—Rapid Communication—

Changes in tumor vascularity depicted by contrast-enhanced EUS as a predictor of prognosis and treatment efficacy in patients with unresectable pancreatic cancer (PEACE): A study protocol

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ABSTRACT

Patients with unresectable pancreatic cancer have a poor prognosis. The analysis of prognostic factors before treatment may be helpful in determining the best therapeutic strategies. The aim of the PEACE study is to assess the vascularity of pancreatic malignant tumors using contrast-enhanced harmonic EUS (CEH-EUS) and to clarify the prognostic value of tumor vascularity in patients with locally advanced and metastatic pancreatic cancer. Hereby, we present the protocol of a prospective, nonrandomized, single-arm, multicenter study aiming to assess changes in tumor vascularity using CEH-EUS before and 2 months after treatment initiation in patients with unresectable, locally advanced/metastatic pancreatic cancer and to examine the correlation between vascular changes and treatment response, progression-free survival, and overall survival.

Key words: Contrast-enhanced endoscopic, endoscopic ultrasound, pancreatic cancer, prognosis, ultrasound

INTRODUCTION

Pancreatic cancer is one of the most lethal and therapeutically resistant malignancies, with a grim prognosis that is attributed to the late clinical presentation and the relative chemoresistance of the disease.[1] At the time of diagnosis, over 80% of patients present with locally advanced or metastatic disease and are, therefore, not suitable for curative resection.[2] There is currently no uniform consensus regarding standard of care for the treatment of unresectable, locally advanced/metastatic pancreatic cancer. Treatment options include chemotherapy alone or induction chemotherapy followed by chemoradiotherapy or stereotactic body radiation therapy (SBRT).[3] However, even with identical therapy regimens, some patients experience improvements in survival and tumor response, whereas other patients only experience inconvenience and increased toxicity. It has been suggested that the burden of treatment should not be added to the suffering of those with advanced pancreatic cancer. Therefore, understanding prognostic factors before treating patients may be helpful in selecting those predicted to have an improved survival and tumor response after treatment.

Studies have shown that angiogenesis is an important factor that influences the prognostic of solid tumors.[4-6] Contrast-enhanced (CE) imaging methods can offer detailed information on tumor vascularity. Changes in tumor vascularity under CE ultrasonography (CE-US) were employed for evaluating the effectiveness of chemotherapy. Sofuni *et al.*[7] used CE-US in patients with unresectable pancreatic cancer treated by chemotherapy. They found that patients with abundant intratumoral blood flow had a significantly better response to treatment, and changes in intratumoral blood flow after treatment were related to prognosis ($P = 0.006$). On the other hand, Masaki *et al.*[8] assessed tumor vascularity of pancreatic cancer using CE-US before systemic chemotherapy. They revealed that the median survival was longer in patients who had avascular tumors compared with patients who had vascular tumors.

Contrast-enhanced EUS (CE-EUS) is a new method which allows detailed characterization of focal pancreatic masses.[9] CE-EUS offers high-resolution images of the pancreas that far surpass those achieved by computed tomography (CT), US, or magnetic resonance imaging. CE-EUS can detect intratumoral vessels in the pancreatic lesions.[10] Dedicated contrast-enhanced harmonic EUS (CEH-EUS) technique, based on a low mechanical index, is available in new EUS systems. It allows high-resolution continuous real-time assessment of the microvascularization during the contrast uptake period (real-time perfusion imaging).[11,12] Several research groups already reported the feasibility of CEH-EUS with low mechanical index.[13,14] Quantitative analysis of tumor vascularity can be performed using time-intensity curve (TIC) analysis-derived parameters, obtained from processing CEH-EUS recordings with a commercially available software. TIC analysis is increasingly being recognized as a standardized quantification tool for perfusion characteristics of intra-abdominal tumors.[15] Rapid processing of CEH-EUS recordings allows trained physicians to objectively analyze otherwise qualitative data provided by contrast enhancement techniques.[16,17] Yamashita *et al.*[10] performed CE-EUS on 39 patients with unresectable pancreatic cancer who were scheduled to undergo chemotherapy. They showed that both progression-free survival and overall survival were significantly longer in patients with intratumoral large vessels ($P = 0.037$ and $P = 0.027$, respectively) and that a positive vessel sign was an independent factor associated with longer survival. However, whether low vascular tumors correlate with the chemoresistance and poor prognosis is still unclear.

RATIONALE AND OBJECTIVES

Patients with unresectable pancreatic cancer have an especially poor prognosis and many severe symptoms. The analysis of prognostic factors before treatment may be helpful in selecting appropriate candidates for chemotherapy and in determining treatment strategies. For example, patients who have a poor prognosis may be treated best with only supportive care because of their short survival. Consequently, the main aim of the PEACE study is to assess the vascularity of pancreatic malignant tumors with CEH-EUS and to clarify the prognostic value of tumor vascularity in patients with advanced pancreatic cancer.

Our hypothesis is that tumors with intratumoral vessels have a better prognosis and are chemosensitive. In an orthotopic model of pancreatic cancer, AsPC-1 cells were less sensitive to gemcitabine when cultured under hypoxic conditions compared with cells treated under normoxic conditions.[18] Therefore, it is possible that hypoxic condition in tumor tissue leads to chemoresistance and poor prognosis in patients with pancreatic carcinoma who received systemic chemotherapy.[19]

Moreover, studies have shown that angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumor blood vessels. Chauhan *et al.*[15] demonstrated that the angiotensin inhibitor losartan reduces stromal collagen and hyaluronan production. Consequently, losartan reduces solid stress in tumors resulting in increased vascular perfusion. Through this physical mechanism, it can improve drug and oxygen delivery to tumors, thereby potentiating chemotherapy and reducing hypoxia in breast and pancreatic cancer models. Accordingly, another aim of our study is to examine the correlation between tumor vascularity and angiotensin inhibitors use in patients using these drugs to control arterial hypertension.

The objectives of the PEACE trial are summarized in Table 1.

STUDY DESIGN

This is a prospective, nonrandomized, single-arm, interventional, multicenter study aiming to assess the changes in tumor vascularity using CEH-EUS before and 2 months after treatment initiation in patients with unresectable, locally advanced/metastatic pancreatic cancer and to examine the correlation between vascular changes and treatment response, progression-free survival, and overall survival [Figure 1].

All patients with a suspicion of pancreatic masses will undergo EUS, including EUS-FNA for confirmation of
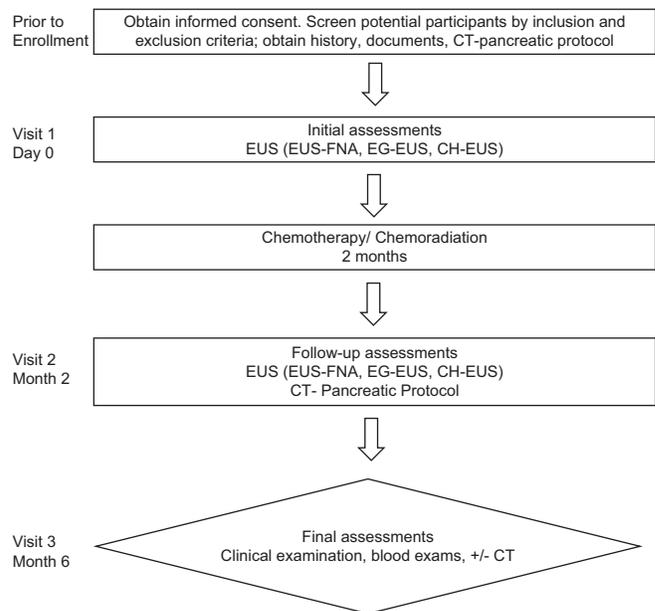

Figure 1: Study design

Table 1. PEACE trial objectives

Primary objective	Secondary objectives
To determine the correlation between CEH-EUS parameters before and after treatment and tumor response. Tumor response will be assessed by contrast-enhanced computed tomography, according to the RECIST	To register CEH-EUS parameters before and after chemotherapy and to describe tumor changes in vascularity after treatment To determine the correlation between CEH-EUS parameters before treatment and overall survival and progression-free survival To determine the correlation between changes in tumor vascularity and PFS and OS To assess quantitative elastography parameters during EUS, before, and after systemic treatment and determine their correlation with overall survival and progression-free survival To examine the correlation between tumor vascularity and angiotensin inhibitors use To compare genomic changes based on whole-exome sequencing and transcriptome sequencing from pre- and post-treatment FNA samples

TIC: Time-intensity curve, CEH-EUS: Contrast-enhanced harmonic EUS, PFS: Progression-free survival, OS: Overall survival, RECIST: Response evaluation criteria in solid tumors, FNA: Fine needle aspiration

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 18-90-year-old men or women	Previous chemotherapy or radiotherapy
Signed informed consent for CH-EUS, EH-EUS, and FNA	Resectable pancreatic tumors
The diagnosis of pancreatic cancer histologically confirmed by FNA/clinical follow-up	
Unresectable, locally advanced, and/or metastatic disease	
Both pancreatic adenocarcinomas and pancreatic neuroendocrine tumors were included	

CH-EUS: Contrast-enhanced EUS

diagnosis, with sequential elastography (EG)-EUS and CEH-EUS. Inclusion and exclusion criteria are listed in Table 2. A positive cytological diagnosis will be taken as a final proof of malignancy of the pancreas mass. The diagnoses obtained by EUS-FNA will be further verified during a clinical follow-up of at least 6 months. Contrast enhanced CT will be performed as pretreatment staging study to assess the diagnosis of pancreatic cancer, local extension of the tumor, and presence of distant and lymph node metastasis. Patients who have received previous chemotherapy or radiotherapy will be excluded from the analysis.

Patients with a confirmed diagnosis of pancreatic cancer (both adenocarcinomas and neuroendocrine tumors were included) will undergo systemic treatment. Selection of the specific treatment regimen will be according to the individual physicians' choice.

Two months after the first course of treatment, CT and EUS (with sequential EG-EUS, CEH-EUS, and EUS-FNA) will be repeated. CT will be performed to evaluate the tumor response. Tumor response will be assessed according to the response evaluation criteria in solid tumors (RECIST).

The patients will be followed up for at least 6 months through clinical examination, biological examinations, and transabdominal ultrasound, eventually with a repeat spiral CT/EUS after 6 months.

METHODS

All patients with a suspicion of pancreatic masses will undergo EUS and CT before and 2 months after the first course of chemotherapy.

EUS and EUS-FNA
Protocol of EUS with EUS-FNA will include linear

EUS instruments with complete examinations of the pancreas. Tumor characteristics (echogenicity, echostructure, and size) will be described as well as the presence/absence of power Doppler signals. EUS-FNA will be performed in all pancreatic masses with at least four passes in the absence of an on-site cytopathologist.

Contrast–enhanced–harmonic EUS procedure
A two-panel image with the usual conventional gray scale B-mode EUS image on the right side and with the contrast harmonic image on the left side will be used, according to the preestablished presets. The starting point of the timer will be considered the moment of intravenous contrast injection (Sonovue 4.8 mL).

CEH-EUS will be performed during usual EUS examinations, with the whole movie (T0-T120s) recorded in a DICOM format on the embedded HDD of the ultrasound system, for later analysis.

A low mechanical index procedure (dynamic wideband contrast harmonic imaging mode) will be used, with a mechanical index of 0.2 and corresponding powers. The following presettings will be used in all centers: contrast mode dCHI-W, WPI-R/P (resolution/penetration for superficial *vs.* deep structures), mechanical index (preferred MI of 0.2 for Pentax-Hitachi and 0.3 for Olympus-Aloka), MI gray scale (0.03), gray map 4, AGC 0, R-filter C, persistence 2, dynamic range 50, B-color 21, smoothing 3, and gamma curve linear.

The contrast agents used for CEH-EUS is Sonovue®, which consists of phospholipids stabilized bubbles of sulfur hexafluoride (SF6).[16] Sonovue® is isotonic, stable, and resistant to pressure, with a viscosity similar to blood. It does not diffuse into the extravascular compartment remaining within the blood vessels until the gas dissolves and is eliminated in the expired air (blood pool contrast agent).[17] The safety profile of Sonovue® showed a very low incidence of side effects; it is not nephrotoxic and the incidence of severe hypersensitivity is similar to other magnetic resonance imaging contrast agents. Sonovue® is approved for clinical use in the European Union countries. The blood supply of the pancreas is entirely arterial, making CH examinations feasible and readily available. Based on the European Federation Societies of Ultrasound in Medicine and Biology Guidelines and Recommendations, updated in 2008, two phases were defined for CE-US and CE-EUS of the pancreas: an

early/arterial phase (starting from 10 to 30 s) and a venous/late phase (from 30 to 120 s).[20]

To minimize human bias, the processing and computer analysis of the digital movies will be performed within the coordinating IT center, with all programmers and statisticians being blinded to the clinical, imaging, and pathological data. Offline analysis of TICs will be performed using Vue-Box, which yields the following quantitative parameters: peak enhancement, wash-in area under the curve (Wi-AUC), rise time, mean transit time (mTT), time to peak (TTP), wash-in rate (WiR), and wash-in perfusion index (WiPI). The software also provides referenced values (expressed in percentages), aligning the set of values for the tumors' regions of interest (ROI) to the parenchymal ones.

EG-EUS procedure

EG-EUS will be performed during usual EUS examinations, before, and 2 months after the first course of treatment, with two movies of 10 s recorded on the embedded HDD to minimize variability and to increase repeatability of acquisition.

A two-panel image with the usual conventional gray scale B-mode EUS image on the right side and with the EG image on the left side will be used. The ROI for EUS-EG is preferably larger than the focal mass (approximately 50%–50%), to include the surrounding structures. If the focal mass is larger than 3 cm, part of the mass will be included in the ROI, as well as the surrounding structures (preferably avoiding large vessels). Very large ROI for the EG calculations will be avoided due to the appearance of side artifacts.

The following presettings will be used in all centers: EG color map 1, frame rejection 2, noise rejection 2, persistence 3, dynamic rage 4, smoothing 2, and blend 50%.

Strain ratio (SR) and strain histogram will be measured, with three measurements made and recorded on the embedded HDD. For SR, the reference area should be placed at the same level with the lesion, if possible.

Contrast–enhanced CT

Contrast-enhanced CT will be obtained before treatment to assess the local extension of the tumor, the presence of lymph nodes, and distant metastases.

A template will be used to report the imaging results [Appendix 1]. It includes morphologic, arterial, venous, and extrapancreatic evaluations. The morphologic evaluation includes the documentation of tumor appearance, size, and location, as well as the presence of narrowing or abrupt cutoff of pancreatic duct or biliary tree. The arterial evaluation includes the assessment of the celiac axis, the superior mesenteric artery, and the common hepatic artery. Arterial variations should be noted, such as vessel contact, solid tissue contact, hazy attenuation or stranding contact, and focal vessel narrowing or contour irregularity. Venous evaluation includes the assessment of the portal vein and the superior mesenteric vein. Documentation of thrombus within the vein and venous collaterals should also be done. The extrapancreatic evaluation includes the documentation of liver lesions, peritoneal or omental nodules, ascites, suspicious lymph nodes, and other present extrapancreatic disease sites.

Contrast enhanced CT will be performed 2 months after the first course of treatment, using the same template, to evaluate the tumor response. Tumor response will be assessed according to the RECISTs. Based on RECIST guidelines, complete response (CR) is defined as the complete disappearance of the tumor, partial response (PR) is defined as ≥30% decrease in the longest diameter (LD), progressive disease (PD) is defined as ≥20% increase in LD, and stable disease (SD) is defined as a decrease or increase less than PR or PD based on the anatomic assessment. Patients with CR or PR are defined as responders, whereas those with PD or SD are defined as nonresponders.[21]

Treatment

Depending on the performance status, monosystemic or combination systemic chemotherapy may be considered as initial therapy for patients with unresectable, locally advanced/metastatic pancreatic adenocarcinoma. If patients present with poorly controlled pain or local invasion with bleeding, starting with upfront chemoradiation therapy or SBRT can be an option. Selection of treatment will be according to the individual physicians' choice. It will be continued until disease progression or unacceptable toxicity.

Moreover, the selection of the systemic treatment for unresectable and/or metastatic neuroendocrine tumors of the pancreas will also be according to the individual physicians' choice.

Data collection

For each patient, the following information will be recorded and uploaded to http://oncobase.umfcv.ro/: age, gender, primary tumor location, primary tumor size, tumor status (metastatic or locally advanced), site of metastasis, serum carcinoembryonic antigen level, serum carbohydrate antigen 19-9 level, prior biliary drainage (presence or absence), antitumoral agent (chemotherapy regimen), angiotensin inhibitors use (drug, dose), parameters of the pancreatic cancer CT reporting template, EUS, CH-EUS, and EG-EUS parameters (echogenicity, echostructure, size, presence/absence of power Doppler signals, SR, SH, PE, Wi-AUC, RT, mTT, TTP, WiR, and WiPI).

Statistical analysis

The progression-free survival and overall survival will be measured from the 1st day of chemotherapy to the date of PD and death, respectively. The statistical significance of the correlation between CEH-EUS and EG-EUS parameters and clinicopathologic parameters will be assessed with the Mann–Whitney U-test, the Kruskal–Wallis test, or the Spearman rank correlation test. PFS and OS will be estimated using the Kaplan–Meier method, and statistical comparisons will be made with the log-rank test. Univariate and multivariate analyses will be performed to determine significant variables related to prognosis with a Cox proportional hazards model. All P values will be obtained with a two-tailed statistical analysis, and $P < 0.05$ will be considered statistically significant.

Supplementary materials

Supplementary information is linked to the online version of the paper on the *Endoscopic Ultrasound* website.

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Conflicts of interest

There are no conflicts of interest.

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APPENDIX 1

CT Pancreatic Cancer

[▼]

Omnipaque-350 IV bolus contrast administration: mL.

Axial 2.5 mm images and sagittal, coronal, and oblique sagittal/coronal images were obtained in the late arterial and portal-venous phases.

[In addition, multiplanar subvolun ▲
                                  ▼]

Clinical information

Pancreatic mass.   [Restaging examination.   ▼] [   ]

Comparison

[None.   ▲
         ▼]

Findings PANCREAS

Primary tumor: [(AP x TR x CC]cm [low-attenuation   ▼]mass in the [▼](series , i mage).

Pancreatic duct: [▼]mm.

[No other pancreatic mass is ide ▲
                                ▼]

MESENTERIC ARTERIES

Arterial anatomy [▼]

Arterial tumor abutment or encasement:

"None" or "macro Pancreas Tum

MESENTERIC VEINS

Superior mesenteric vein (SMV) first jejunal branch [▼] to SMA.

SMV terminates as [two major ilea].

Inferior mesenteric vein (IMV) drains into the
[▼].

Venous tumor abutment or encasement:

"None" or "macro Pancreas Tum

Portal venous system: [Normal and pa]

Inferior vena cava (IVC): [Normal.]

HEPATOBILIARY SYSTEM

Focal liver lesions: [None.]

Biliary tree [▼][No intra-or ext]CBD mm.

Gallbladder: [Present   ▼].

LOCOREGIONAL SPREAD

Lymph nodes: [No adenopath]

Peritoneum: [Negative. No r]

Omentum: [Negative. No r]

Ascites: [None.]

OTHER FINDINGS

Stomach, small bowel, and large bowel: [_____ ▼]

Genitourinary system: [Normal.]

Adrenal glands: [Normal.]

Spleen: [Normal.]

Lower chest: [Normal.]

Bones: [No suspicious]

SUMMARY - RECIST 1.1

Primary Tumor: [_____] cm (largest dimension), series , image .

Lymph Node #1: mm (largest short axis), series , image .

Lymph Node #2: mm (largest short axis), series , image .

Liver Lesion #1: [_____] cm (largest dimension), segment [_____] , image .

Liver Lesion #2: [_____] cm (largest dimension), segment [_____] , image .

Conclusion

1. Pancreatic mass.
Location: [Pancreatic he] mass
Size: [_____] cm, [_____ ▼] .

2. Metastatic disease: [None.]

3. Adenopathy: [No adenopath] .

4. Vascular involvement: [No arterial or v] .

5. [_____]