

BEFAST STUDY

[⁶⁸Ga]Ga-FAPI total body PET/CT for Better and Faster imaging in cancer

Protocol: [⁶⁸Ga]Ga-FAPI total body PET/CT for improving
diagnostic sensitivity and preoperative staging in
gastroesophageal cancer and pancreatic cancer

General information:

Title: [⁶⁸Ga]Ga-FAPI total body PET/CT for improving diagnostic sensitivity and preoperative staging in gastroesophageal cancer and pancreatic cancer

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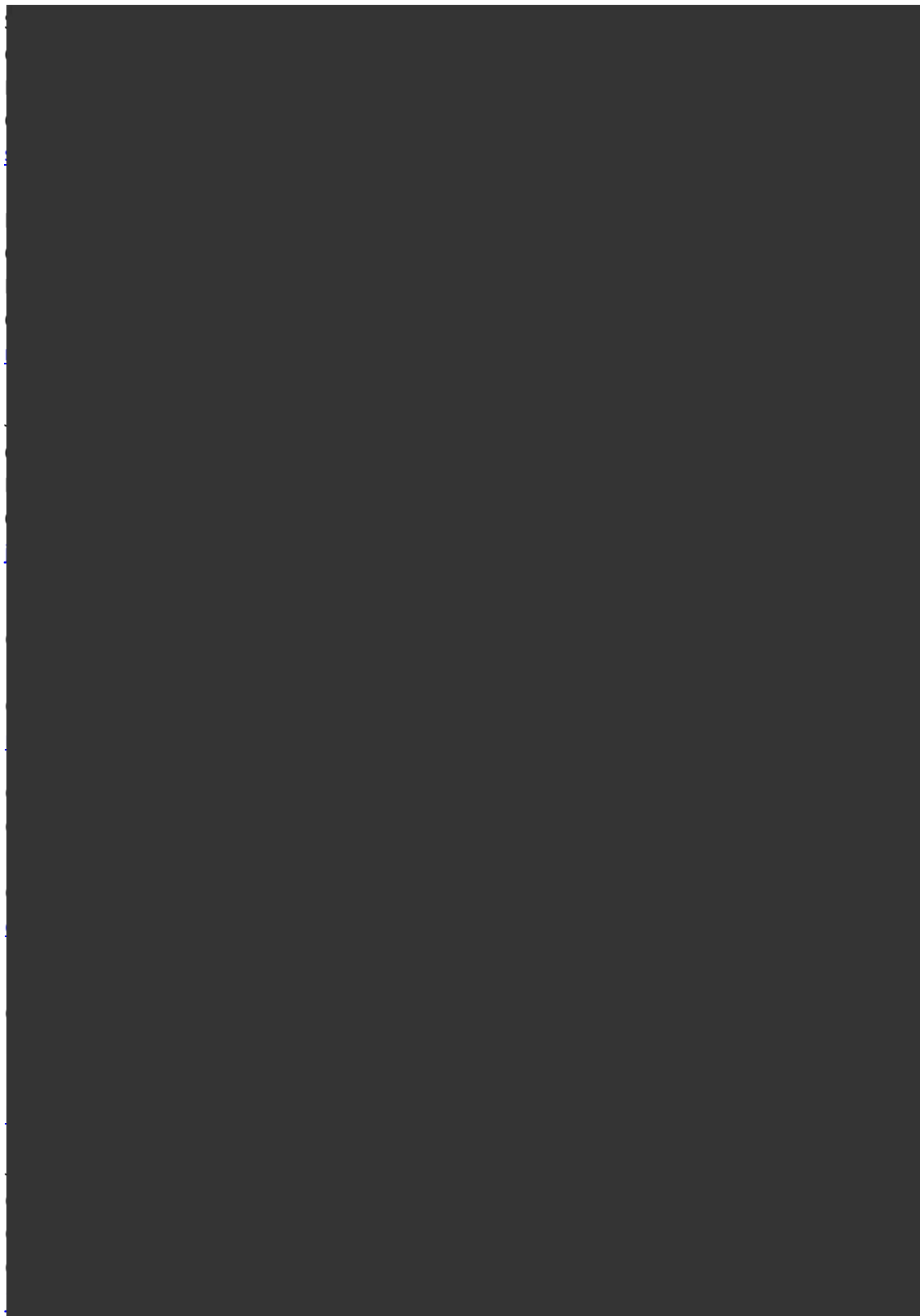
The information of the current PI is available on the European clinical trial information system (CTIS) website: <https://euclinicaltrials.eu/>. Information on this trial can be retrieved by using the EU trial number (2023-503632-41-01) as a search criteria.

Person authorized to sign the protocol or amendments on behalf of sponsor:



List of advisors:





Localization of trial:

The localization of the trial is available at the CTIS website: <https://euclinicaltrials.eu/>. Information on this trial can be retrieved by using the EU trial number (2023-503632-41-01) as a search criteria.

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Statement:

The presented trials will be conducted in accordance to the protocol and laws and regulations on clinical trials provided by the Danish state and the European Union as well as with the principles of good clinical practice.

Permission to conduct clinical trial related monitoring and inspection

The involved departments at Rigshospitalet and the investigator have given permission for the clinical trial related monitoring and regulatory inspection with direct access to source data and documents. The regulatory inspections and monitoring will be performed by representatives from the Danish Medical Agency, the National Committee on Health Research Ethics, and the GCP-unit of Copenhagen University Hospital, respectively.

Timeframe:

The protocol consists of two trials: Trial A and Trial B. Both trials will be initiated in the autumn/winter of 2023/2024, and we estimate an inclusion period of three years. The trial will end 1 year after the last participant has undergone the [⁶⁸Ga]Ga-FAPI-46 total body (TB) PET/CT which is estimated to the winter of 2027/2028.

Signature



Glossary of Abbreviations

Abbreviation	Definition
PET	Positron Emission Tomography
CT	Computed Tomography
TB	Total Body
[¹⁸ F]FDG	2-[¹⁸ F]fluoro-2-deoxy-D-glucose (chemical name)
FAP	Fibroblast Activation Protein
FAPi	Fibroblast Activation Protein inhibitor
[⁶⁸ Ga]	Gallium-68
[⁶⁸ Ga]Ga-FAPi-46	[⁶⁸ Ga]gallium (S)-2,2',2''-(10-(2-(4-(3-((4-(2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethylcarbamoyl)-quinolin-6-yl)(methyl)amino)-propyl)piperazin-1-yl)-2-oxoethyl) 1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (chemical name)
TME	Tumor microenvironment
TNM	Tumor, Node, Metastasis
CAF	Cancer Associated Fibroblasts
MRI	Magnetic Resonance Imaging
MDT	Multidisciplinary Team
GEJ	Gastroesophageal Junction
mSv	Millisievert
mBq	Megabecquerel
IV	intravenous
SUV _{max,mean}	Standardized Uptake Value, maximum and mean
SD	Standard Deviation
PPV	Positive Predictive Value
NPV	Negative Predictive Value
PFS	Progression Free Survival
IMPd	Investigational medicinal product dossier
CRF/eCRF	Case Report Form/Electronic Case Report Form
PI	Principal Investigator
AE	Adverse Event
AR	Adverse Reaction
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected unexpected serious Adverse Reaction
CIMT	Centre of IT and Medical Technology
GCP-unit	Good Clinical Practice-unit
ICH-GCP	International Conference on Harmonisation-Good Clinical Practice

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1. Purpose:

The overall aim of the study is to evaluate the diagnostic sensitivity of the tracer [⁶⁸Ga]Gallium (S)-2,2',2''-(10-(2-(4-(3-((4-(2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethylcarbamoyl)-quinolin-6-yl)(methyl)amino)-propyl)piperazin-1-yl)-2-oxoethyl) 1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid ([⁶⁸Ga]Ga-FAPI-46) with total body (TB) positron emission tomography (PET)/computed tomography (CT) compared to standard imaging in patients with gastroesophageal cancer and pancreatic cancer. We also want to evaluate the potential benefits of [⁶⁸Ga]Ga-FAPI-46 TB PET/CT in terms of logistic and patient comfort.

2. Background:

Positron emission tomography (PET) with the radioactive tracer 2-[¹⁸F]fluoro-2-deoxy-D-glucose ([¹⁸F]FDG) combined with computed tomography (CT) is a scanner modality that plays a key-role in staging, response evaluation and follow-up in many types of cancer(1-3).

The radioactive tracer is an isotope fluorine 18 (¹⁸F) bound to the glucose analogue 2-[¹⁸F]fluoro-2-deoxy-D-glucose ([¹⁸F]FDG). Patients are injected with the tracer prior to the scan, and cells will take up the radioactive glucose analogue (4). The basis for imaging with [¹⁸F]FDG PET is the increased glucose uptake and metabolic trapping in cancer cells of the radioactive tracer(5). The CT component helps to visualize the anatomical location of the increased metabolism (4).

Even though imaging with [¹⁸F]FDG PET/CT has improved staging and response evaluation in many cancers, it still lacks sensitivity and specificity in some diagnostic settings. This is especially evident in malignancies localized to the abdomen, more precisely gastroesophageal cancer and pancreatic cancer.

Gastroesophageal cancer includes tumors in esophagus, gastroesophageal junction (GEJ) and gastric cancer. 1100 new cases were diagnosed in 2020 in Denmark (6). 2/3 of the patients have incurable disease at the time of diagnosis, due to metastatic disease or general poor condition of the patient(7). Thus 1/3 of the patients are offered curative treatment with surgical resection combined with neoadjuvant or adjuvant chemotherapy, which is a burdensome treatment with potential postoperative complications and a poor 5-year survival rate (7-9). The treatment options are discussed on a multidisciplinary team (MDT) conference with surgeons, oncologists, pathologists, radiologists and nuclear medicine specialists. This is mandatory for all patients. To be able to select the correct patients for curative treatment, an elaborate diagnostic procedure is performed. This consists of endoscopy with biopsies, non-invasive imaging modalities and potentially laparoscopy. [¹⁸F]FDG-PET/CT is used for staging and preoperative evaluation of potentially curative patients. [¹⁸F]FDG-PET/CT outperforms CT alone in detecting distant metastases and has higher specificity in detection of malignant lymph nodes compared to CT in esophagus cancer. However, [¹⁸F]FDG-PET/CT has lower diagnostic sensitivity in specific histological subtypes of gastric cancer(7). This is particularly evident for the histological subtype, non-cohesive type of gastric carcinoma. The subtype present with a lower expression of GLUT-1 and a related lower FDG-uptake compared to the cohesive type of gastric carcinoma (10). The lower uptake results in a lower detectability of the subtype and ultimately, a higher risk of under staging. The subtype is according to the WHO classification of 2019 further categorized into two subtypes: Poorly cohesive carcinoma (PCC) and signet ring cell carcinoma (SRCC) (11). PCC present a poorer prognosis compared to other subtypes of gastric carcinoma with more advanced stages of disease at the time of diagnosis and a more aggressive tumor biology (12). Additionally, physiological accumulation of [¹⁸F]FDG in normal organs such as the gastrointestinal tract, liver, kidneys, urinary tract, heart and the

brain may challenge the interpretation of [^{18}F]FDG PET/CT in or near these organs(2). This is evident in evaluation of metastatic disease in gastroesophageal cancer, which metastasizes to the peritoneum. This is notoriously difficult to visualize on [^{18}F]FDG-PET/CT as well as CT and MRI(13). Thus, 20% of patients with lower esophagus and GEJ cancer may have extended disease, not detectable on non-invasive imaging, partly due to small metastasis in peritoneum. Therefore laparoscopy is mandatory before curative treatment, which has high sensitivity for peritoneal carcinomatosis(7). In 2020, 1180 new cases of pancreas cancer were diagnosed in Denmark(14). Like gastroesophageal cancer, few patients (20%) meet the criteria of curative surgery, and even after resection the 5 year survival rate is poor (15, 16). All patients are referred to MDT conference before treatment decision.

Diagnostic imaging in pancreatic cancer has proven to be challenging. The current standard imaging is a multidetector CT, which has high sensitivity in terms of evaluating the tumor stage and resectability of the tumor(17), alternatively MRI is used. However, there are limitations with standard imaging modalities in terms of initial staging, treatment evaluation after preoperative chemotherapy and target planning during radiotherapy (17-19). [^{18}F]FDG PET/CT is only used as a supplement in the initial staging of pancreas cancer, as it is mostly useful for detecting non-hepatic distant metastases. [^{18}F]FDG PET/CT has low specificity in primary diagnostics and staging, probably due to low specificity in distinguishing between inflammation due to pancreatitis and cancer (18). This lack of specificity in discriminating between inflammation and cancer is another pitfall in the clinical use of [^{18}F]FDG PET/CT, which is due to an unspecific uptake of [^{18}F]FDG in inflammatory and infectious processes(2). Analogous to gastroesophageal cancer, the unspecific uptake of [^{18}F]FDG in organs in the abdomen might also limit the use of [^{18}F]FDG-PET/CT in staging and diagnostic evaluation of pancreas cancer.

In recent years, development of tracers targeting the tumor microenvironment (TME) has shown great promise. The TME is composed of non-malignant cells and has been recognized as an important part of tumor development (20). Cancer associated fibroblasts (CAFs) are a group of hyperactive stromacells within the TME which promote tumor growth, inflammation, metastasis, angiogenesis and drug resistance (21). CAFs express a variety of targetable factors, including the transmembrane glycoprotein fibroblast activation protein (FAP). FAP is expressed in 90% of epithelial neoplasms, and the presence of FAP on CAFs is associated with tumor growth and migration (20, 22). The so-called FAPI is a specific enzyme inhibitor that binds to FAP on CAFs (23). FAPI can be combined with different radioactive components to create radioactive tracers for use in PET imaging. Especially FAPI-variants bound to gallium-68 ([^{68}Ga]Ga-FAPI) have been evaluated (22). Unlike [^{18}F]FDG, [^{68}Ga]Ga-FAPI does not reflect characteristics of the tumor and inflammatory cells (increased glucose metabolism), but the pro-carcinogenic microenvironment including CAFs.

PET/CT imaging with [^{68}Ga]Ga-FAPI variants has shown high sensitivity in diagnosing primary tumor (estimated pooled sensitivity of 1.0), as well as distant metastasis (estimated pooled sensitivity of 0.93) in different cancer types(24). This tracer is unique as it offers low uptake in most normal tissue and high uptake in many cancer types, including gastroesophageal and pancreatic cancer (25-27), thus improving tumor-to-background-ratio (TBR) compared to standard [^{18}F]FDG PET/CT. Further, imaging with FAPI has shown promising results in detecting and characterising peritoneal carcinomatosis in patients with abdominal malignancies (13). In addition to improved diagnostic capabilities across a wide range of solid tumors, imaging with FAPI offers several potential advantages for patient comfort and logistics. First, no fasting or any other preparation prior to [^{68}Ga]Ga-FAPI PET imaging is required, second preliminary studies

suggest that imaging can be performed as early as 10 min post-injection(28).

Imaging with [⁶⁸Ga]Ga-FAPI PET/CT has proven to be safe, with no tracer-related adverse events(29-32). More than 1000 patients have been scanned with this tracer without any other reporting of side effects. In addition, a recently published paper by Hirnas et al presented data on 303 patients scanned with [⁶⁸Ga]Ga-FAPI-46 (33).

The effective radiation dose of different types of FAPI-ligands bound to ⁶⁸Ga varies between 0.008-0.016 millisieverts (mSv)/megabecquerel(MBq), which is lower than the effective dose of the standard [¹⁸F]FDG, 0.020 mSv/MBq (34).

For the variant [⁶⁸Ga]Ga-FAPI-46, administration of 200 MBq will cause a total body effective radioactive dose of 1.56+/-0.26 mSv (29). Based on the experience from dosimetry and biodistribution studies and later phase II studies, the dose prescribed in this study is up to 2MBq/kg of [⁶⁸Ga]Ga-FAPI-46, with a minimum dose of 100 MBq and a maximum dose of 246 MBq (29, 35).

Within the past couple of years, PET technology has significantly improved with the introduction of total Body (TB) PET. TB PET/CT is a three-dimensional medical imaging device that can cover the entire human body at once, with dramatically increased sensitivity. Following this endeavour, Siemens developed a 106-cm-long PET/CT scanner (Biograph Vision Quadra PET/CT). This scanner only covers skull vertex to upper thighs, which is still a relevant field of view for most indications. Early experiences with this scanner have demonstrated very high sensitivity (by a factor 10-40 compared to current state of art PET/CT) and improved image quality (36, 37). In September 2021 a Biograph Vision Quadra PET/CT was installed at Rigshospitalet as one of the first centres worldwide. In addition to the improved sensitivity, it will be possible to maintain the standard quality of a PET image and reduce other factors, which influence the quality, such as reducing radiotracer dosage and imaging time (38).

The combination of [⁶⁸Ga]Ga-FAPI-46 and TB PET/CT could improve logistics and patient comfort. Current PET/CT with [¹⁸F]FDG requires patients to fast for 4-6 hours and wait for 60 mins after tracer injection before scanning. This adds to the relatively complex logistics and patient stress associated with a [¹⁸F]FDG PET/CT scan. With [⁶⁸Ga]Ga-FAPI-46 and TB PET/CT, the time a patient needs to spend at the hospital for a PET/CT scan could potentially be reduced from approx. 2 hours to 45 mins by moving from [¹⁸F]FDG-PET/CT to [⁶⁸Ga]Ga-FAPI-46 TB PET/CT.

Thus, [⁶⁸Ga]Ga-FAPI-46 TB PET/CT seems to have the potential to improve diagnostic imaging and treatment evaluation for patients with gastroesophageal cancer and pancreas cancer. Furthermore, it has the potential to improve logistics and patient comfort.

3. Trial objectives:

The aim of this study is to evaluate [⁶⁸Ga]Ga-FAPI-46 TB PET/CT as a non-invasive diagnostic tool to improve preoperative staging and treatment evaluation in patients suffering from gastroesophageal cancer and pancreatic cancer.

3.1 Study hypotheses:

- [⁶⁸Ga]Ga-FAPI-46 TB PET/CT is more sensitive to metastatic disease in the abdomen and peritoneum compared to standard imaging modalities.
- [⁶⁸Ga]Ga-FAPI-46 TB PET/CT enables functional cancer imaging of high accuracy in less than 30 min without patient preparation.

3.2 Primary objectives

- 1) Sensitivity of lesions suspicious of malignancy of [⁶⁸Ga]Ga-FAPI-46 TB PET/CT within 30 min of injection of the tracer compared with the sensitivity of current standard imaging modalities ([¹⁸F]FDG PET/CT, CT, MRI).

Sensitivity will be measured as the proportion of true positive malignant findings(39) on [⁶⁸Ga]Ga-FAPI-46 TB PET/CT within 30 mins of injection of the tracer. This will be done, by comparing the lesions suspicious of malignancy found on [⁶⁸Ga]Ga-FAPI-46 PET/CT, and standard imaging with the results from the curative surgery and/or a composed reference standard, which consist of all available imaging, 6 months follow up and blinded expert opinion (please refer to section 4.8.1).

3.3 Secondary objectives:

- 1) Sensitivity of lesions suspicious of malignancy of [⁶⁸Ga]Ga-FAPI-46 TB PET/CT after 60 min of injection of the tracer, as well as accuracy, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Sensitivity (the proportion of true positive findings), specificity (the proportion of true negative findings), PPV (the proportion of positive findings, which are true positives) and NPV (the proportion of negative findings which are true negatives)(39) will be measured by comparing the lesions suspicious of malignancy found on [⁶⁸Ga]Ga-FAPI-46 PET/CT and standard imaging with the results from the curative surgery and/or a composed reference standard, which is composed of all available imaging, 6 months follow up and blinded expert opinion (please refer to section, 4.7 and 4.8.1).

- 2) Estimated potential impact/change in patient management.

This will be measured as the proportion of patients with change in TNM-stage, correctly diagnosed by the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT that has a consequence on patient management (e.g. treatment strategy, please refer to section 4.7 and 4.8.1).

- 3) Description of FAPI-uptake from lesions suspicious of malignancy.

The uptake of [⁶⁸Ga]Ga-FAPI-46 in primary tumor and potential metastases will be quantified with standardized uptake value (SUV) measurements, such as SUV_{max}, SUV_{mean} and standard deviation (SD) (please refer to section 4.7 and 4.8.1).

3.4 Exploratory objectives:

- 1) Patients' experience of a [⁶⁸Ga]Ga-FAPI-46 TB PET/CT compared to standard imaging modalities.

This will be evaluated using a questionnaire on the patients' experience during the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT. The scores will be compared with previous studies evaluating patient experience during [¹⁸F]FDG PET/CT (please refer to section 4.8.2).

- 2) Uptake of [⁶⁸Ga]Ga-FAPI-46 from lesions suspicious of malignancy and correlation with progression free survival (PFS) after 1 year follow up).

FAPI-uptake in lesions suspicious of malignancy will be correlated with PFS after 1-year follow-up. PFS is defined as the time from the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT to progression of disease or death of any cause (please refer to section 4.8.2).

4 Methods/trial design:

4.1 Study design

This project will consist of a phase II nonrandomized prospective clinical trial evaluating [⁶⁸Ga]Ga-FAPI-46 TB PET/CT on two separate groups, group A and group B.

Group A will include patients with pancreatic cancer referred to curative treatment (surgery) with a diagnostic CT, MRI, or [¹⁸F]FDG PET/CT with no initial sign of metastatic disease to the peritoneum.

Group B will include patients with lower esophagus, GEJ, or gastric cancer (gastroesophageal cancer).

- Group B1 will include patients with no initial sign of metastatic disease on [¹⁸F]FDG PET/CT, CT, or MRI and referred to diagnostic surgery (laparoscopy) during initial staging to rule out metastatic disease in the peritoneum/mesentery.
- Group B2 will include patients with the histological subtypes SRCC or PCC at the time of diagnosis (verified with a diagnostic biopsy). Patients will be included if the MDT conference decides on either curative or palliative intended oncological treatment.

In each group we will include 30 patients with evaluable [⁶⁸Ga]Ga-FAPI-46 TB PET/CT.

For group A and B1 [⁶⁸Ga]Ga-FAPI-46 TB PET/CT will be performed before curative surgery or laparoscopy. Participants will be given a small questionnaire immediately after the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT regarding the experience. Participants will be included for one [⁶⁸Ga]Ga-FAPI-46 TB PET/CT, a questionnaire, and a follow-up period for 1 year after the project scan.

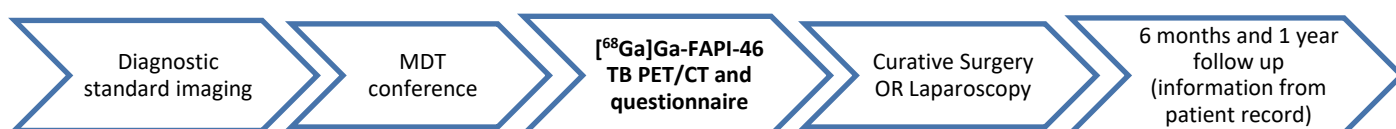
For group B2, the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT will be performed before initiation of oncological treatment. A second [⁶⁸Ga]Ga-FAPI-46 TB PET/CT scan will be performed after treatment start in close relation to the standard CT scan for routine clinical treatment evaluation. The repeated scan after chemotherapy will inform us of the different modalities/scans' ability to evaluate disease during chemotherapeutic treatment. Participants will be included for two [⁶⁸Ga]Ga-FAPI-46 TB PET/CT, a questionnaire, and a follow-up period for 1 year after the second project scan.

For details on procedure, dose, and frequency of injection of the tracer during the PET/CT scan please refer to the section 4.5. All eligible participants will receive the standard treatment and follow up care of their cancer, no matter their participation status.

Information on data management including definition of source data please refer to section 9.0.

4.2 Trial procedure:

Group A and B1:



Group B2:



4.3 Test groups

Group A: Patients with suspected pancreas cancer and at the time of referral considered candidates for curative surgery, decided by the MDT. The study will include 30 patients with evaluable [68Ga]Ga-FAPI-46 TB PET/CT.

Group B: Patients with gastroesophageal cancer (lower esophagus, GEJ, or gastric cancer).

- Group B1 patients are potential candidates for curative treatment, undergoing laparoscopy to rule out distant metastases in the peritoneum/mesenterium. The study will include 30 patients with evaluable [68Ga]Ga-FAPI-46 TB PET/CT.
- Group B2 patients present with the histological subtypes SRCC and PCC at the time of diagnosis (verified with a diagnostic biopsy). Patients will be included if the MDT conference decides on either curative or palliative intended oncological treatment. The study will include 30 patients with evaluable [68Ga]Ga-FAPI-46 TB PET/CT.

4.3.1 Inclusion criteria for group A

- 1) Male or female, ≥18 years old
- 2) Patients with suspected pancreatic cancer based on morphological findings on standard imaging
- 3) CT or MRI or [18F]FDG PET/CT evaluated on MDT with no initial sign of distant metastases
- 4) Subjects must have been considered suitable for curative surgery at the time of the referral
- 5) Subjects must be able to read and understand the patient information in Danish to give informed consent

4.3.2 Inclusion criteria for group B1

- 1) Male or female ≥ 18 years old
- 2) Histological verified carcinoma from the lower esophagus, GEJ, or stomach
- 3) Subjects must be considered operable and resectable at the time of referral for MDT
- 4) Subjects must be able to read and understand the patient information in Danish to give informed consent

4.3.3 Inclusion criteria for group B2

- 1) Male or female ≥ 18 years old
- 2) Histological verified SRCC or PCC from the lower esophagus, GEJ, or stomach
- 3) Subjects with localized disease assigned to perioperative chemotherapy or subjects with metastatic disease assigned to palliative systemic treatment.
- 4) Subjects must be able to read and understand the patient information in Danish to give informed consent

4.3.4 Exclusion criteria for group A + B

- 1) Pregnancy or lactation
- 2) Weight more than the maximum limit of a PET/CT-scanner bed (140 kg)
- 3) History of allergic reaction due to compounds similar to the chemical composition of [^{68}Ga]Ga-FAPI-46

If the patient is fertile, the patient will be asked about potential pregnancy and a urinary pregnancy test will be performed before inclusion. If the patient is postmenopausal (defined by the Danish Medical Agency as having absence of menstruation in at least 12 months before inclusion (40)) or infertile due sterilisation no pregnancy test will be performed. The result of the pregnancy test will be documented in the electronic case report form (eCRF). The reason for not performing the pregnancy test will also be documented in the eCRF.

If the patient exhibits signs of severe allergic reaction after injection of the tracer, the patient will be excluded from the study.

If the PET/CT scan reveals that the tracer has been injected subcutaneously, the patient will be excluded from the trial.

4.3.5 Withdrawal of participants and discontinuation of the trial

Patients must be withdrawn from the trial if the following occurs:

- 1) The participant withdraw his/hers consent
- 2) The participant cannot go through with the [^{68}Ga]Ga-FAPI-46 TB PET/CT

All data on participants, including excluded and withdrawn participants, will be stored for 25 years after trial finalization according to the current regulation.

Data on participants who are excluded or withdrawn before the [^{68}Ga]Ga-FAPI-46 TB PET/CT will not be used for the final diagnostic accuracy analysis. However, the data will be used to document total amount of excluded and withdrawn participants and reasons for this. Participants in group A, who have not undergone surgery, or in group B1, who are not considered suitable for diagnostic laparoscopy and potentially curative

treatment at the MDT-conference, will be used for specific secondary endpoints, but not diagnostic accuracy analyses.

All participants, including participants, who are excluded or withdrawn after the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT, will be observed during the PET/CT scan for adverse reaction and adverse events, and will be contacted 24 hours after they have undergone the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT and questioned on adverse reaction/adverse events.

The study will be terminated by the sponsor/principal investigator (PI) in case of unexpected or unacceptable side effects. However, we do not expect to end the trial prematurely due to safety, as no serious adverse reaction, or events have been reported in previous trials.

An interim analysis will be performed after 10 [⁶⁸Ga]Ga-FAPI-46 TB PET/CT scans to evaluate quality of the scans (please refer to section 6). The study will be terminated if the interim analysis show insufficient results ([⁶⁸Ga]Ga-FAPI-46 -uptake in the primary tumor in less than 5 of 10 patients).

4.3.6 Compensation for potential dropouts and excluded and withdrawn patients

Only patients with evaluable [⁶⁸Ga]Ga-FAPI-46 TB PET/CT scans are accounted for in the final sample size. Thus patients excluded or withdrawn from the study before the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT will be replaced until at total number of 30 patients with evaluable [⁶⁸Ga]Ga-FAPI-46 TB PET/CT are met.

4.4 Recruitment of Patients

The PI will delegate the recruitment of patients to a co-investigator or delegated research personnel. A written agreement between the PI and the co-investigator, or delegated research personnel, regarding these tasks will be made.

4.4.1 Group A:

Patients with suspected pancreatic cancer referred to the Dept. of Surgical Gastroenterology, Rigshospitalet will be sought enrolled. Physicians from the Dept. of Surgical Gastroenterology will screen patients. Potential candidates will be recruited by physicians, at the first planned consultation after the MDT conference, at the Department of Surgical Gastroenterology, Rigshospitalet. If the patient is interested in participation, the physician will contact the co-investigator of the study. In case the co-investigator is unavailable, this task will be delegated to other research personnel. The co-investigator or delegated research personnel will ask the physician to evaluate the participants' electronical medical record (Sundhedsplatformen, SP) for inclusion and exclusion criteria. Potential candidates will then be offered a consultation on the participation in the study. The patients will be informed of the opportunity to bring a family member, friend or an assessor to the consultation. The co-investigator or delegated research personnel will conduct this consultation, at the Dept. of Clinical Physiology and Nuclear Medicine or Dept. of Surgical Gastroenterology, Copenhagen University Hospital Rigshospitalet.

4.4.2 Group B1:

Patients with suspected gastroesophageal cancer referred for primary evaluation for operability and resectability at the Dept. of Surgical Gastroenterology, Rigshospitalet will be sought enrolled during their first consultation at the department. Information on these patients will be accessed via SP to screen for potential candidates with regard to inclusion and exclusion criteria. This is performed by a health professional from the Dept. of Surgical Gastroenterology before obtaining informed consent. The

information includes clinical data such as comorbidities, sex, age, performance status, ASA, TNM-stage, diagnostic and clinical examinations and referrals. During the primary evaluation, the physicians will recruit potential candidates. If the patient is interested in participation, the physician will contact the co-investigator of the study. In case the co-investigator is unavailable this task will be delegated to other research personnel. The co-investigator or delegated research personnel will offer the patient inclusion and obtain informed consent. This inclusion consultation will be conducted at the Dept. of Surgical Gastroenterology, Rigshospitalet or at the Dept. of Clinical Physiology and Nuclear Medicine. The patient will be informed of the opportunity to bring a family member, friend or an assessor to the consultation.

Patients with gastroesophageal cancer are often treated in a fast track leaving a very short window between MDT conference and surgery. Thus, in order to secure the patient at least 24 hours to consider participation in the study, patients will be screened and informed before the final decision on resectability and operability has been made at the MDT conference

4.4.3 Group B2:

Patients with suspected gastroesophageal cancer referred for primary evaluation for operability and resectability at the Dept. of Surgical Gastroenterology, Rigshospitalet will be sought enrolled if the patients present with the histological subtypes SRCC and PCC at the time of diagnosis (verified with a diagnostic biopsy). In addition, the patients need to be referred to the Dept. of Oncology, Rigshospitalet for curative or palliative intended oncological treatment by the MDT. The enrolment will take place at the Dept. of Surgical Gastroenterology, Rigshospitalet, when the patient is informed about the MDT decision. Information on these patients will be accessed via SP to screen for potential candidates regarding inclusion and exclusion criteria. This is performed by a health professional from the Dept. of Surgical Gastroenterology before obtaining informed consent. The information includes clinical data such as comorbidities, sex, age, performance status, ASA, TNM-stage, diagnostic and clinical examinations, and referrals. If the patient is interested in participation, the physician will contact the co-investigator of the study. In case the co-investigator is unavailable this task will be delegated to other research personnel. The co-investigator or delegated research personnel will offer the patient inclusion and obtain informed consent. This inclusion consultation will be conducted at the Dept. of Surgical Gastroenterology, Rigshospitalet or at the Dept. of Clinical Physiology and Nuclear Medicine. The patient will be informed of the opportunity to bring a family member, friend, or an assessor to the consultation.

4.5 [⁶⁸Ga]Ga-FAPI-46 TB PET/CT scan

Information on production, preparation and handling of the tracer [⁶⁸Ga]Ga-FAPI-46 is described in the investigational medicinal product dossier (IMPD). The compound is finalized for administration at the Dept. of Clinical Physiology and Nuclear Medicine, Cyclotron section and Radiochemistry, Rigshospitalet, who will comply with directions described in the IMPD.

[⁶⁸Ga]Ga-FAPI-46 is a sterile solution for intravenous injection. All incoming raw materials will be registered and tested. For each synthesis raw materials used will be documented in a dedicated batch record ensuring full traceability. The investigational medicinal product (IMP) are accounted for in the "IMP accountability log", where used IMP's as well as destructed IMP's are accounted for. Methods for quality control are validated. [⁶⁸Ga]Ga-FAPI-46 will only be released when all quality control tests are within specifications. The released product will be accompanied with a dose sheet containing information about the batch number,

the volume, the calibration time, and the available doses at different time points within the shelf-life of the product. Final release will be performed by a person qualified to do so by The Danish Medicines Agency (Qualified Person). The Dept. of Clinical Physiology and Nuclear Medicine will handle the bookkeeping regarding the use of the compound. The tracer has proven to be safe, and no adverse reactions have been reported (29-31).

When the [^{68}Ga]Ga-FAPI-46 is administered, the batch number, the injected/administered dose and the time of injection/administration will be documented on a PET administration sheet ("PET arbejdseddell"), which is correlated to each individual participant with their CPR number. This sheet will be saved, which also will secure full traceability.

Included patients in group A will, as a minimum, have undergone a diagnostic CT scan of the abdomen during the initial diagnostic examination. This has been done on the referring institution.

Included patients in group B will, as a minimum, have undergone a standard [^{18}F]FDG PET/CT for routine clinical purpose. This has been done on the referring institution or at the Department of Clinical Physiology and Nuclear Medicine at Rigshospitalet.

Within a timeframe of approximately three weeks of the standard imaging, and prior to any treatment participants will undergo a [^{68}Ga]Ga-FAPI-46 PET/CT scan at the Siemens Biograph Vision Quadra scanner, or a Siemens Biograph Vision scanner if the Quadra scanner is unavailable, at the Department of Clinical Physiology and Nuclear Medicine, PET section 3982, Rigshospitalet. No special patient preparation is needed.

Group B2 patients will undergo a second [^{68}Ga]Ga-FAPI-46 PET/CT scan after treatment start in close relation to the standard CT scan for routine clinical treatment evaluation.

Upon arrival, the participant will be placed in a bed in a relaxed prone position. The participant will be informed about the outline of the scan, and questioned about relevant conditions (allergies, potential pregnancy etc.). If the participant is female and fertile, and if the pregnancy test from the inclusion consultation is more than 48 hours old, we will perform another urinary pregnancy test. If the pregnancy test is negative, the patient can go through with the project scan. The test result will be documented on the PET administration sheet by the scanning personnel and afterwards documented in the eCRF.

A peripheral venous catheter is placed the cubital fossae for tracer injection. The participant will be injected with 1-2MBq/kg of [^{68}Ga]Ga-FAPI-46, with a minimum dose of 100 MBq and a maximum dose of 246 MBq (29, 35). The [^{68}Ga]Ga-FAPI-46 batch number, the injected dose and the time of injection will be documented on the PET administration sheet. This document will be saved and is regarded as source data (please refer to section 9.2).

The participant will then undergo a dynamic PET scan of 65 min. If the patient is unable to lie in the scanner for 65 min or if the patient has to be scanned on Biograph Vision PET/CT, two static PET scans will be performed instead. The first of the static PET scans will be conducted within 30 min of injection and the second 60 min post-injection, each scan lasting 5-10 mins. The PET scan

will cover an area from skull vertex to upper-thighs in both scenarios.

Depending on the type of standard imaging during the initial diagnostic examination, the patient will receive either a diagnostic CT scan or a low-dose CT scan. This will be performed prior to the PET scan/scans. A diagnostic CT scan will require intravenous (IV) administration of a CT contrast agent (please refer to section 4.6.2). A blood test is required with creatinine and estimated glomerular filtration rate (eGFR) measurements according to local guidelines. The blood sample will have been taken during the participant's primary evaluation of their disease. The results will be available from participant's electronic medical record (SP). If the eGFR is too low for contrast use or the blood sample test-result is more than 3 months old, the PET/CT scan will be performed without IV CT contrast administration. A second ultra-low-dose CT scan will also be performed. This is necessary for the PET attenuation correction. The ultra-low-dose CT scan will be performed at the 60 min mark for the dynamic scan or before the second static PET scan.

The radiation dose of the [⁶⁸Ga]Ga-FAPI-46 PET/CT is approximated to 5.5 mSv, when a low-dose CT scan is used, and 11.5-14.5 mSv if a diagnostic CT scan is used. The radiation dose for second ultra-low-dose CT scan is approximately 0.5 mSv. Patients will be observed during the scan by research personnel (Co-investigator or delegated research personnel). After 24 hours the patient will be contacted by co-investigator or delegated research personnel to check the patients' condition. Any adverse event will be recorded and the reporting standards stated in section 7 will be followed.

The CT contrast is an authorized medicinal product and will be used in accordance with the marketing authorization as a radiographic contrast agent for diagnostic use.

4.6 List of medicinal products:

4.6.1 Investigational medicinal products

Product name	Active ingredient	Type of medicinal product	Regulatory status	Reference Safety information (RSI)
[⁶⁸ Ga]Ga-FAPI-46	[⁶⁸ Ga]Ga-FAPI-46	A positron emission tomography (PET) radioligand for detecting Fibroblast Activation Protein (FAP)	No marketing authorization	Investigators Brochure and IMPD

4.6.2 Auxiliary medicinal products

Product name	Active ingredients	Purpose in the study	Regulatory status	Reference Safety information (RSI)
Visipaque	Iodixanol	Radiographic contrast agent for use in contrast enhanced CT imaging for PET/CT	Marketing authorization	Product resume, see appendix 1.

4.7 Interpretation of [⁶⁸Ga]Ga-FAPI-46 TB PET/CT scan

The [⁶⁸Ga]Ga-FAPI-46 TB PET/CT scans will be evaluated by a team of minimum one experienced specialist in clinical physiology and nuclear medicine and a radiologist. The team will be blinded from surgery findings and the findings on standard imaging. For group B2, the team will also be blinded for findings on the first [⁶⁸Ga]Ga-FAPI-46 TB PET/CT scan, when evaluating the second [⁶⁸Ga]Ga-FAPI-46 TB PET/CT scan. However, if the participants are scanned with a low-dose CT during the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT, the team of experts will be able to refer to the diagnostic CT from the diagnostic [¹⁸F]FDG PET/CT. In addition, they will have access to the basic information of the patient such as primary cancer diagnosis. All findings on the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT will be documented and defined as malignant or benign. The uptake of [⁶⁸Ga]Ga-FAPI-46 in primary tumor and potential metastases will be quantified (e.g. SUV_{max}, SUV_{mean}, SD). Results from the scan assessment and quantitative measurements will be documented directly in the eCRF. The [⁶⁸Ga]Ga-FAPI-46 TB PET/CT will be reviewed for conditions that requires urgent medical attention (e.g. pulmonary embolism). If any such condition is visible, the participants' primary physician will be contacted and the condition will be handled or treated by the physician according to local guidelines.

4.8 Endpoint assessment:

4.8.1 Primary and secondary objectives

Sensitivity is the proportion of true positive findings and specificity is the proportion of true negative findings. PPV is the proportion of positive findings that are true positives, and NPV is the proportion of negative findings that are true negatives (36).

Lesions suspicious of malignancy on standard imaging ([¹⁸F]FDG PET/CT, CT or MRI) and [⁶⁸Ga]Ga-FAPI-46 TB PET/CT within 30 min of injection and after 60 min of injection will be compared to the findings from the curative surgery (group A), diagnostic laparoscopy (group B1) and second scan (B2) as well as the composed reference standard (all available imaging, 6 months follow up and blinded expert opinion). The surgery will also inform the presence of any metastases in the abdomen. The second scan will inform on changes during chemotherapeutic treatment. Based on this comparison, the sensitivity, specificity, PPV and NPV and overall accuracy of both the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT and the standard imaging will be calculated.

FAPI-uptake in lesions suspicious of malignancy will be quantified (e.g. SUV_{max}, SUV_{mean} and SD).

Changes in TNM-stage and secondarily patient management after the curative surgery group A, diagnostic laparoscopy (B1) or after treatment start (B2) will be documented. An expert in oncology or gastrointestinal surgery will assess changes in patient management blindly. The conclusion from this assessment will be compared to the findings from [⁶⁸Ga]Ga-FAPI-46 TB PET/CT after 10 and 60 min. Based on this comparison, the proportion of patients with change in TNM-stage, correctly diagnosed by the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT that has a consequence on patient management (e.g. treatment strategy) will be estimated.

4.8.2 Exploratory objectives:

Patients will be given a small questionnaire immediately after the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT, to fill out by his or herself (please refer to the appendix 2). The questionnaire must be returned before the patients leave the department. The questionnaire is inspired by a questionnaire from a previous study exploring patient experiences during an [¹⁸F]FDG PET/CT(41) and with inspiration from local and national

questionnaires on patient experience during visits to radiology departments provided by the Capital Region of Denmark. The results from this questionnaire will be compared with the results from previous studies exploring patient experiences during PET/CT. The questionnaire will be regarded as source data and results from the questionnaire will be recorded in the eCRF.

FAPI-uptake in lesions suspicious of malignancy will be correlated with PFS after 1 year follow-up. PFS is defined as the time from the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT to progression of cancer disease, recurrence of cancer disease, or death of any cause.

5 Statistics:

5.1 Sample size:

A sample size was estimated based on a previous study, evaluating the sensitivity of [⁶⁸Ga]Ga-FAPI-04 PET/CT in detecting peritoneal carcinomatosis in comparison with [¹⁸F]FDG PET/CT in different types of cancer including, gastric and pancreatic cancer(13). The overall sensitivity of [⁶⁸Ga]Ga-FAPI PET/CT and [¹⁸F]FDG PET/CT was estimated to 98% and 72% respectively.

With an alpha-value of 5% and power of 80%, 35 true positives need to be included to be able to detect a similar difference in sensitivity (26%) between the two types of scans (maximum probability of disagreement)(42). The prevalence of gastroesophageal cancer patients with extended disease not detectable on standard imaging is approximated 20% of patients referred for laparoscopy (7). The same number of patients with pancreatic cancer referred for curative surgery have extended disease first recognized intraoperatively (clinical data from our institution).

To enable 35 true positives, we would need to include 175 patients. We have chosen to test the diagnostic potential of [⁶⁸Ga]Ga-FAPI-46 PET/CT using an adaptive approach of sample size calculation. First, we will include 30 patients in each group and recalculate the prevalence to find the optimal sample size for future studies (42-44). The trials could then be extended to evaluate a larger group of patients based on the recalculated sample size. The pilot data on the 30 patients will also verify the diagnostic capability of [⁶⁸Ga]Ga-FAPI-46 PET/CT before including the maximal number of subjects.

5.2 Statistical analyses:

All statistical analyses will be conducted using the programs SPSS or R.

Descriptive statistics will be performed to evaluate patient characteristics, tumor characteristics, changes in patient management, and data from the questionnaire. A paired t-test or a non-parametric paired test will be used to compare differences in uptake between [⁶⁸Ga]Ga-FAPI-46 and [¹⁸F]FDG in malignant lesions. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for detecting lesions suspicious of malignancy will be calculated for all included imaging modalities. This will be calculated by comparing the visual results with the results from the surgery and/or the composed standard reference using a 2x2 table. For comparison of sensitivity, specificity, and accuracy between the diagnostic scans, an exact McNemar Chi-square test will be used.

Association between uptake of FAPI in lesions suspicious of malignancy and correlation with PFS will be evaluated using Cox proportional Hazards model or logistic regression.

Confidence intervals will be reported. Two-tailed p-value of <0.05 will be considered significant.

If any substantial changes in the original statistical plan are made (e.g. change in sample size), this will be reported as an amendment. In the Clinical Trial Regulation, substantial amendments are named substantial modifications and a substantial modification (amendment) will be submitted via CTIS to the Danish Medicines Agency, and the National Committee on Health Research Ethics of Denmark.

Data from the included patients with an evaluable [⁶⁸Ga]Ga-FAPI-46 PET/CT scan will be used for all the statistical analyses. Data on participants who are excluded or withdrawn before the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT will not be used for the final diagnostic accuracy analysis. However, the data will be used to document total amount of excluded and withdrawn participants and reasons for this. Data on participants in group A, who have not undergone surgery, or in group B1, who are not considered suitable for diagnostic laparoscopy and potentially curative treatment at the MDT-conference, will be used for specific secondary and exploratory endpoints, but not the diagnostic accuracy analyses. Data that turns out to be incorrect or false will not be used in the final analysis. Data not used will be stored in the eCRF.

6 Interim analysis:

An interim analysis will be performed after 10 [⁶⁸Ga]Ga-FAPI-46 TB PET/CT scans to evaluate quality and usefulness of the scans. The analysis will determine if the scans have the quality to be used for interpretation and evaluation of lesions suspicious of malignancy, and if the quality of the scans allow readings of uptake-values in suspected lesions. [⁶⁸Ga]Ga-FAPI-46-uptake in the primary tumor in 5/10 patients is expected. In addition, the sponsor/PI will evaluate the safety of the study. If any unexpected serious adverse reactions or serious adverse events have occurred at that time point, the trial will be stopped. We do not expect to end the trial prematurely due to safety, as no serious adverse reaction or events have been reported in previous trials.

7 Side effects and Risks

7.1 Side effects of the tracer

[⁶⁸Ga]Ga-FAPI-46 tracer: No adverse reaction or events have been reported in the first radiation dosimetry and biodistribution studies of [⁶⁸Ga]Ga-FAPI-46 (29, 45, 46) and in later phase II studies (30, 31). More than 1000 patients have been scanned with this tracer without any other reporting of side effects. There is, however, always a risk of unexpected side effects or allergic reactions as with all other medications.

7.2 Risks during the study

Total Body PET/CT: The participants receive radiation from the radioactive component of the tracer and from the low dose CT scan or diagnostic CT scan. The radiation dose is up to 6 mSv for the [⁶⁸Ga]Ga-FAPI-46 PET/CT with the low-dose and ultra-low-dose CT scan and up to 12-15 mSv for the [⁶⁸Ga]Ga-FAPI-46 PET/CT with a diagnostic and ultra-low-dose CT scan. The [⁶⁸Ga]Ga-FAPI-46 PET/CT has a relatively low radiation dose and equivalent to 2-5 times the annual background radiation in Denmark (3mSv). For comparison, a standard [¹⁸F]FDG PET/CT with diagnostic CT is approximately 15-18.3 mSv (47). For group A and B1 undergoing one [⁶⁸Ga]Ga-FAPI-46 PET/CT scan, the accumulative radiation dose increases the life-time risk of untreatable cancer with $5\% \cdot 0.006 \text{ Sv} = 0.03\%$ for the PET/CT with low dose CT and $5\% \cdot 0.015 \text{ Sv} = 0.075\%$ for the PET/CT with a diagnostic CT compared to the rest of the population (48). The lifetime risk of dying from untreatable cancer for the general population is 25%. Thus these scans increase the lifetime

risk from 25% to 25.03% or 25.075%. For group B2 undergoing two [⁶⁸Ga]Ga-FAPI-46 PET/CT scans, the accumulative radiation dose increases the life-time risk of untreatable cancer with $5\% * 0.006 \text{ Sv} * 2 = 0.06\%$ for two PET/CT with low dose CT and $5\% * 0.015 \text{ Sv} * 2 = 0.15\%$ for two PET/CT with a diagnostic CT compared to the rest of the population (48). The lifetime risk of dying from untreatable cancer for the general population is 25%. Thus these scans increase the lifetime risk from 25% to 25.06% or 25.15%.

Light side effects may occur after administration of CT contrast, such as taste of metal and in rare cases nausea. One potential serious adverse reaction is an allergic reaction caused by the injection of CT contrast agent, which occurs rarely (<1%).

Other risks during PET/CT scans include claustrophobia and fear of needles. During the insertion of the needle, there is a minimal risk of infection and hematoma.

7.3 Safety

A qualified medical doctor will be present in the department during the [⁶⁸Ga]Ga-FAPI-46 PET/CT scans. Emergency equipment is available in accordance with current procedures of the department, including cardiopulmonary resuscitation (CPR) and oxygen supply/suction. The staff of the department are trained to handle emergencies and the applicable standard procedures will be followed in case of anaphylaxis or other allergic reactions, e.g. to the CT contrast.

In case the participants experience an adverse reaction or show signs of an adverse reaction or allergic reaction, the participant will be appointed and, if necessary, treated and followed by one or more doctors involved in the patients' treatment. If a serious adverse reaction occurs during the [⁶⁸Ga]Ga-FAPI-46 PET/CT scans, the patient will be admitted at Rigshospitalet through the Trauma Center and treated by the staff at the relevant department. If serious adverse reaction occurs after the scan outside of Rigshospitalet, the patient will be admitted to a local hospital and treated by the local staff.

7.4 Registration of side effects and events

The risk of side effects or adverse events when using [⁶⁸Ga]Ga-FAPI-46 is expected to be low based on previous studies. During the first 24 hours after administration, adverse events (AE), serious adverse events (SAE) will be reported in the eCRF and assessed as potential adverse reactions (AR). There are no expected AR or serious adverse reactions (SAR) to the administration of [⁶⁸Ga]Ga-FAPI-46.

The half-life of the radioactive probe [⁶⁸Ga] (bound to the FAPI compound) is 68 min, and it is estimated that a majority of the probe is non-measurable within 3xhalf-life. Preclinical studies have also shown that a majority of FAPI-compounds are excreted within the first 24 hours (45, 49). Therefore, it is believed that potential side effects of the tracer will be evident within the first 24 hours after administration.

The following definitions on AE, SAE, AR, SAR and suspected unexpected serious adverse reactions (SUSARS) as well as reporting standards are based on the "Detailed guidance on the collection, verification and presentation of adverse even/reaction arising from clinical trials on medicinal products for human use", stated by the European Commission.

An AE is defined as "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment". The PI is

responsible for carrying out causality assessment of AEs and will update the protocol accordingly.

An adverse reaction (AR) is defined as “all untoward and unintended responses to an investigational medicinal product related to any dose administered”.

An SAE is defined: “any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect”. SAEs must be reported within 24 hours by the investigators to the sponsor/PI with the exception of those, not requiring immediate reporting defined by the protocol.

SAR is defined as the above-mentioned AR, however with the addition of “serious” which covers the following: “... results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect”. SARs are divided into the expected and unexpected SARs, where the unexpected adverse reaction is defined as: “an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator’s brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)”(50).

As there are no expected serious adverse reactions to the administration of [⁶⁸Ga]Ga-FAPI-46, all SARs will be considered SUSARs .

SUSARS will be reported by the sponsor immediately to the regulatory authorities via EudraVigilance, as soon as possible and no longer than 15 days. If the SUSARS result in death or is life threatening, the sponsor will report the incident within seven days after being made aware of the case. Within eight days after this reporting, the sponsor needs to send all relevant information in a follow-up report. The reporting of SUSARS will be done in accordance to the current reporting practice. Any report must be accompanied by comments on any consequences for the trial. Throughout the duration of the trial, the sponsor will annually report a list of occurred suspected serious adverse reactions and a report on the subject’s safety via Clinical Trial Information System (CTIS). All ARs and AEs will be reported in the final report to CTIS within 1 year after the end of the trial.

Side effects related to the CT contrast (nausea, taste of metal, an allergic reaction caused by the injection of CT contrast agent), will not be considered an SAE. These will however be included in the annual safety report from the sponsor.

The reference safety information (RSI) that will be used to assess AR and AE will be IMPD and Investigator’s Brochure for the tracer [⁶⁸Ga]Ga-FAPI-46 and the product resume for the CT contrast agent (please refer to appendix 1, product resume section 4.3 and 4.8).

8 Collection of biological material

No biological material will be collected from the participants as a part of the trial.

9 Data Management:

9.1 Respect for participants' physical and mental integrity and right to privacy:

The Danish health law, the Danish Data Protection Act and General Data Protection Regulation (GDPR) protect all participants in this trial (51). The data will be collected and handled in accordance with Directive 95/46/EEC. The trial will be reported to The Knowledge Centre of Data Protection Compliance at the Capital Region.

According to the Data Protection Act and Law Enforcement Directive, data will be securely kept at the Dept. of Clinical Physiology and Nuclear Medicine, Rigshospitalet. The trial master file including physical project files (e.g. questionnaire and the PET administration sheet) will be securely stored at the Department of Clinical Physiology and Nuclear Medicine using a double-lock system. A list revealing the identity of each participant will be kept at the Dept. of Clinical Physiology and Nuclear Medicine, Rigshospitalet on a local computer drive. These folders have restricted access, which only can be granted from the Centre of IT and Medical Technology (CIMT, Capital region), and the owner of the locked folders, which is an investigator. The eCRF will be stored in the database REDcap. Access to data in REDcap will be restricted to specified research workers. To gain access to REDcap, research workers need to be granted access by CIMT, Capital Region. A 2-step verification log-in is required to access REDcap. The owner of the eCRF (also called the project owner) will have the responsibility to grant access to the data set. The project owner of the eCRF will be an investigator.

Fully anonymized data will be stored in 25 years after the collected data has been processed (estimated to the autumn 2027), in accordance to the current regulation. At any given time the Good Clinical Practice (GCP)-unit, the National Committee on Health Research Ethics and the Danish Medicines Agency will be able to gain access to the source data in the patient medical record for monitoring and inspection. Research workers involved in the trial will also have access to the medical records for included participants. All data will be handled confidentially.

In the case of any data security breaches, the procedures and guidelines from the Capital Region and Rigshospitalet will be followed to mitigate possible adverse effects.

9.2 Information from and interpretation of the [⁶⁸Ga]Ga-FAPI-46 PET/CT scans:

Batch number of [⁶⁸Ga]Ga-FAPI-46, injected dose and time of injection of [⁶⁸Ga]Ga-FAPI-46 and patients' height and weight will be documented on the PET administration sheet during the [⁶⁸Ga]Ga-FAPI PET/CT scan. This is a routine procedure for the scanning personnel at the Dept. of Clinical Physiology and Nuclear Medicine. This PET administration sheet will be regarded as source data and will be saved. The information will be recorded in the eCRF. Quantitative measurements from the [⁶⁸Ga]Ga-FAPI-46 PET/CT scan will be documented in the eCRF. The results from the scan assessment will also be documented directly in the eCRF.

9.3 Information and interpretation of standard imaging ([¹⁸F]FDG PET/CT, CT or MRI)

Quantitative data and description of the standard imaging procedures, which is used for treatment decision during the MDT, will be registered in the eCRF. The description will be registered in eCRF and obtained from

the electronic medical record (see section 9.4). Quantitative measurements will be derived from the scans on a standard imaging programme used for analysis of PET/CT scans. This will be documented as a screenshot and uploaded to the eCRF.

9.4 Questionnaire on the experience of the [⁶⁸Ga]Ga-FAPI-46 PET/CT scan:

The questionnaire will be regarded as source data and results from the questionnaire will be recorded in the eCRF.

9.5 Information from the clinical record:

The following information will be registered in the eCRF for each trial participant and regarded as source information from the participant's electronic medical record (SP) and utility programs connected to the electronic medical record:

Group A:

Variable	Reasons for registration
Age, gender, BMI	For publication background variables are required to verify that the participants are representative of the investigated group.
Inclusion and exclusion criteria	To be able to include/exclude participants of the trial. This data will be acquired before the patient has given written and informed consent. This data covers: comorbidities, gender, age, performance status, ASA, TNM-stage, medicines, allergies and clinical examinations, referrals, MDT conference decision.
Cancer diagnosis, classified by the TNM classification system, anatomical location, and histological type	For publication, background variables are required to verify that the participants are representative of the investigated group.
Other diseases and medication	Other known disease/malignancies may affect the interpretation of the [⁶⁸ Ga]Ga-FAPI-46 TB PET scan.
Lap tests: biochemistry, creatinine, and eGFR	Creatinine and eGFR are necessary to determine administration of IV CT contrast.
Standard imaging (CT, MRI, or [¹⁸ F]FDG PET/CT)	Date and description of the routine diagnostic examinations used for the MDT conference decision. This data is necessary to be able to compare the diagnostic sensitivity of [⁶⁸ Ga]Ga-FAPI-46 TB PET scan to routine examinations.
Findings during curative surgery including pathology, histology, and analysis of ascites fluid	Findings during surgery are part of the golden standard. This data is necessary to be able to calculate sensitivity, specificity, accuracy, NPV and PPV of imaging modalities.
Follow-up data six months, and one year after [⁶⁸ Ga]Ga-FAPI-46 TB PET : scans, clinical records, histology, blood	Follow up data are part of the golden standard. The data is necessary to be able to calculate sensitivity, specificity, accuracy, NPV and PPV of imaging modalities.

samples, and pathology samples	
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Group B1:

Variable	Reasons for registration
Age, gender, BMI	For publication, background variables are required to verify that the participants are representative of the investigated group.
Inclusion and exclusion criteria	To be able to include/exclude participants of the trial. This data will be acquired before the patient has given written and informed consent. This data covers: comorbidities, sex, age, performance status, ASA, TNM-stage, tumor pathology, medicines, allergies and clinical examinations, referrals, MDT conference decision.
Cancer diagnosis, classified by the TNM classification system, anatomical location, pathology, and histological type	For publication, background variables are required to verify that the participants are representative of the investigated group.
Other disease and medication	Other known disease/malignancies may affect the interpretation of the [⁶⁸ Ga]Ga-FAPI-46 TB PET scan.
Lap tests: biochemistry, creatinine, and eGFR	Creatinine and eGFR are necessary to determine administration of IV CT contrast.
Standard imaging (such as CT, MRI, or [¹⁸ F]FDG PET/CT)	Date and description of the routine diagnostic examinations used for the MDT conference decision. This data is necessary to be able to compare the diagnostic sensitivity of [⁶⁸ Ga]Ga-FAPI-46 TB PET scan to routine examinations.
Findings during curative surgery including pathology, histology, and analysis of ascites fluid	Findings during surgery are part of the golden standard. The data is necessary to be able to calculate sensitivity, specificity, accuracy, NPV and PPV of imaging modalities.
Follow-up data six months, and one year after [⁶⁸ Ga]Ga-FAPI-46 TB PET: scans, clinical records, histology, pathology answers, and blood samples	Follow-up data is part of the golden standard. The data is necessary to be able to calculate sensitivity, specificity, accuracy, NPV and PPV of imaging modalities.

Group B2:

Variable	Reasons for registration
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Age, gender, BMI	For publication, background variables are required to verify that the participants are representative of the investigated group.
Inclusion and exclusion criteria	To be able to include/exclude participants of the trial. This data will be acquired before the patient has given written and informed consent. This data covers: comorbidities, sex, age, performance status, ASA, TNM-stage, tumor pathology, medicines, allergies and clinical examinations, referrals, MDT conference decision.
Cancer diagnosis, classified by the TNM classification system, anatomical location, pathology, and histological type	For publication, background variables are required to verify that the participants are representative of the investigated group.
Other disease and medication	Other known disease/malignancies may affect the interpretation of the [⁶⁸ Ga]Ga-FAPI-46 TB PET scan.
Lap tests: biochemistry, creatinine, and eGFR	Creatinine and eGFR are necessary to determine administration of IV CT contrast.
Standard imaging (such as CT, MRI, or [¹⁸ F]FDG PET/CT)	Date and description of the routine diagnostic examinations used for the MDT conference decision. This data is necessary to be able to compare the diagnostic sensitivity of [⁶⁸ Ga]Ga-FAPI-46 TB PET scan to routine examinations.
Findings during perioperative surgery including pathology, histology, and analysis of ascites fluid	Findings during surgery are part of the golden standard. The data is necessary to be able to calculate sensitivity, specificity, accuracy, NPV and PPV of imaging modalities.
Course of chemotherapeutic treatment	To estimate the influence of the treatment between the scans. Changes in planned treatment, e.g. dose reduction, postponement, supportive treatment and reasoning, e.g. biochemistry, side effect.
Follow-up data six months, and one year after the second [⁶⁸ Ga]Ga-FAPI-46 TB PET: scans, clinical records, histology, pathology answers, and blood samples	Follow-up data is part of the golden standard. The data is necessary to be able to calculate sensitivity, specificity, accuracy, NPV and PPV of imaging modalities.

10 Quality control and monitoring:

The trial will be conducted in accordance with the protocol and the laws and regulations of the Danish state as well as applicable regulations from the European Commission. In addition, the trial will be conducted in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) regulations and the common principals of good clinical practice, quality assurance, and quality control.

The GCP-unit of Copenhagen University Hospital will monitor the trial. The monitoring visits will ensure that the trial is conducted according to the protocol, and to the GCP regulations.

11 Finances

The initiative of the trial was taken by Chief Physician and Professor B [REDACTED]. The study is developed in collaboration with specialist from the Department of Clinical Physiology and Nuclear Medicine, Department of Oncology and Department of Surgical Gastroenterology and Transplantation, Copenhagen University Hospital Rigshospitalet, as well as the Department of Oncology at Herlev Hospital.

The Danish Cancer Society funds this project with a donation of 2.165.000 dkk. This includes a Ph.D.-scholarship for a co-investigator (1.725.000 dkk). Expenses for the tracer [⁶⁸Ga]Ga-FAPI-46 are also covered by the same funding from the Danish Cancer Society (330.000 dkk). Salary for other research workers will be sought by external funds. Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet will cover the expenses of the TB PET/CT and salary for the sponsor/PI. Please also refer to the budget in the appendix 3.

The Danish Cancer Society has funded the Ph.D.-scholarship and expenses for the [⁶⁸Ga]Ga-FAPI-46 tracer for two clinical trials; this is one of them. The donation is transferred in defined amounts annually to the Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet, which will distribute the funding.

None of the involved in the study has any conflicts of interest. None of the involved has any economical association or other connection to the Danish Cancer Society.

There will be no economic compensation for the participants in the trial or any reimbursement for travel to and from the hospital.

12 Science and ethics

The trial will be conducted in accordance with the protocol and the laws and regulations of the Danish state as well as applicable regulations from the European Commission. In addition, the trial will be conducted in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) regulations, and the common principals of good clinical practice.

All eligible participants will receive the standard treatment and follow-up care of their cancer, no matter their participation status. The patients will not be informed of the results from the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT, and the results will not affect their individual treatment. This is clearly stated in the participant information pamphlet. Participants, who wish to gain access to the results from the trial, are allowed to do so, when the trial is finished.

The potential risks of the trial are believed to be low. The increased radiation burden is approximately 2-5 times of the annual background radiation in Denmark (3mSv), for [⁶⁸Ga]Ga-FAPI-46 TB PET with low dose CT respectively [⁶⁸Ga]Ga-FAPI-46 TB PET with contrast enhanced CT. The increase in life-time risk of untreatable cancer will be 0.03-0.075% for group A and B1, and 0.006-0.15% for group B2 compared to the rest of the population. Based on previous experience with the tracer [⁶⁸Ga]Ga-FAPI-46 the risk of experiencing side effects is low.

The combination of the tracer [⁶⁸Ga]Ga-FAPI-46 and TB PET/CT is believed to improve diagnostic imaging and staging for patients with pancreatic cancer and gastroesophageal cancer, which will improve the initial treatment decision and management of the patients. We believe that these potential benefits outweigh the potential risk of the trial.

12.1 Guidelines for participants' information and written consent

For the inclusion consultation, the participant will be informed of the opportunity to bring a family member, friend or an assessor. The PI will delegate the recruitment of patients to a co-investigator or other research personnel, who will conduct the consultation and obtain informed consent, at the Department of Clinical Physiology and Nuclear Medicine or Department of Surgical Gastroenterology, Copenhagen University Hospital, Rigshospitalet in a quiet and secluded room. A sign on the door will secure that the conversation will proceed uninterrupted.

It is mandatory for the co-investigator and delegated research personnel to be medical doctors and have relevant research experience or experience with the participant population. They also need to have undergone a GCP-course either an e-learning course or a physical course. A written agreement between the PI and the co-investigator/delegated research personnel, regarding these tasks, will be made.

Potential participants will be given verbal and written information on the trial. The guidelines from National Committee on Health Research Ethics on how to perform the consultation will be followed.

The verbal information will be given comprehensively and in common Danish, which will be adapted to the individual participant's needs. The information will explain the objectives of the trial, procedures, the potential risks and side effects of the tracer [⁶⁸Ga]Ga-FAPI-46. It will be clearly stated that risk of side effects are assumptions based on previous studies and that the risk of unexpected side effects is present. The written information, which includes the written consent and participant's information pamphlet, will also be presented to the participants.

Participant will be encouraged to contact the PI with any questions on the study. The contact information will be provided in the written participant information pamphlet.

After the consultation, participants will be offered 24 hours to consider the offer of inclusion in the trial before signing the consent statement.

The participation is voluntary, and the participant can withdraw their consent at any time point. The consent statement will include the dated signature of the participant and the person who has given the study information. A copy of the consent statement will be offered to the participant as well as the participant information pamphlet, and a leaflet from the National Committee on Health Research Ethics: "The rights of a trial subject in a biomedical research project" ("Dine rettigheder som forsøgsperson i forsøg med medicin").

For more details on recruitment of potential participants please refer to section 4.4.

12.2 Written consent

All participants must sign a written consent form to be able to participate in the trial.

The participants must allow that anonymous scan-pictures can be used for publicly available publications, teaching purposes, and external evaluation. This will be clearly stated in the written consent form.

The participant must also allow researchers involved in the trial (sponsor/PI, co-investigators, and delegated research personnel) to obtain information from his/her medical record necessary to conduct the research. Participants must also allow representatives from the Danish Medical Agency, the GCP-unit of Copenhagen University Hospital and the National Committee on Health Research Ethics to examine his/her medical record for quality assessment, quality control, and security of the trial. All information will be handled confidentially.

The investigators or delegated research personnel are responsible for obtaining the written consent from the participant, before the participant undergo any trial-related procedures.

For more details on data management and information on collected data from the medical record before and after written consent, please refer to section 4.4 and 9.5.

13 Publication of results

The trial will be registered at clinicaltrials.gov as well as CTIS. During the publications process, the Vancouver Recommendations will be followed. The results will be published on CTIS and in international English-speaking peer reviewed journals as open access. All results will be published including positive, negative, and inconclusive findings. As stated in the participant information, anonymized scan-pictures can be used in both papers and presentations. The order of authors on the primary publications will be a co-investigator as first author and last author will be Barbara Malene Fischer. Both preliminary and final results will potentially be presented at relevant international conferences.

14 Insurance

The trial will be conducted at Rigshospitalet and the sponsor/PI is an employed/will be employed by Rigshospitalet and the Capital Region. Thus, participants in the study are legally regarded as patients, and will be covered by the normal insurance of patients hospitalized at Rigshospitalet as well as the normal insurance for patients stated by the Danish Law (Den offentlige patienterstatningsordning).

15 Timeframe of the trial

The inclusion of patients is expected to start in the autumn/winter of 2023/2024, and inclusion period is expected to last for 2 years for the trial. All patients have a follow-up period of 1 year. The trial will end 1 year after the last participant has completed their [⁶⁸Ga]Ga-FAPI-46 TB PET/CT. Data will be stored for 25 years when the collected data has been processed.

16 Protocol Synopsis

BEFAST STUDY: [⁶⁸Ga]Ga-FAPI-46 total body PET/CT for Better and Faster imaging in cancer

Protocol:[⁶⁸Ga]Ga-FAPI-46 total body PET/CT for improving diagnostic sensitivity and preoperative staging in gastroesophageal cancer and pancreatic cancer

EU trial number:

2023-503632-41-01

Rationale of the study:

[¹⁸F]FDG PET/CT plays a key role in diagnostic cancer imaging. However, the modality lacks diagnostic accuracy in abdominal malignancies, more precisely gastroesophageal cancer and pancreatic cancer. This is primarily due to physiological accumulation of the tracer [¹⁸F]FDG in normal organs near these cancer sites, which makes the interpretation of the scans challenging. [⁶⁸Ga]Ga-FAPI-46 is a promising new PET tracer that targets the microenvironment near malignant tumors. Preliminary studies on [⁶⁸Ga]Ga-FAPI PET has shown promising results in detecting primary tumor and distant metastases especially in abdominal malignancies. In addition to improved diagnostic capabilities, imaging with FAPI offers several potential advantages for patient comfort and logistics. First, no fasting or any other preparation prior to [⁶⁸Ga]Ga-FAPI PET imaging is required, second preliminary studies suggest that imaging can be performed as early as 10 min after injection of the tracer.

Quality of PET scanners have dramatically improved with the introduction of Total Body (TB) PET. Siemens have developed a type of TB PET/CT called the Biograph Vision Quadra, which covers skull vertex to upper thighs. Early experiences with this scanner have demonstrated very high sensitivity (by a factor 10-40 compared to current state of art PET/CT) and improved image quality. This improved sensitivity enables a reduction in imaging time, while maintaining image quality. Thus, the combination of [⁶⁸Ga]Ga-FAPI-46 and TB PET/CT has the potential to improve diagnostic imaging and treatment evaluation for patients with pancreatic cancer and gastroesophageal cancer. Furthermore, it has the potential to improve logistics and patient comfort.

Study hypotheses:

- [⁶⁸Ga]Ga-FAPI-46 TB PET/CT is more sensitive to metastatic disease in the abdomen and peritoneum compared to standard imaging modalities ([¹⁸F]FDG PET/CT, CT, and MRI).
- [⁶⁸Ga]Ga-FAPI-46 TB PET/CT enables functional cancer imaging of high accuracy in less than 30 min without patient preparation.

Objectives and endpoints:

The aim of this study is to evaluate [⁶⁸Ga]Ga-FAPI-46 TB PET/CT as a non-invasive diagnostic tool to improve preoperative staging and treatment evaluation in patients suffering from gastroesophageal cancer and pancreatic cancer.

The primary endpoint will be sensitivity for lesions suspicious of malignancy on [⁶⁸Ga]Ga-FAPI-46 PET within 30 min of injection of the tracer. This will be compared with the sensitivity of standard imaging.

The findings from the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT and standard imaging procedures will be compared to

findings during surgery or a second [⁶⁸Ga]Ga-FAPI-46 TB PET/CT. The surgery will inform the presence of any metastasis in the abdomen. The second will inform on changes during chemotherapeutic treatment. These findings will be supplemented with a composed reference standard including all available imaging, 6 months follow-up and blinded expert opinion. Secondary endpoints will be sensitivity of [⁶⁸Ga]Ga-FAPI-46 PET/CT after 60 mins as well as specificity, positive predictive value, negative predictive value, and accuracy of all three imaging modalities. The potential impact/change in patient management will also be estimated. The exploratory endpoints will be the patient experience after the [⁶⁸Ga]Ga-FAPI-46 TB PET/CT scan, which will be evaluated using a questionnaire. In addition, FAPI-uptake in lesions suspicious of malignancy will be correlated to progression free survival after 1 year.

Trial Design and trial population

The project will investigate the above-mentioned hypotheses by performing a non-randomised phase II clinical trial evaluating [⁶⁸Ga]Ga-FAPI-46 TB PET/CT in two different groups of patients: group A and group B.

Group A will include 30 patients with pancreatic cancer referred to curative treatment (surgery) with a diagnostic CT, MRI or [¹⁸F]FDG PET/CT with no initial sign of metastatic disease to the peritoneum.

Group B1 will include 30 patients with gastroesophageal cancer referred to diagnostic surgery (laparoscopy) during initial staging to rule out metastatic disease in the peritoneum/mesentery after no signs of distant metastases on routine [¹⁸F]FDG PET/CT, MRI, or CT.

Group B2 will include patients with the histological subtypes SRCC or PCC at the time of diagnosis (verified with a diagnostic biopsy). Patients will be included if the MDT conference decides on either curative or palliative intended oncological treatment.

Participants will undergo one [⁶⁸Ga]Ga-FAPI-46 TB PET/CT before curative treatment (Group A), before laparoscopy (Group B2) or before oncological treatment (Group B). Participants in group B2 will undergo a second [⁶⁸Ga]Ga-FAPI-46 TB PET/CT during chemotherapeutic treatment. All participants will fill out one questionnaire and have a follow-up period of 1 year.

Intervention

The [⁶⁸Ga]Ga-FAPI-46 PET/CT scans will be performed at the Siemens Biograph Vision Quadra or a Siemens Biograph Vision scanner if the Quadra scanner is unavailable. No special patient preparation is needed. However, if the participant is female and fertile, and if the pregnancy test from the inclusion consultation is more than 48 hours old, we will perform another urinary pregnancy test. This will be done to rule out pregnancy before injection of the tracer. The participant will be injected with 1-2MBq/kg of [⁶⁸Ga]Ga-FAPI-46, with a minimum dose of 100 MBq and a maximum dose of 246 MBq. The participant will then undergo a dynamic PET scan of 65 min or two static PET scans if the participant is unable to lie in the scanner for 65 min or if the patient has to be scanned on Biograph Vision PET/CT. The first of the static PET scans will be conducted within 30 min of injection and the second 60 min post-injection, each scan lasting 5-10 mins. The PET scan will cover an area from skull vertex to upper-thighs in both scenarios. The patient will also undergo a diagnostic CT scan or a low-dose CT scan, which will be performed prior to the PET scan/scans. A diagnostic CT scan will require intravenous (IV) administration of a CT contrast agent. A second ultra-low-dose CT scan will also be performed. This is necessary for the PET attenuation correction. The ultra-low-

dose CT scan will be performed at the 60 min mark for the dynamic scan or before the second static PET scan.

Safety and risks

No adverse reaction or events have been reported after injection with [⁶⁸Ga]Ga-FAPI-46 in previous studies. More than 1000 patients have been scanned with this tracer without any other reporting of side effects. In addition, Hirmas et al. recently published a paper in which they present data on 303 patients scanned with [⁶⁸Ga]Ga-FAPI-46 (33). More information on the tracer [⁶⁸Ga]Ga-FAPI-46 is found in the Investigational Medicinal Product Dossier (IMPD) and in the Investigator's Brochure attached in the application.

The potential risks of the trial are believed to be low. The increased radiation burden is up to 6 and 12-15 mSv for [⁶⁸Ga]Ga-FAPI-46 TB PET with low-dose CT respectively [⁶⁸Ga]Ga-FAPI-46 TB PET with contrast enhanced CT, which is 2-5 times the annual background radiation in Denmark (3mSv). The increase in life-time risk of untreatable cancer will be 0.03-0.075% for group A and B1, and 0.006-0.15% for group B2 compared to the rest of the population.

Ethics and data protection

The trial will be conducted in accordance the Danish and European laws and regulations on clinical trials, as well as ICH-GCP regulations and the common principals of good clinical practice. The Danish health law, the Danish Data Protection Act and General Data Protection Regulation (GDPR) protect all participants in this trial (43). The trial will be reported to The Knowledge Centre of Data Protection Compliance at the Capital Region. All eligible participants will receive the standard treatment and follow-up care of their cancer, no matter their participation status.

Combination of the tracer [⁶⁸Ga]Ga-FAPI-46 and TB PET/CT is believed to improve diagnostic imaging and staging for patients with pancreatic cancer and gastroesophageal cancer, which will improve the initial treatment decision and management of the patients. We believe that these potential benefits outweigh the potential risk of the trial.

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https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=population&mode_population=countries&population=900&populations=900&key=total&sex=0&cancer=13&type=0&statistic=5&prevalence=0&population_group=15&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmssc=1&include_nmssc_other=1&population_group_list=208,233,246,352,372,428,440,578,752,826&half_pie=0&donut=0&population_group_globe_id=924.

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18 Appendix

Appendix 2: Questionnaire

Patient experience during [⁶⁸Ga]Ga-FAPI-46 Total Body PET/CT

Title:

Din oplevelse af projektskanningen [⁶⁸Ga]Ga-FAPI-46 helkrops PET/CT

(Your experience of the project examination [⁶⁸Ga]Ga-FAPI-46 Total Body PET/CT)

Spørgsmål (Question)	Svar - OBS sæt kun ét kryds (Answers - only choose one of the following statements)
1. Vidste du på forhånd hvad en PET/CT scanning var? (Did you know what a PET/CT scan was, before the examination?)	<input type="checkbox"/> I høj grad (very much) <input type="checkbox"/> I nogen grad (Quite a lot) <input type="checkbox"/> I mindre grad (Some) <input type="checkbox"/> Slet ikke (Not at all)
2. Vidste du på forhånd hvordan helkrops [⁶⁸ Ga]Ga-FAPI-46 PET/CT undersøgelsen blev udført? (Did you know how the [⁶⁸ Ga]Ga-FAPI-46 TB PET/CT examination was conducted before the procedure?)	<input type="checkbox"/> I høj grad (very much) <input type="checkbox"/> I nogen grad (Quite a lot) <input type="checkbox"/> I mindre grad (Some) <input type="checkbox"/> Slet ikke (Not at all)
3. Følte du dig tryk under undersøgelsen? (Did you feel safe during the examination?)	<input type="checkbox"/> I høj grad (very much) <input type="checkbox"/> I nogen grad (Quite a lot) <input type="checkbox"/> I mindre grad (Some) <input type="checkbox"/> Slet ikke (Not at all)
4. Følte du dig fanget under undersøgelsen? (Did you feel trapped during the examination?)	<input type="checkbox"/> I høj grad (very much) <input type="checkbox"/> I nogen grad (Quite a lot) <input type="checkbox"/> I mindre grad (Some) <input type="checkbox"/> Slet ikke (Not at all)
5. Oplevede du at undersøgelsen var udmattende? (Did you feel the examination was exhausting?)	<input type="checkbox"/> I høj grad (very much) <input type="checkbox"/> I nogen grad (Quite a lot) <input type="checkbox"/> I mindre grad (Some) <input type="checkbox"/> Slet ikke (Not at all)
6. I hvor høj grad, levede undersøgelsen op til dine forventninger? (Did the examination live up to your expectations?)	<input type="checkbox"/> I høj grad (very much) <input type="checkbox"/> I nogen grad (Quite a lot) <input type="checkbox"/> I mindre grad (Some) <input type="checkbox"/> Slet ikke (Not at all)

Underskrift (Signature)_____

Dato (Date)_____

Appendix 3: Budget

Expenses	dkk	Duration	Total expenses:	Covered by the department*:	Covered by Danish Cancer Society	Covered by other funds	Balance	Sought covered by other funds
Salary								
PhD-scholarship	575 000 dkk/year	3 years (2023-2026)	1 725 000 dkk		1 725 000 dkk			
Running Costs:								
Ph.D.-tuition fee	50 000 dkk/year	3 years (2023-2026)	150 000 dkk			150 000 dkk		
Expenses to total body PET/CT:	9500 dkk/scan	60 scans, 2 years (2023-2024)	570 000 dkk	570 000 dkk				
Tracer expenses ([⁶⁸ Ga]Ga-FAPI-46):	5500 dkk/scan	60 scans, 2 years (2023-2024)	330 000 dkk		330 000 dkk			
Publications expenses	25 000/year	2 years (2024-2025)	50 000 dkk	50 000 dkk				
Travel expenses								
Transportation	12 500 dkk/year	2 years (2024-2025)	25 000 dkk				25 000 dkk	25 000 dkk
Accommodation	12 500 dkk/year	2 years (2024-2025)	25 000 dkk				25 000 dkk	25 000 dkk
Other								
Scholarship for a medical student	10 000 dkk/month	2x 6 months (2023-2025)	120 000 dkk				120 000 dkk	120 000 dkk
Total:			2 995 000 dkk	620 000 dkk	2 055 000 dkk	150 000 dkk	170 000 dkk	170 000 dkk

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