Statistical Analysis Plan (SAP)

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

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Abbreviations

AUC	Area under the curve
CT	Computed tomography
FDG	Fluorodeoxyglucose
p.i.	post injectionem
PET/CT	Positron emission tomography/computed tomography
ROC	Receiver operating characteristic
SUVmax	Maximum Standard Uptake Value
TOF	Time-of-Flight
TSH	Thyroid stimulating hormone

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1. Introduction

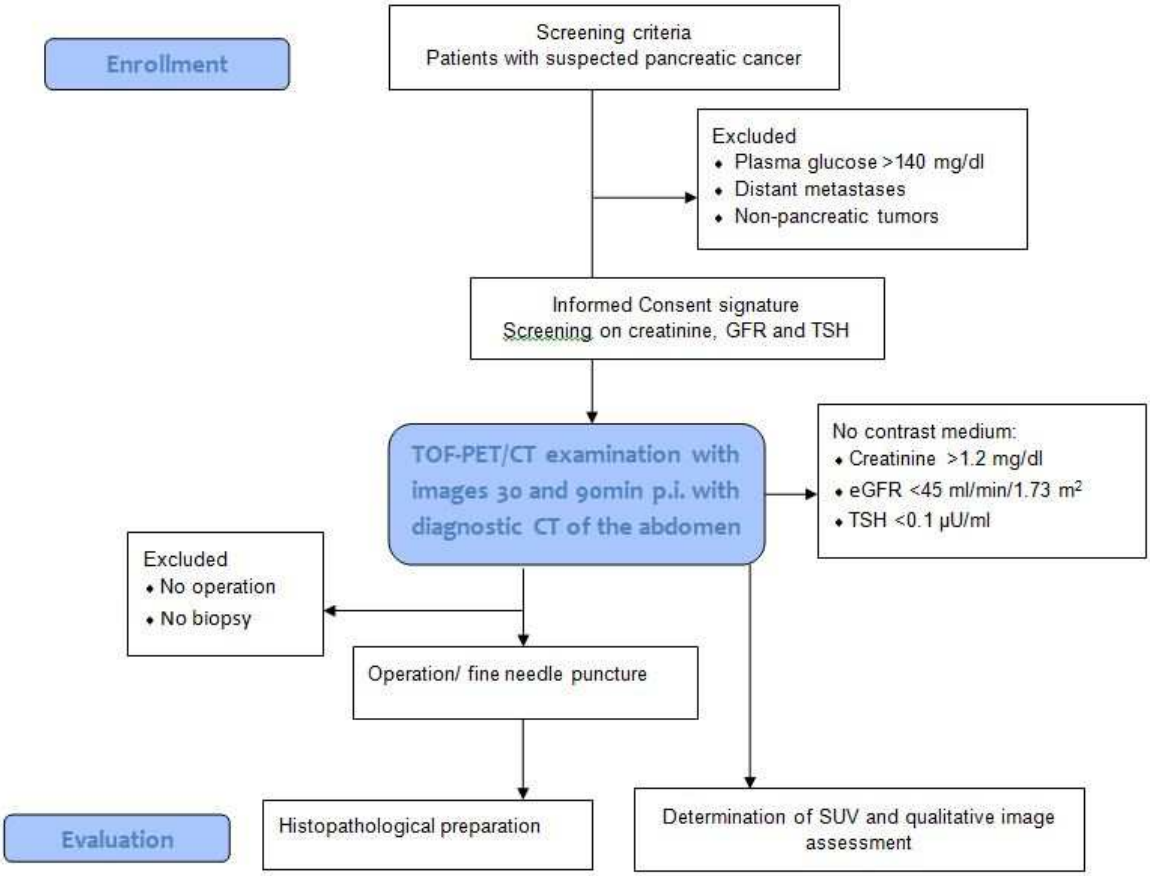
The study aims to improve the differentiation between malignant and benign lesions in the pancreas in patients with suspected pancreatic cancer by images 30min und 90min p.i. and a diagnostic CT of the abdomen with contrast medium in the context of TOF-18F-FDG PET/CT and thus to improve the quality of PET/CT findings. Also, a cut-off value of SUV (primary outcome measure) will be determined in correlation with the histopathological results to better differentiate between malignant and benign lesions of the pancreas. Secondary outcome measures are the better demarcation of pancreatic lesions of the adjacent anatomical structures as well as the tumor size.

2. Study design

Study subjects will be recruited from the patients with suspected pancreatic cancer who 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, Dr. Susanne Stanzel and other staff members will provide the information, and in case of participation at the study, the Informed Consent (enclosed) will be signed. Patients had to be sober and should have a plasma glucose level < 140 mg/dl. Furthermore, the creatinine level < 1.2 mg/dl (for values >1.2 mg/dl no administration of contrast medium) and TSH level (for values <0.1 µU/ml no administration of contrast medium) will be checked.

The study is a prospective single-center clinical trial with one arm. During this clinical study at intervals of 4 weeks, the following examinations will be performed: PET/CT-examination, surgery or fine needle puncture. If the patients do not have a fine needle puncture or surgery, they are automatically excluded from the study due to missing histopathological findings. The study design is shown in Figure 1 below.

Figure 1 Flowchart of screening and inclusion process



2.1 Sample size planning

One hundred eighteen patients would be required to demonstrate an improvement in specificity of 25% (to 70%) with the new method assuming a specificity of the current method of 45% at a prevalence of malignant lesions of 70% (corresponding to 30% benign lesions). The calculation of these values is based on a formula that selects the sample size so that the lower limit of the 95% confidence interval by the expected specificity of the new method most probably exceeds the specificity value of the current method, i.e., the confidence interval no longer contains this value. With a power of (in this case) 90%, you can say that the specificity of the new method is higher than the old one.

3. Aims and objectives

The aim of the study is to analyze if 30 and 90min p.i. images and a diagnostic CT of the abdomen in the context of TOF-18F-FDG-PET/CT can improve the differentiation between malignant and benign lesions in the pancreas in patients with suspected pancreatic cancer.

4. Outcomes

This section will present the outcomes investigated to answer the study aims and objects. The analyses are described in section 6 Analyses.

4.1 Primary outcome

SUVmax at 30 and 90 min p.i. in the PET/CT images with and without TOF over the pancreatic lesion.

4.2 Secondary outcome

Better demarcation of pancreatic lesions of the adjacent anatomical structures as well as the tumor size in cm.

4.3 Safety outcomes

Adverse events

Possible adverse events are reported in the case report form.

Concomitant medications

Usage of diabetes or thyroid medications before PET/CT examination will be recorded.

5. Populations to be analyzed

There is only one population in this clinical trial. All patients undergo a TOF-18F-FDG PET/CT examination with images 30 and 90min p.i. with a diagnostic CT of the abdomen. In all patients exist PET images with and without TOF.

6. Analyses

All outcomes will be presented using ROC-analysis or descriptive statistics. SPSS version 25 and R will be used for all statistical analysis.

6.1 Primary outcome

The primary analysis will compare the SUVmax values of all detected pancreatic lesions in the PET/CT images 30 and 90min p.i. with and without TOF using ROC-analysis. AUC values with and without TOF 30 and 90min p.i. will be compared using the DeLong-test. Sensitivity and specificity of SUVmax of each imaging modality (with and without TOF) in correlation with the

histopathological results will be calculated. Furthermore, a cut-off value of SUVmax for differentiating malignant and benign pancreatic lesions will be computed using ROC-analysis. Besides, sensitivity, specificity, diagnostic accuracy and the positive and negative predictive value of the results of the PET/CT findings in correlation with the histopathological results will be calculated.

6.2 Secondary outcome

The number of patients with increased tracer-uptake over the pancreatic lesion with and without TOF, and thus the better demarcation of pancreatic lesions of the adjacent anatomical structures will be compared using the McNemar test. Also, differences between the SUVmax values with and without TOF will be compared using the t-test. Furthermore, the mean tumor size including the standard deviation will be calculated.