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Polarization gating spectroscopy of normal-appearing duodenal mucosa to detect pancreas cancer

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Abstract

BACKGROUND—According to field effect theory, by detecting microvasculature changes in the early increase of blood supply (EIBS) in the surrounding tissue neoplastic lesions can be identified from a distance.

OBJECTIVE—To determine the feasibility and efficacy of a fiberoptic probe containing novel Polarization Gating Spectroscopy (PGS) technology to identify patients with pancreatic adenocarcinoma (PAC) by field effect theory.

DESIGN—Prospective cohort (pilot) study

SETTING—Outpatient tertiary care center

PATIENTS—Adult (≥18 years) patients undergoing EGD-EUS were screened. Patients with PAC were included in the “cancer” group and patients without PAC were included in the “control” group. We excluded patients with other known malignancies and gastro-duodenal premalignant lesions.

INTERVENTIONS and MAIN OUTCOME MEASURES—Spectroscopic measurements of EIBS variables, such as deoxyhemoglobin concentration (DHb) and mean blood vessel radius (BVR), were obtained from five peri-ampullary locations. The Mann-Whitney rank sum test was used for the statistical analysis ($p \leq 0.05$).

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RESULTS—Fourteen patients (mean age: 72 years,79% male) in the cancer group and 15 patients (mean age 63 years,60% male) in the control group were included in the final analysis. At the ampullary site, both DHb (p=0.001) and BVR (p=0.03) were higher in PAC patients than in the controls. The DHb alone (92% sensitivity,86% specificity) or in combination with BVR (92% sensitivity,71% specificity) can differentiate PAC from controls with high accuracy.

LIMITATIONS—Small sample size, Unmatched controls

CONCLUSIONS—Spectroscopic measurements of EIBS by fiberoptic probes are feasible. Preliminary evidence suggests that in vivo measurement of normal-appearing duodenal tissue can differentiate PAC patients from a distance with high accuracy.

Keywords

Pancreas adenocarcinoma; Spectroscopy; fiberoptic probe

Background and Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States and is associated with a poor prognosis. The mortality rate is approximately 74% at 1 year and 94% at 5 years.[1] The average life expectancy after diagnosis is approximately 5 to 8 months.[2] At present, successful surgical resection is the only curative therapy that can improve long-term survival. However, it can be achieved only when a tumor is detected at an early stage.[3] Unfortunately, due to non-specific symptoms associated with pancreatic cancer, it is commonly detected in the later stages of the disease.[4]

In the past decade, there has been significant improvement in the quality of imaging studies (e.g. CT scan, MRI, Endoscopic ultrasound) and development of disease specific molecular markers (e.g. CA 19–9). However, their use has failed to significantly improve the mortality rate of pancreatic cancer.[5] Unfortunately, fewer than 20% of patients are considered eligible candidates for curative surgical resection at the time of diagnosis.[6] This suggests that although modern imaging methods may define the diagnosis of pancreatic cancer with more precision, they have failed to improve the prognosis associated with it. Therefore, identifying patients with early pancreatic cancer and developing screening strategies for high-risk patients is of immense importance.[7, 8] So far, there have been no definite biomarkers or imaging techniques proven to be a safe, sensitive, and cost effective strategy for pancreatic cancer screening in the general population. However, recent technological advances have been able to detect early neoplastic changes in the field of tissue surrounding the pancreas and other solid tumors for its early detection.[9–12]

In this study, we hypothesized that pancreatic adenocarcinoma (PAC) could be detected by measuring the changes in the early increase in blood supply (EIBS)[13] found in the surrounding normal-appearing duodenal tissue with Polarization Gating Spectroscopy (PGS) technology.

We aim to evaluate the feasibility and efficacy of PGS measurements in the duodenum during endoscopy procedures and to evaluate EIBS markers, deoxyhemoglobin

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concentration (DHb), and average blood vessel radius (BVR) in patients with PAC versus controls.

Materials and Methods

Study Design and Sample Size

This pilot study was a single center, open label, prospective cohort study performed at the Mayo Clinic in Jacksonville, Florida in partnership with the Biomedical Engineering Department of Northwestern University in Evanston, Illinois. We planned to recruit a total of 15 patients with pathologically confirmed PAC (cancer group) and 15 patients without PAC (control group) to compare spectroscopic measurements. The sample size was based on both feasibility and the primary aim to gain sufficient pilot data to provide reasonable point estimates for each measurement to plan future studies. The Institutional Review Board of Mayo Clinic approved the study and all patients signed the informed consent documentation.

Study patients

We screened all patients who were pre-scheduled to receive Esophagogastroduodenoscopy (EGD) with upper Endoscopic Ultrasound (EUS). Patients with a known, recent history of PAC (untreated) were included in the cancer group, and patients without a known history of PAC were included in the control group. Patient's eligibility in the cancer group or the control group was determined based on the inclusion and exclusion criteria of our study (see Table 1). All patients in the cancer group were diagnosed with pancreatic adenocarcinoma. Patients with pancreatic neuroendocrine tumors were excluded from the study. As described in the exclusion criteria, patients in the control group had no malignant or premalignant lesions in the pancreas or gastro-duodenal area. Patients with chronic pancreatitis were excluded from the PAC group, but not from the control group. All patients with visible inflammatory conditions in the upper gastrointestinal tract were excluded from both the PAC group and the control group. Patients in the control group received an upper EUS for the indication of abdominal pain. Patients with EGD/upper EUS findings that did not meet the exclusion criteria were considered a “screen failure” and were excluded from the final study analysis.

Polarization Gating Spectroscopy (PGS)

PGS is an optical method, which measures the intensity of light scattering with the help of both polarization and wavelength (λ) (see Figure 1). The polarization dependence of the scattered light allows depth-selective interrogation of tissue. The collection of polarized light parallel ($I_{\|}$) and perpendicular ($I_{\perp}$) to the incident beam allows the analysis of the $I_{\|}$, $I_{\perp}$, and difference between $I_{\|}$ and $I_{\perp}$ of the signals.[14] PGS light signals interrogate progressively deeper into the tissue at estimated maximum penetration depths of 200, 270, and 400 μm at the ampulla, respectively. Analysis of the wavelength dependence of these signals allows measurements of oxyhemoglobin concentration (OHb), deoxyhemoglobin concentration (DHb), and the mean blood vessel radius (BVR) via a modified Beer-Lambert algorithm (see supplement 1 for details).[14–16]

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The measurement method with a PGS fiber-optic probe has been described previously in detail.[16, 17] The PGS measurement unit consists of the following components: (1) a mobile cart with a light source, a spectrometer, a computer processor, monitor, a keyboard, and calibration equipment (figure 2-A) and (2) a fiber-optic probe (figure 2-B). The fiber-optic probe is reusable. It was sterilized and reprocessed with Cidex® solution (Ethicon endo-surgery Inc., Cincinnati, Ohio) in a similar standardized fashion as with other endoscopes.

Procedural Details

Each patient received EGD with upper EUS as scheduled by an experienced endoscopist participating in the study (M.W., M.R., T.W.). All patients were sedated with monitored anesthesia under the guidance of an anesthesiology provider.

Before obtaining each spectroscopic measurement, calibration of the fiber-optic system was performed using air, water, and 99% diffuse reflectance standards. The air and water standards accounted for stray reflections in the probe, whereas the reflectance standard was used to account for the intensity spectrum of the light source and system. During EGD, the optic probe was inserted inside the accessory channel of the upper endoscope and advanced to the tip of the endoscope (see figure 2-C). The optic probe was gently brought in contact with the peri-ampullary duodenal mucosa at five different desired locations: (1) directly on the ampulla, (2) approximately 5 mm proximal from the ampulla, (3) approximately 5 mm distal from the ampulla, (4) 1 cm proximal from the ampulla, and (5) 1 cm distal from the ampulla. We obtained spectroscopy measurements four times in each of these five peri-ampullary locations (see figure 2-D). The rest of the EGD and upper EUS-FNA endoscopy procedures were then completed as clinically indicated. All results, including FNA results (if obtained), were recorded. During the procedure, all visualized mucosal abnormalities were recorded and photographed.

Patients were monitored and then discharged after the endoscopy procedure per standard protocol. Upon discharge, participants were provided information to contact the study investigator if they developed any new or worsening symptoms. Any reported post-procedural adverse events were recorded.

Data analysis

After obtaining spectroscopy measurements, the data was stored in the spectroscopy processor and transferred to Northwestern University biomedical engineering laboratory for final analysis. Spectra measurements at each desired location with an $\frac{I_{||}}{I_{\perp}}$ ratio between 1 and 5, $I_{||}$ signal intensity >1% of the reflectance standard intensity, and oxygenation saturation greater than 2% were considered optimal quality. Spectra not meeting the above criteria were excluded from the final analysis. These criteria ensured avoidance of inadequate intensity signals in the analysis. EIBS variables, DHb, and BVR were calculated from each spectra, and their average value at each desired periampullary location was calculated. A given periampullary location had to possess at least 2 satisfactory for the average values to be included in the final analysis. To minimize the bias, the engineer performing the data analysis was blinded to the patient status (cancer versus control).

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Demographic information was described using frequency statistics. The DHb and BVR measurements were compared between patients in cancer and the control group by using the Mann-Whitney rank sum test using Minitab version 16.1.1 (Minitab Inc., State College, PA). At various cutoff values on the receiver operating characteristic (ROC) curve, the sensitivity and specificity of DHb and BVR were determined to differentiate patients with PAC from controls. The leave-one-out cross-validation procedure was performed using Stata version 8 (StataCorp, College Station, TX). The results were assessed for any effect of potential confounding factors, such as age, gender, ethnicity, history of smoking or alcohol use, tumor size, or tumor location, using the analysis of covariance (ANCOVA) test. We used a p-value of less than 0.05 to determine the statistical significance of the test results. This manuscript was prepared and reviewed by the contributing authors of this study. Additionally, all authors had access to the study data and had reviewed and approved the final manuscript.

Results

We enrolled a total of 37 patients in the study. Of these, five patients with neuroendocrine tumors and 2 patients with duodenal anatomy limiting the use of the probe were excluded due to “screen failure.” We recruited a total 15 patients with PACs to the cancer group and 15 patients without PACs to the control group. These individuals met all inclusion and exclusion criteria of the study. Among the 15 patients in the cancer group, 1 patient was excluded from the final analysis due to suboptimal measurements. In the final analysis, 14 patients in the cancer group were compared with 15 patients in the control group. The demographics of the recruited patients in the cancer and control groups are shown in Table 2. Among the 15 patients in the control group, 2 patients were found to have chronic pancreatitis based on five or more EUS features. The rest of the patients had normal pancreatic architecture and received the diagnosis of functional abdominal pain. The preparation of the cart and the spectroscopic measurements took an average approximately 10 minutes.

Ampulla – Optimal Location for Spectroscopy Measurements

Among all five peri-ampullary locations, the EIBS variables, DHb ($p = 0.001$) and BVR ($p = 0.03$) measured directly from the ampulla had the least variability and showed maximal ability to differentiate the PAC patients from controls (supplement 2). Below, we will discuss the details of the measurements obtained directly from the ampulla.

Accuracy to Differentiate Patients with PAC

The scatterplot of DHb and BVR measurements from the ampulla between patients in the cancer and control groups is shown in figure 3-A. The scatterplot demonstrates the higher levels of both DHb and BVR among patients in the cancer group compared with patients in the control group. After plotting DHb and BVR measurements on ROC curves (figure 3-B, 3-C), their sensitivity and specificity were determined using variable cutoff values (see table 3). In ROC curve analysis, DHb measurements alone achieved a sensitivity of 92% and specificity of 86% to differentiate PAC from controls. DHb in combination with BVR measurements achieved a sensitivity of 92% and specificity of 71% to differentiate PAC

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from controls. After performing leave-one-out cross-validation analysis, the DHb retained a sensitivity of 92% and specificity of 71%.

After excluding patients with chronic pancreatitis (n=2) from the control group, DHB measurements alone retained a sensitivity of 92% and specificity of 67% to differentiate PAC from controls, and DHB in combination with BVR measurements retained a sensitivity of 92% and specificity of 50%.

Effects of Confounding Factors

We observed no statistically significant effect of age, race, and history of smoking tobacco or alcohol use on the EIBS measurements between the 2 groups (see Table 4). DHb measurements were found to be higher in males than in females (p=0.02), whereas gender did not show a statistically significant effect on BVR measurements (p=0.22).

In terms of tumor characteristics, the average size of the PAC tumor was 3.3 cm (± 1.0 cm standard deviation). The distribution of the PAC tumors was 43% (n=6) in head/neck region and 57% (n=8) in the body/tail region of the pancreas. Tumor size and tumor location in the pancreas did not show any statistically significant effect on the EIBS measurements.

Adverse Events

None of the patients who participated in our study reported any adverse events during or after the endoscopy procedure with this spectroscopic measurement.

Discussion

Our study results suggest that patients with PAC have field effect changes in the normal-appearing duodenal mucosa that is distant from the site of the tumor. PGS, a novel optical biomarker, is able to distinguish PAC from non-cancer controls by detection of EIBS changes in the microvasculature of the adjacent normal-appearing duodenum. We found that measurement of EIBS markers, DHb, and BVR in the duodenal mucosa by PGS fiber-optic probe was simple, feasible, and safe during the endoscopy. In this early study, DHb alone or in combination with BVR can differentiate patients with PAC from controls with high sensitivity and specificity.

Development and progression of neoplastic lesions are known to be associated with EIBS (primarily through angiogenesis) and high oxygen demand.[16, 18] Field effect theory proposes that neoplastic changes, such as epigenetic alteration and angiogenesis,can be present in the contiguous normal tissues. Detecting such changes can reveal the presence of a neoplastic lesion from a distance.[16, 18] The use of field effect biomarkers have already been reported in colon cancer[12], stomach cancer[19], lung cancer[20], and breast cancer.[21]

Recently, the development of modern molecular technologies such as 4-dimensional elastic light-scattering spectroscopy (4D-ELF), and low-coherence enhanced backscattering spectroscopy (LEBS) have been replicated in a miniature form called polarization gated spectroscopy (PGS) to explore the molecular abnormalities in tissue micro-architecture that appears histologically normal.[11] PGS allows quantitative assessment of the absorption

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spectra and light scattering in real time based on how the light interacts with the tissue.[14, 22–25]

According to theory, field effect changes may be present at several locations surrounding the pancreas, but the measurement of optical and biochemical biomarkers from the duodenum is appealing due to its accessibility and anatomic continuation with the pancreatic tissue and the potential for fewer adverse events related to pancreatic duct manipulation. PGS via a fiber-optic probe is a relatively convenient device applied via the accessory channel of the standard upper endoscope. The preparation and measurement processes add only a few minutes to endoscopy procedure time. PGS technology uses the subset of normal white light (specific wavelength between 450 nm – 650 nm), which does not impose any risk of radiation injury. The spectroscopic measurement involves bringing the fiber-optic probe in contact with the tissue surface and therefore, adds very limited risks to the planned endoscopy procedure. Contrary to other advanced imaging techniques (e.g. confocal microscopy, magnification narrow band imaging), PGS technology can objectively quantify field effect changes without the need of complex training in image interpretation or, in the case of confocal endomicroscopy, a contrast agent.[26]

A prior study of spectroscopy measurements on an ex vivo duodenal biopsy sample showed a 95% sensitivity and 91% specificity in detecting the presence of pancreatic cancer[27], which is comparable to our study results of spectroscopic measurements obtained in vivo. Common confounding factors, such as age, race, history of smoking tobacco, history of alcohol use, tumor size, and tumor location, did not show significant impact on spectroscopic measurements in either group.

Limitations

The number of the patients in the cancer and control groups is relatively small to derive to any strong conclusion. However, having approximately 15 patients in each group is a reasonable number of patients for a pilot study designed to understand the feasibility, safety, and rough estimation of the efficacy of this technology to determine the presence of PAC. We performed a leave-one-out cross-validation statistical analysis, which showed comparable accuracy of the results.

The patient demographics showing higher older male patients in the cancer (PAC) group are suggestive of a potential referral bias and a possible representation of similar demographics of the PAC patients in the general population. However, other confounding variables did not show statistically significant effects on the spectroscopic measurements. Similar to prior reports, DHb measurements were also found to be higher in male patients compared with female patients.[28] The cause of gender differences in DHb measurement is currently unknown.

Spectroscopy technology has limitations in differentiating EIBS changes from the neoplastic lesion versus tissue inflammation. After excluding patients with visible inflammation in the gastro-duodenal region, the results achieved high accuracy to differentiate the presence of PAC from controls. So far, the effect of chronic pancreatitis on the spectroscopic measurements is not well understood. To increase the validity of the study results, a small

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number of patients with chronic pancreatitis were included in the control group. However, the study sample size is not large enough to accurately determine the true effect of chronic pancreatitis on the spectroscopic measurements. There was some theoretical limitation of the front viewing endoscope within the duodenum necessitating a tangential view to obtain spectral measurement of the periampullary tissues. However, the standard upper endoscope, instead of the side-viewing ERCP scope, was chosen to increase its potential applicability and reduce the risk of damaging the delicate fiber-optic probe by the elevator. In our experience, we have found that the fiber-optic probe is quite sturdy with no significant issue maneuvering it through the endoscope. Although the intensity of pressure applied to the tissue with the probe is subjective, the equipment provides immediate feedback if there is poor contact, prompting a repeat measurement. It does not however compensate for excessive contact nor artifacts from luminal contents (bile) or mucosal abrasion. Fortunately, these were rare and adjusted for by moving the probe to a nearby location.

Future implications

This PGS technology has been shown to be a safe, feasible, and accurate option to differentiate the presence of PAC during endoscopy. However, its validity and the effect of potential confounding variables have yet to be tested in a large number of patients with PAC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

4DELF	four-dimensional elastic light-scattering spectroscopy
AUC	area under the curve
ANCOVA	analysis of covariance
BVR	mean blood vessel radius
DHb	deoxyhemoglobin concentration
EGD	esophagogastroduodenoscopy
EIBS	early increase in blood supply
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound

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FNA	fine needle aspiration
LEBS	low-coherence enhanced backscattering spectroscopy
OHb	oxygenated hemoglobin
PAC	pancreas adenocarcinoma
PGS	Polarization Gating Spectroscopy
ROC	Receiver operating characteristic

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Take-home Message

- The detection of the field effect changes such as early increase in blood supply surrounding the malignant lesion can potentially be useful to detect a malignant lesion from a distance. We can detect variables of early increase in the blood supply with a simple through-the-endoscope fiber-optic probe and can predict the presence of pancreas adenocarcinoma with high accuracy.
- Such technology may bring additional tools to stratify the malignant potential of the pancreatic lesion.

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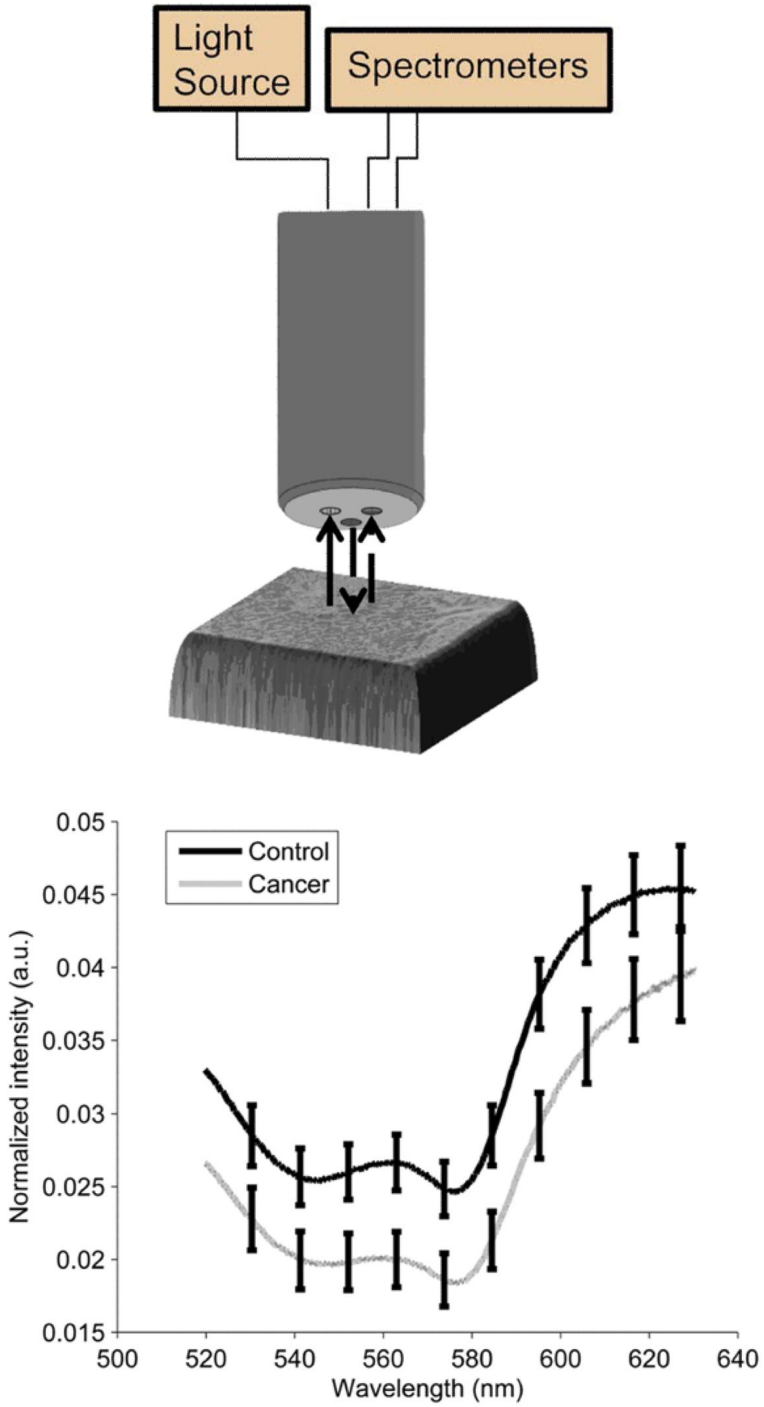

Figure 1.
Schematic of the polarization-gated probe (A) and representation of data acquisition graph (B).

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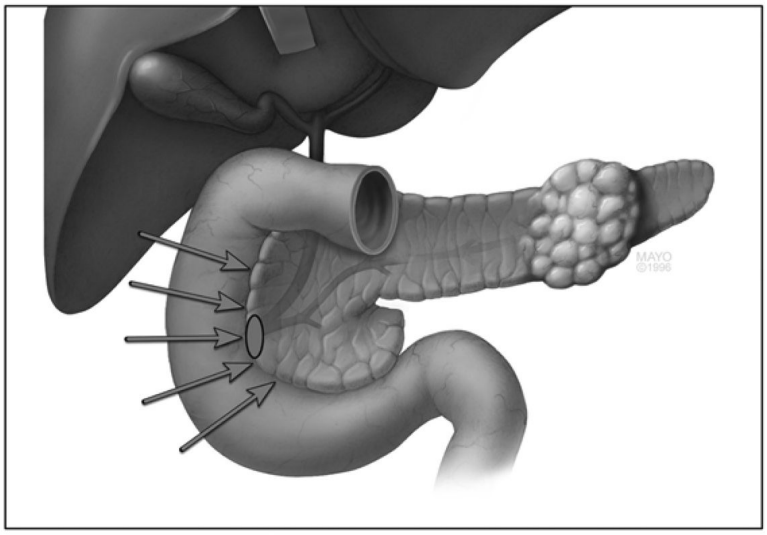

Figure 2.

(A) Spectroscopy processor, monitor, and keyboard of polarization gating spectroscopy measurement unit. (B) Fiber-optic probe of polarization gating spectroscopic measurement unit. (C) Polarization gating fiber-optic probe fed through the accessory channel of the standard upper endoscope (D) Peri-ampullary locations where spectroscopy measurements were obtained.

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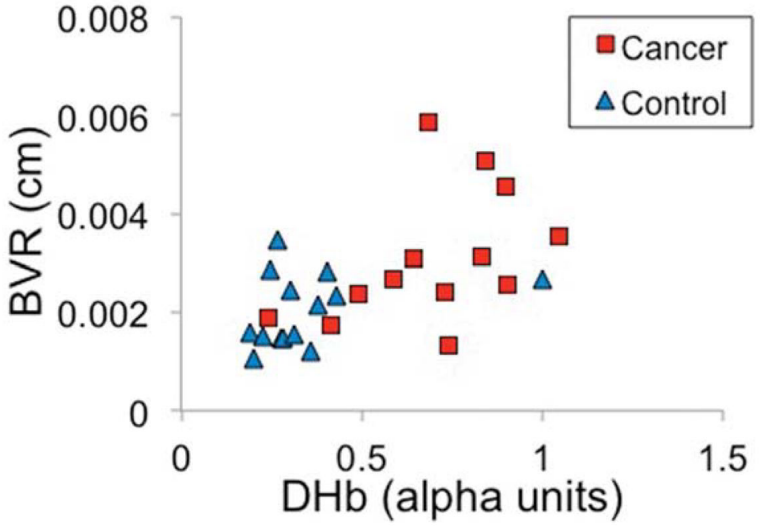

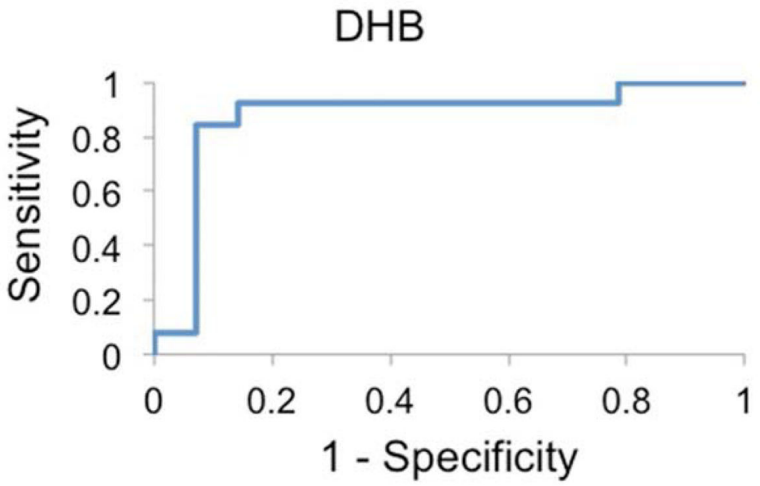

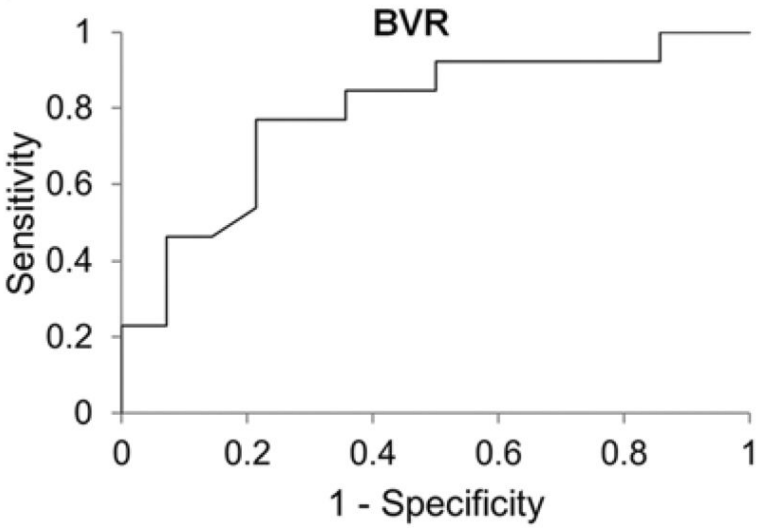

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Figure 3.

(A) The scatterplot of ampullary measurements among patients in “cancer” and “control” group. (B) Receiving Operating Curve (ROC) using DHb (C) ROC using BVR to differentiate presence of pancreas cancer compared with control.

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Table 1

Inclusion and exclusion criteria of the study

Inclusion Criteria	Age 18 years or older
	Able to provide informed written consent
	Patient scheduled for previously planned EGD with upper EUS
	Patients with known adenocarcinoma of the pancreas included in the cancer group
	Patients with abdominal imaging studies (e.g. CT abdomen or MRI abdomen) negative for malignancy in past 5 years included in the control group
Exclusion Criteria	Unable to obtain biopsy specimen or fine-needle aspiration results of the pancreas lesion (e.g. coagulation disorder, inadequate sample)
	Presence of malignant lesion* in the pancreas or the duodenum (e.g. Neuroendocrine tumor, Gastrointestinal stromal tumor)
	Known familial disorder with high risk of pancreas cancer development (e.g. Familial adenomatous polyposis syndrome, Hereditary non-polyposis colorectal cancer syndrome, Juvenile polyposis syndrome)
	Significant family history of pancreatic cancer (at least one first degree relative with pancreas cancer)
	Presence of premalignant lesions (e.g. Duodenal adenoma, Pancreas intraductal papillary mucinous neoplasm)
	Active visible inflammation/ulcer in the stomach or the duodenum.
	Patients with known chronic pancreatitis were excluded from the cancer group†
	Know pregnancy or sexually active females of childbearing age not receiving an accepted form of birth control method

*Other than pancreas adenocarcinoma

†Chronic pancreatitis patients were allowed to be included in the “control” group only

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Table 2

Demographics of patients in “cancer” and “control” groups.

Demographic Variables	“Cancer” group (n=14)	“Control” group (n=15)
Mean age (± SD)	72 years (± 10 years)	63 years (± 11 years)
Male gender	11 (79%)	9 (60%)
White ethnicity	13 (93%)	13 (87%)
History of smoking tobacco	7 (50%)	9 (60%)
History of alcohol use	6 (43%)	13 (87%)

(SD- Standard Deviation)

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Table 3

Accuracy of blood vessel radius (BVR) and deoxyhemoglobin concentration (DHb) measurements.

Variables	Sensitivity	Specificity	AUC in ROC
Deoxyhemoglobin (DHb)	92%	86%	0.87
Blood vessel radius (BVR)	77%	79%	0.79
Combine DHb and BVR	92%	71%	0.88

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Table 4

Effect of various confounding variables on measurements obtained in patients with pancreas cancer compared with controls.

Confounding Variables	DHb (p-value*)	BVR (p-value*)
Age	0.40	0.65
Gender	0.02	0.46
White ethnicity	0.23	0.19
History of active smoking	0.82	0.27
History of active alcohol use	0.94	0.93

* Statistical analysis was performed using ANCOVA test