Protocol

Evaluation of the diagnostic value of TOF-18F-FDG PET/CT in patients with suspected pancreatic cancer

September 2013

Content

Summary..... 2
Background information..... 4
Study hypothesis..... 6
Aim of the study..... 6
Study process..... 7
Patients..... 8
Patient recruitment..... 8
Protocol: PET/CT..... 9
Data handling..... 10
References..... 11

Summary

According to the application for the responsible ethics committee of the Medical University of Graz a study is to be performed for the „*evaluation of the diagnostic value of TOF-18F-FDG PET/CT in patients with suspected pancreatic cancer*“.

The essential idea of the study is the analysis of the use of early (30min p.i.) and delayed (90min p.i) imaging as well as a diagnostic CT of the abdomen with contrast medium and pancreas protocol for characterization of pancreatic masses with TOF (Time-of-Flight)-18F-FDG-PET/CT.

According to current scientific evidence, there are no studies in the literature regarding the characterization of pancreatic masses by the "Time-of-Flight"-technique (TOF) within PET/CT. Usually, the differentiation between chronic pancreatitis and pancreatic carcinoma is often not possible. Likewise, the differentiation of the pancreas from surrounding anatomical structures (duodenum) in PET/CT with low dose CT is often not possible. An exact diagnosis of a possible malignancy or benignancy, as well as the precise anatomical localization of the detected lesion, is however of decisive importance for the further therapeutic procedure [1-4]. If a benign lesion is present, an extensive operation (Whipple operation) may not be necessary.

As a rule, patients with suspected pancreatic cancer are assigned to the Division of Nuclear Medicine for 18F-FDG PET-CT imaging. Early (30min p.i.) and delayed images (90min p.i.) are taken to better distinguish between malignant from inflammatory lesions. After the PET/CT examination, a TOF-reconstruction is performed, which does <u>not</u> require the presence of the patient, but improves the image quality to differentiate the lesion in the pancreas better. For better anatomical demarcation of the pancreas of adjacent structures (duodenum) additionally a diagnostic CT of the abdomen (up to the iliac crest) with pancreas protocol (2 phases) with i.v. administration of iodine-containing contrast medium (Visipaque®) and oral administration of a negative contrast medium (500 ml water) for intestinal distension is additionally performed. After consultation with the referring physician, it must be ensured for reasons of radiation hygiene that the patients do not have a diagnostic CT with contrast agent <u>before</u> the PET/CT examination. If this is not possible, a diagnostic CT of the upper abdomen (up to the lower liver margin) is performed with pancreas protocol with 2 phases (arterial and portal venous).
In most cases these patients are operated, only in the rarest of cases, a biopsy/brush swab is carried out beforehand. The histopathological preparation of the surgical specimen is then performed. These steps are <u>routine</u>. This approach is to be retained in the project. These steps are

1) Assignment of the patient to the TOF-PET-CT (with images 30min und 90min p.i.)
2) Performing a diagnostic CT of the abdomen with parenteral and oral contrast media and pancreas protocol as part of the PET/CT examination
3) Routine performance of the operation/fine needle puncture
4) Routine histopathological evaluation

With the help of the enclosed Informed Consent, the patient‘s information and written consent are duly given. Furthermore, in the case of administration of parenteral contrast medium, the relevant information is routinely provided using a contrast medium information sheet.

The administration of parenteral contrast media is performed according to the ESUR Guidelines [1].

Background information

Several studies dealt with the question of differentiating between benign and malignant processes of the pancreas using 18F-FDG PET/CT imaging. However, a reliable statement can currently only be made by histopathological assessment (considered the gold standard). For this reason, a priori no conclusion can currently be drawn as to the malignancy or benignity of the lesion in question. According to recent studies, malignant pancreatic diseases occur in patients with suspected pancreatic carcinoma and condition after pancreatoduodenectomy or fine needle aspiration with a frequency of 66-81% (47-78% of which are adenocarcinomas), benign diseases with a frequency of 19-34%, of which about 60% are inflammatory diseases and 40% benign cystic tumors [2-5].
In this study, patients with suspected benign diseases that are not operated and do not have a fine needle biopsy and are only monitored by radiological follow-ups are excluded.

According to the current status of science, there are no studies in the literature concerning the characterization of pancreatic lesion expansions using the "Time-of-Flight"-technique (TOF) in the framework of PET/CT. The TOF technique is a new reconstruction algorithm in PET/CT that can only be applied to newer devices. High-definition PET technology can significantly improve spatial resolution (to 2 mm) and increase sensitivity (TOF) by a factor of 3. The combination of both techniques (HD-PET with TOF) is called Ultra HD-PET.
The 18F-FDG PET/CT is indicated for staging in patients with suspected pancreatic carcinoma and was also classified as 1a indication for differentiation between inflammation and pancreatic carcinoma according to the 3rd German Interdisciplinary Consensus [6]. In patients with suspected pancreatic carcinoma, diagnosis is often only possible with difficulty due to the limited anatomical assignment of small focal lesions and discreetly increased tracer-uptake, differentiation between benign and malignant is often not possible, i.e., differentiation between chronic pancreatitis and a malignant process is often only possible to a minimal extent. According to clinical studies [7;8;21-26], the TOF-technique and additional i.v. administration of iodine-containing contrast medium and oral administration of a negative contrast medium can significantly improve the sensitivity and anatomical differentiation of the target organ from adjacent structures. However, this technique has not yet been used in patients with suspected pancreatic cancer.
Another already established method to better distinguish inflammatory from malignant lesions in PET/CT is to take images at two different time points and to compare the Standard Uptake Value (SUV), a measure of regional accumulation intensity, at these two times [3;17;18]. Here an increased FDG-uptake already in the early images is classified as benign/inflammatory, and an increase in FDG -

uptake in the delayed images is classified as malignant. A missing FDG uptake both in the early and the delayed images is considered benign.

The diagnostic procedure of 18F-FDG PET is based in case of oncological questions on the mechanism that tumor cells show an increased glucose metabolism and that these areas become visible in nuclear medical imaging through increased 18F-FDG tracer uptake. The SUV has established itself as a semi-quantitative measure of uptake concerning patient weight (SUV/bw), which is used both for staging and for determining tumor boundaries [3;9-14;17-20;21;27-31]. For further curative as well as palliative treatment, knowledge of the exact tumor boundaries is essential for the further treatment steps. On the one hand, these are needed for measurement and differentiation (from vital structures) as well as for planning (knowledge of the exact tumor size) in further treatment [32-34]. To date, CT and MRI have mainly been used as morphological methods to delimit tumors and to assess the resectability, whereby functional imaging often plays a decisive role in therapy decisions but is currently hardly taken into account for the problems of delimitation and resectability.

PET/CT is routinely performed in the suspected case of pancreatic cancer [6-20]. Subsequently, a subtotal pancreaticoduodenectomy (Whipple operation) with lymphadenectomy is performed routinely in cases of urgent suspicion of malignancy and PET scintigraphically confirmed absence of distant metastases. Thereby in addition to the pancreatic head and the duodenum the gall bladder, distal bile duct, and gastric antrum are removed. At the University Clinic for Surgery Graz, a previous sonographic or CT-controlled biopsy is usually not performed due to the danger of sting canal metastases in the case of resectable tumors. If necessary, a diagnostic laparotomy is performed. Even a negative fine needle puncture that may have been performed beforehand does not rule out an operation. However, in the rare case of a CT-guided biopsy alone without subsequent surgery, such patients should also be included in the present study. PET as well as the operation/fine needle puncture are routine clinical procedures and are therefore not explained further.

In the area of pancreatic lesions, it is difficult to distinguish adjacent anatomical structures (duodenum). For this reason, in the present study additionally, a parenteral iodine-containing (Visipaque®) and a negative oral contrast medium (500 ml water) will be administered. One difficulty of such studies is that the dignity of the tumor can only be determined after histopathological examination of the surgical specimen.

Study hypothesis

Early- (30min p.i.) and delayed images (90min p.i.), diagnostic CT of the abdomen with contrast medium and Time-of-Flight (TOF)-reconstruction within the framework of 18F-FDG PET/CT allow an improvement in the differentiation of malignant from benign lesion expansions of the pancreas.

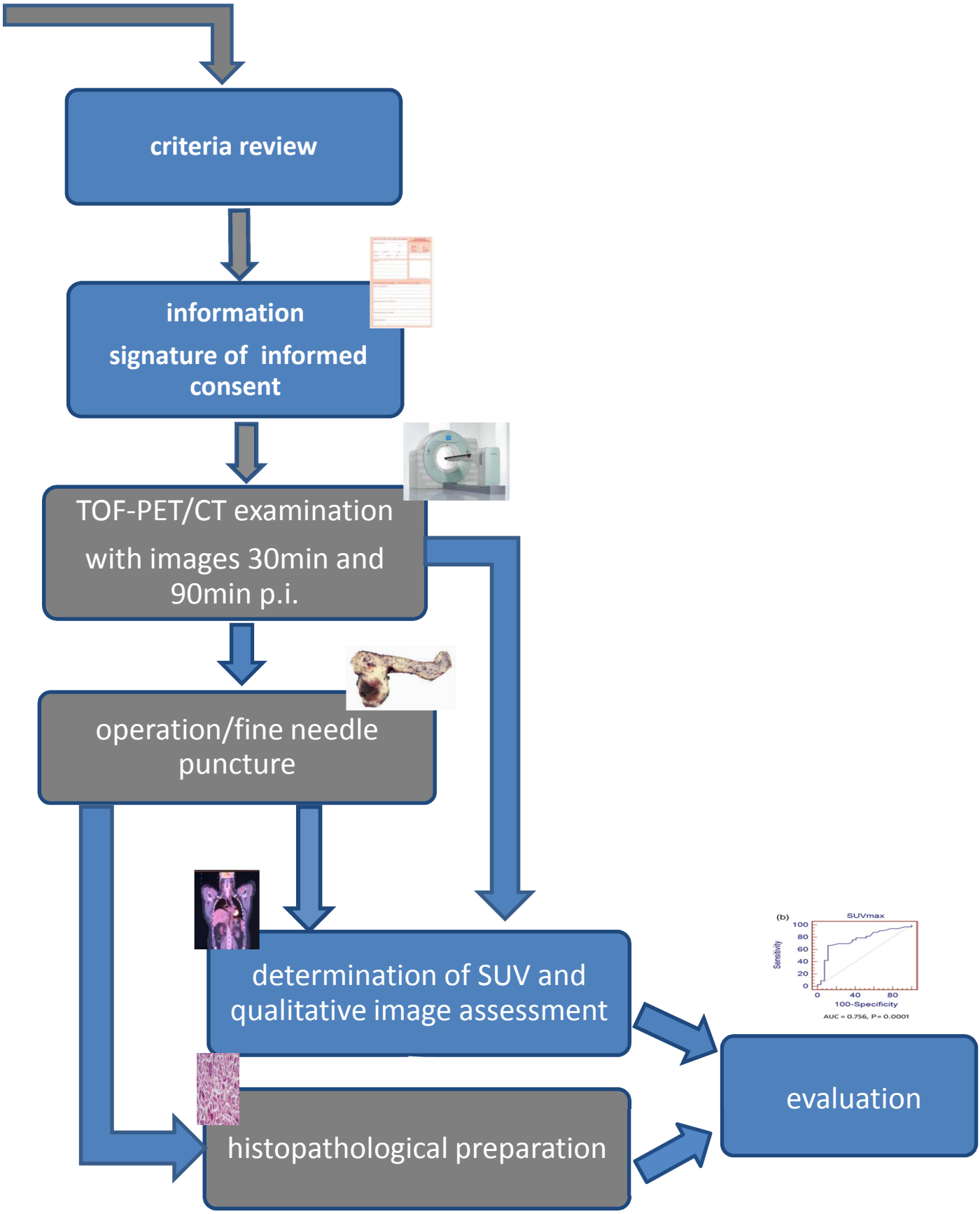
Aim of the study

The aim of the study is to improve the differentiation between malignant and benign lesions in the pancreas in patients with suspected pancreatic cancer by images 30min und 90min p.i. and a diagnostic CT of the abdomen with contrast medium in the context of TOF-18F-FDG PET/CT and thus to improve the quality of PET/CT findings. Also, a cut-off value of SUV will be determined in correlation with the histopathological results to better differentiate between malignant and benign lesions of the pancreas.

Study process

Assignment with suspected diagnosis

Legend:
- grey: routine examination
- blue: study-specific work steps



Patients

118 patients are to be diagnosed continuously according to protocol.

Inclusion criteria:

- patients with suspected pancreatic cancer (morphologically suspect)
- operation/fine needle puncture

PET/CT examination with TOF-reconstuction algorithm and contrast medium:

- sober
- plasma glucose level < 140 mg/dl
- position capability
- checking of: • creatinine value < 1.2 mg/dl (for values >1.2 mg/dl no administration of contrast medium) and eGFR-value > 45 ml/min/1.73 m² (for values < 45 ml/min/1.73 m² no administration of contrast medium)
  • TSH-value 0.1-4.0 µU/ml (for values <0.1 µU/ml no administration of contrast medium)

Exclusion criteria:

- patients under 18 years
- plasma glucose level > 140 mg/dl
- patients with histopathologically confirmed distant metastases at the time of PET/CT examination
- patients with non-pancreatic tumors
- patients, who **will not undergo surgery** or had **no fine needle puncture (FNP)** and therefore have no histopathological findings of the pancreas
- pregnancy

Patient recruitment

As a rule, the patients are referred to the Division of Nuclear Medicine for diagnostic staging using 18F-FDG PET/CT. As part of the preparation of the patients for the PET/CT examination, the principle investigator and other staff members will provide the information, and in case of participation at the study, the Informed Consent (enclosed) will be signed.

Protocol: PET/CT

After the patients have been admitted to PET/CT operation/fine needle biopsy must be performed within a maximum of 4 weeks.

Patient preparation

- Blood sugar control < 140 mg/dl
- Administration of the tracer in the PET application room

Application

- Intravenous injection of maximal 370 MBq 18F-FDG (fluorodeoxyglucose)
  - depending on the body weight (according to EANM European Dose-Card corresponds to approx. 7mSv patient dose)

Patient preparation

- Rest for 30 minutes (tempered and darkened) while oral administration of 500 ml water (negative contrast medium)
- Immediately before the start of the examination empty the bladder as thoroughly as possible
- Remove all metallic objects from the test area to avoid artifacts
- Comfortable supine position of the patient during acquisition

Examination device

- Siemens Biograph mCT 40

Protocol

- CT according to 120kV 50mAs eff. (scout, quality standard low dose)
- Whole body (skull base to thigh): static acquisition of 6 bed-positions (depending on patient size) of 2 minutes each (with BMI >30 acquisition time extend by 1 minute per position)
- 90min p.i. image (abdomen): static image of 2-3 bed-positions (depending on patient size) at 2 minutes each (with BMI >30 acquisition time extend by 1 minute per position)

Image evaluation, SUV-calculation

- Evaluation station: Siemens SYNGO MMWP

Work area

- University Clinic of Radiology, Division of Nuclear Medicine, room 440/438, 4th floor

Protocol diagnostic CT of the abdomen with pancreas protocol and contrast medium

Examination device

- Siemens Biograph mCT 40

Protocol

- CT according to 120kV 220mAs in spiral mode (according to a standard dose length product of approx. 450 resp. 225 mGycm, corresponding to approx. 6.7 mSv patient dose with diagnostic

CT to the iliac crest or approx. 3.3 mSv with diagnostic CT to the lower liver margin). The dose length products were derived from measurements on the patient and the phantom.

- Reconstruction to 5mm layer thickness with an increment of Schichtdicke 3 mm
- i.v.-administration of 1,4 ml/kg body weight (bw) Visipaque® (Iodixanol) at a rate of 3 ml/s and image acquisition over 2 phases (arterial, portal venous) up to the iliac crest/ to the lower liver margin with already performed CT of the abdomen with pancreas protocol before at least 2 weeks

Data-handling

The patient data is encoded with a consecutive number and managed in an Excel spreadsheet. The colleagues working on the project make the entries in this table.

References

[1] Stacul F, van der Molen AJ, Reimer P, Webb JAW, Thomsen HS, et al. Contrast induced nephropathy: updated ESUR contrast media safety committee guidelines. *Eur Radiol* 2011; 21:2527-2541.

Incidence and prevalence of malignant and benign diseases of the pancreas:

[2] Santhosh S, Mittal BR, Bhasin D, Srinivasan R, Rana S, et al. Role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the characterization of pancreatic masses: Experience from tropics. *J Gastroenterol Hepatol* 2013; 28: 255-261.
[3] Nagamachi S, Nishii R, Wakamatsu H, Mizutani Y, Kiyohara S, et al. The usefulness of ^{18}F-FDG-PET/MRI fusion image in diagnosing pancreatic tumor: comparison with ^{18}F-FDG PET/CT. *Ann Nucl Med* 2013; 27:554-563.
[4] van Gulik TM, Reeders JWAJ, Bosma A, Moojen TM, Smits NJ, et al. Incidence and clinical findings of benign, inflammatory disease in patients resected for presumed pancreatic head cancer. *Gastrointest Endosc* 1997; 46:417-423.
[5] van Heerde MJ, Biermann K, Zondervan PE, Kazemier G, van Eijck CHJ, et al. Prevalence of autoimmune pancreatitis and other benign disorders in pancreatoduodenectomy for presumed malignancy of the pancreatic head. *Dig Dis Sci* 2012; 57:2458-2465.

Diagnosis of pancreatic carcinoma using F-18-FDG-PET-CT:

[6] Reske SN, Kotzerke J. 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* 2001; 28:1707-23.
[7] Pfannenberg AC, Aschoff P, Brechtel K, Müller M, et al. Value of contrast-enhanced multiphase CT in combined PET/CT protocols for oncological imaging. *Br J Radiol* 2007; 80:437-445.
[8] Strobel K, Heinrich S, Bhure U, Soyka J, Veit-Haibach P, et al. Contrast-Enhanced ^{18}F-FDG PET/CT: 1-Stop-Shop Imaging for Assessing the Resectability of Pancreatic Cancer. *J Nucl Med* 2008; 49:1408-1413.
[9] Takanami K, Hiraide T, Tsuda M, Nakamura Y, Kaneta T, et al. Additional value of FDG PET/CT to contrast-enhanced CT in the differentiation between benign and malignant intraductal papillary neoplasms with mural nodules. *Ann Nucl Med* 2011; 25:501-510.

[10] Orlando LA, Kulasingam SL, Matchar DB. Meta-analysis: the detection of pancreatic malignancy with positron emission tomography. *Aliment Pharmacol Ther* 2004; 20:1063-70.

[11] Heinrich S, Goerres GW, Schäfer M, Sagmeister M, Bauerfeind P, et al. Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and ist cost-effectiveness. *Ann Surg* 2005; 242:235-43.

[12] Rasmussen I, Sorensen J, Langstrom B, Haglund U. Is positron emission tomography using 18F-fluorodeoxyglucose and 11C-acetate valuable in diagnosing indeterminate pancreatic masses ? *Scand J Surg* 2004; 93:191-7.

[13] Sperti C, Pasquali C, Decet G, Chierichetti F, Liessi G, et al. F-18-fluorodeoxyglucose positron emission tomography in differentiating malignant from benign pancreatic cysts: a prospective study. *J Gastrointest Surg* 2005; 9:22-9.

[14] Zimny M, Bares R, Fass J, Adam G, Cremerius U, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography in the differential diagnosis of pancreatic carcinoma: a report of 106 cases. *Eur J Nucl Med* 1997; 24:678-82.

[15] De Gaetano AM, Rufini V, Castaldi P, Gatto AM, Filograna L, et al. Clinical applications of ^{18}F-FDG PET in the management of hepatobiliary and pancreatic tumors. *Abdom Imaging* 2012; 37:983-1003.

[16] Okano K, Kakinoki K, Akamoto S, Hagiike M, Usuki H, et al. 18F-fluorodeoxyglucose positron emission tomography in the diagnosis of small pancreatic cancer. *World J Gastroenterol* 2011; 17:231-235.

[17] Lyshchik A, Higashi T, Nakamoto Y, Fujimoto K, Doi R, et al. 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* 2005; 32:389-397.

[18] Nakata B, Chung YS, Nishimura S, Nishihara T, Sakurai Y, et al. 18F-fluorodeoxyglucose positron emission tomography and the prognosis of patients with pancreatic carcinoma. *Cancer* 1997; 79:695-699.

[19] Rose DM, Delbeke D, Beauchamp RD, Chapman WC, Sandler MP, et al. 18-fluorodeoxyglucose-positron emission tomography (18FDG-PET) in the management of patients with suspected pancreatic cancer. *Ann Surg* 1998; 229:729-738.

[20] Buck AK, Herrmann K, Eckel F, Beer AJ. Positron Emission Tomography. Pancreatic and hepatobiliary cancers, In: Juweid ME, Hoekstra OS, eds. *Methods in Molecular Biology.* Heidelberg: Springer Science+Business Media, LLC; 2011: 727, 243-264.

Studies on the clinical significance of TOF-technology:

[21] Kerschbaumer S., Gstettner C., Aigner R. Evaluation of the clinical impact of Time-of-Flight (TOF) PET/CT scans for F18-FDG whole body protocol on a Siemens Biograph mCT. EANM Scientific Program, Poster Session, Tracking Number 2012-S-1013-EANM.
[22] Hausmann D, Bittencourt LK, Sertdemir M, Weidner A, Büsing K, et al. Evaluation der diagnostischen Genauigkeit der 18F-Cholin PET/CT mit Time-of-Flight-Rekonstruktionsalgorithmus (TOF) bei Prostatakarzinompatienten mit biochemischem Rezidiv. 94. Deutscher Röntgenkongress 2013, Vorträge, VO 310.1, S207-S208.
[23] Werner ME, Karp JS. TOF PET offset calibration from clinical data. *Phys Med Biol* 2013; 58:4031-46.
[24] Panin VY, Aykac M, Casey ME. Simultaneous reconstruction of emission activity and attenuation coefficient distribution from TOF data, acquired with external transmission source. *Phys Med Biol.* 2013; 58:3649-69.
[25] Surti S, Scheuermann J, El Fakhri G, Daube-Witherspoon, ME, Lim R et al. Impact of Time-of-Flight PET on Whole-Body Oncologic Studies: A Human Observer Lesion Detection and Localization Study. J Nucl Med 2011; 52:712–719.
[26] Lois C, Jakoby BW, Long MJ, Hubner KF, Barker DW, et al. An Assessment of the Impact of Incorporating Time-of-Flight Information into Clinical PET/CT Imaging. *J Nucl Med* 2010; 51:237-245.

Studies on the importance of the SUV in PET/CT:

[27] Nguyen NC, Kaushik A, Wolverson MK, Osman MM. Is there a common SUV threshold in oncological FDG PET/CT, at least for some common indications? A retrospective study. *Acta Oncol* 2011; 50:670–677.
[28] Osman MM, Cohade C, Nakamoto Y, Marshall LT, Leal JP, Wahl RL. Clinically significant inaccurate localization of lesions with PET/CT: frequency in 300 patients. *J Nucl Med* 2003; 44:240–243.
[29] Siegel R, Naishadham D, Jemal A. Cancer statistics 2013. *CA Cancer J Clin* 2013; 63:11–30.
[30] Sugaware Y, Zasadny K, Neuhoff AW, RL Wahl RL. Reevaluation of the standardized uptake value for FDG variations with the body weight and methods for correction. *Radiology*1999; 213:521-525.
[31] Visser EP, Boerman OC, Oyen WJ. SUV: From Silly Useless Value to Smart Uptake

Value. *J Nucl Med* 2010; 51:173–175.

Intervention planning / therapy planning:

[32] Brianzoni E, Rossi G, Ancidei S, Berbellini A, Capoccetti F, Cidda C et al. Radiotherapy planning: PET/CT scanner performances in the definition of gross tumour volume and clinical target volume. *Eur J Nucl Med Mol Imaging* 2005; 32:1392–1399.

[33] Gupta T, Beriwal S. PET/CT-guided radiation therapy planning: From present to the future. *Indian J Cancer* 2010; 47:126-133.

[34] MacManus M, Nestle U, Rosenzweig KE, Carrio I, Messa C, Belohlavek O, et al. (2009): Use of PET and PET/CT for Radiation Therapy Planning: IAEA expert report 2006–2007. *Radiother Oncol* 2009; 91:85–94.