierichetti, F., Liessi, G., & Pedrazzoli, S. (2005). F-18-fluorodeoxyglucose positron emission tomography in differentiating malignant from benign pancreatic cysts: a prospective study. *J.Gastrointest.Surg.* **9**, 22-28.

Spinelli, K. S., Fromwiller, T. E., Daniel, R. A., Kiely, J. M., Nakeeb, A., Komorowski, R. A., Wilson, S. D., & Pitt, H. A. (2004). Cystic pancreatic neoplasms: observe or operate. *Ann.Surg.* **239**, 651-657.

Stefanidis, D., Grove, K. D., Schwesinger, W. H., & Thomas, C. R., Jr. (2006). The current role of staging laparoscopy for adenocarcinoma of the pancreas: a review. *Ann.Oncol.* **17**, 189-199.

Stokkel, M. P., Draisma, A., & Pauwels, E. K. (2001). Positron emission tomography with 2-[18F]-fluoro-

2-deoxy-D-glucose in oncology. Part IIIb: Therapy response monitoring in colorectal and lung tumours, head and neck cancer, hepatocellular carcinoma and sarcoma. *J.Cancer Res.Clin.Oncol.* **127**, 278-285.

Strobel, K., Heinrich, S., Bhure, U., Soyka, J., Veit-Haibach, P., Pestalozzi, B. C., Clavien, P. A., & Hany, T. F. (2008). Contrast-enhanced 18F-FDG PET/CT: 1-stop-shop imaging for assessing the resectability of pancreatic cancer. *J.Nucl.Med.* **49**, 1408-1413.

Sundin, A., Eriksson, B., Bergstrom, M., Bjurling, P., Lindner, K. J., Oberg, K., & Langstrom, B. (2000). Demonstration of [11C] 5-hydroxy-L-tryptophan uptake and decarboxylation in carcinoid tumors by specific positioning labeling in positron emission tomography. *Nucl.Med.Biol.* **27**, 33-41.

Sundin, A., Garske, U., & Orlefors, H. (2007). Nuclear imaging of neuroendocrine tumours. *Best.Pract.Res. Clin.Endocrinol.Metab* **21**, 69-85.

Tann, M., Sandrasegaran, K., Jennings, S. G., Skandarajah, A., McHenry, L., & Schmidt, C. M. (2007). Positron-emission tomography and computed tomography of cystic pancreatic masses. *Clin.Radiol.* **62**, 745-751.

Tempero, M. A., Uchida, E., Takasaki, H., Burnett, D. A., Steplewski, Z., & Pour, P. M. (1987). Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. *Cancer Res.* **47**, 5501-5503.

Timmers, H. J., Hadi, M., Carrasquillo, J. A., Chen, C. C., Martiniova, L., Whatley, M., Ling, A., Eisenhofer, G., Adams, K. T., & Pacak, K. (2007). The effects of carbidopa on uptake of 6-18F-Fluoro-L-DOPA in PET of pheochromocytoma and extraadrenal abdominal paraganglioma. *J.Nucl.Med.* **48**, 1599-1606.

Tsujino, M., Sugiyama, T., Nishida, K., Takada, Y., Takanishi, K., Ishizawa, M., & Hirata, Y. (2005). Noninsulinoma pancreatogenous hypoglycemia syndrome: a rare case of adult-onset nesidioblastosis. *Intern.Med.* **44**, 843-847.

Tutt, A. N., Plunkett, T. A., Barrington, S. F., & Leslie, M. D. (2004). The role of positron emission tomography in the management of colorectal cancer. *Colorectal Dis.* **6**, 2-9.

Valk, P. E., Abella-Columna, E., Haseman, M. K., Pounds, T. R., Tesar, R. D., Myers, R. W., Greiss, H. B., & Hofer, G. A. (1999). Whole-body PET imaging with [18F]fluorodeoxyglucose in management of recurrent colorectal cancer. *Arch.Surg.* **134**, 503-511.

van der Waaij, L. A., van Dullemen, H. M., & Porte, R. J. (2005). Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. *Gastrointest.Endosc.* **62**, 383-389.

van der Harst H. E., de Herder, W. W., Bruining, H. A., Bonjer, H. J., de Krijger, R. R., Lamberts, S. W., van de Meiracker, A. H., Boomsma, F., Stijnen, T., Krenning, E. P., Bosman, F. T., & Kwekkeboom, D. J. (2001). [(123) I]metaiodobenzylguanidine and [(111)In]octreotide uptake in begnign and malignant pheochromocytomas. *J.Clin.Endocrinol.Metab* **86**, 685-693.

van Kouwen, M. C., Jansen, J. B., van Goor, H., de Castro, S., Oyen, W. J., & Drenth, J. P. (2005). FDG-PET is able to detect pancreatic carcinoma in chronic pancreatitis. *Eur.J.Nucl.Med.Mol.Imaging* **32**, 399-404.

van Vliet, E. P., Heijenbrok-Kal, M. H., Hunink, M. G., Kuipers, E. J., & Siersema, P. D. (2008). Staging investigations for oesophageal cancer: a meta-analysis. *Br.J.Cancer* **98**, 547-557.

Varadhachary, G. R., Tamm, E. P., Crane, C., Evans, D. B., & Wolff, R. A. (2005). Borderline resectable pancreatic cancer. *Curr.Treat.Options.Gastroenterol.* **8**, 377-384.

Vargas, R., Nino-Murcia, M., Trueblood, W., & Jeffrey, R. B., Jr. (2004). MDCT in Pancreatic adenocarcinoma: prediction of vascular invasion and resectability using a multiphasic technique with curved planar reformations. *AJR Am.J.Roentgenol.* **182**, 419-425.

Visser, B. C., Yeh, B. M., Qayyum, A., Way, L. W., McCulloch, C. E., & Coakley, F. V. (2007). Characterization of cystic pancreatic masses: relative accuracy of CT and MRI. *AJR Am.J.Roentgenol.* **189**, 648-656.

Votrubova, J., Belohlavek, O., Jaruskova, M., Oliverius, M., Lohynska, R., Trskova, K., Sedlackova, E., Lipska, L., & Stahalova, V. (2006). The role of FDG-PET/CT in the detection of recurrent colorectal cancer. *Eur.J.Nucl. Med.Mol.Imaging* **33**, 779-784.

Wakabayashi, H., Akamoto, S., Yachida, S., Okano, K., Izuishi, K., Nishiyama, Y., & Maeta, H. (2005). Significance of fluorodeoxyglucose PET imaging in the diagnosis of malignancies in patients with biliary stricture. *Eur.J.Surg.Oncol.* **31**, 1175-1179.

Wakabayashi, H., Nishiyama, Y., Otani, T., Sano, T., Yachida, S., Okano, K., Izuishi, K., & Suzuki, Y. (2008). Role of 18F-fluorodeoxyglucose positron emission tomography imaging in surgery for pancreatic cancer. *World J.Gastroenterol.* **14**, 64-69.

Witt, H., Apte, M. V., Keim, V., & Wilson, J. S. (2007). Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. *Gastroenterology* **132**, 1557-1573.

Yao, J. C., Hassan, M., Phan, A., Dagohoy, C., Leary, C., Mares, J. E., Abdalla, E. K., Fleming, J. B., Vauthey, J. N., Rashid, A., & Evans, D. B. (2008). One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J.Clin.Oncol.* **26**, 3063-3072.

Yokoyama, Y., Nagino, M., Hiromatsu, T., Yuasa, N., Oda, K., Arai, T., Nishio, H., Ebata, T., & Nimura, Y. (2005). Intense PET signal in the degenerative necrosis superimposed on chronic pancreatitis. *Pancreas* **31**, 192-194.

Yuan, S., Yu, Y., Chao, K. S., Fu, Z., Yin, Y., Liu, T., Chen, S., Yang, X., Yang, G., Guo, H., & Yu, J. (2006). Additional value of PET/CT over PET in assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer. *J.Nucl.Med.* **47**, 1255-1259.

Zasadny, K. R., Tatsumi, M., & Wahl, R. L. (2003). FDG metabolism and uptake versus blood flow in women with untreated primary breast cancers. *Eur.J.Nucl.Med. Mol.Imaging* **30**, 274-280.

Zatelli, M. C., Torta, M., Leon, A., Ambrosio, M. R., Gion, M., Tomassetti, P., De Braud, F., Delle, F. G., Dogliotti, L., & degli Uberti, E. C. (2007). Chromogranin A as a marker of neuroendocrine neoplasia: an Italian Multicenter Study. *Endocr.Relat Cancer* **14**, 473-482.

Zimny, M., Buell, U., Diederichs, C. G., & Reske, S. N. (1998). False-positive FDG PET in patients with pancreatic masses: an issue of proper patient selection? *Eur.J.Nucl.Med.* **25**, 1352.

Öberg, K., Astrup, L., Eriksson, B., Falkmer, S. E., Falkmer, U. G., Gustafsen, J., Haglund, C., Knigge, U., Vatn, M. H., & Välimäki, M. (2004). Guidelines for the management of gastroenteropancreatic neuroendocrine tumours (including bronchopulmonary and thymic neoplasms). Part I-general overview. *Acta Oncol.* **43**, 617-625.

Öberg, K. & Eriksson, B. (2005). Endocrine tumours of the pancreas. *Best.Pract.Res.Clin.Gastroenterol.* **19**, 753-781.

Örlefors, H., Sundin, A., Garske, U., Juhlin, C., Öberg, K., Skogseid, B., Langström, B., Bergström, M., & Eriksson, B. (2005). Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. *J.Clin.Endocrinol.Metab* **90**, 3392-3400.

Örlefors, H., Sundin, A., Lu, L., Öberg, K., Langström, B., Eriksson, B., & Bergström, M. (2006). Carbidopa pretreatment improves image interpretation and visualisation of carcinoid tumours with 11C-5-hydroxytryptophan positron emission tomography. *Eur.J.Nucl.Med.Mol.Imaging* **33**, 60-65.