Title: Pancreatic Cancer Screening for at-risk Individuals (Pancreas Scan Study)

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Study Protocol

Introduction

Pancreas cancer is estimated to become the second most common cause of cancer related death for men and women in the United States by 2030. The 5-year survival of patients with pancreatic cancer remains below 10%. Surgery offers the only hope for long-term survival, but less than 20% of patients present with localized surgically resectable disease. One study suggested that screen detected cancers may have better outcomes, however data on benefits of screening are extremely limited. Pancreas cancer screening is not performed for average-risk individuals, but is presently recommended for high-risk individuals, who have a lifetime pancreatic cancer risk of at least 5%.

Background

Patients with pancreas cancer have poor prognosis, with 5-year survival rates remaining below 10% (Siegel, Miller, & Jemal, 2020). Pancreas cancer is the fourth most common cause of cancer related deaths in the United States. It is estimated that by the year 2030, pancreatic cancer will overtake colo-rectal cancer and breast cancer to become the second most common cause of cancer related death for men and women in the United States (Rahib et al., 2014). In 2019 alone, over 56,000 people were diagnosed of pancreas cancer and 80% died of the disease (Siegel et al., 2020). The five-year survival of pancreas cancer is 2.9% for metastatic disease, 12.4% for regional disease and 37% for localized disease (van Roessel et al., 2018). Almost 80% of pancreas cancer cases are diagnosed at advanced and surgically inoperable stage. This has led to growing interest in pancreas cancer screening. Pancreas cancer screening in high-risk groups could detect cancer at an early and more treatable stage where cancer outcomes are better. In a study by Canto M et al, 10 of 14 screen-detected cancers were found in patient who followed screening protocol (Canto et al., 2018). Nine patients had cancers that were surgically resectable Stage 1 or 2 cancers; and one patient had metastatic cancer. In contrast, 4 patients were diagnosed with symptomatic pancreatic cancer after they stopped screening or were non-compliant with screening. Three of these 4 patients were found to have metastatic

disease. The 3-year survival was significantly higher in the screen-detected cancers when compared with cancers that were diagnosed outside of the screen protocol (85% versus 25%).

Pancreatic cancer screening studies thus far have been small, enrolled a heterogenous patient population and evaluated non-standardized outcomes (Borgida et al., 2017; Gangi, Malafa, & Klapman, 2018; Kogekar, Diaz, Weinberg, & Lucas, 2019; Kwon et al., 2019; Lachter et al., 2018). There has been variation regarding definitions for high-risk groups for pancreatic cancer screening. In addition, there has not been agreement with regard to appropriate age when screening should be initiated. Our goal is to conduct a large prospective multicenter study to evaluate the yield and outcomes of pancreas cancer screening in patients who are high-risk for pancreas cancer. We plan to use International Cancer of the Pancreas Screening (CAPS) Consortium recommendations to standardize study population, screening methodology and study outcomes(Goggins et al., 2020).

Methods

Our goal is to conduct a prospective multicenter study to evaluate yield and outcomes of pancreas cancer screening in high-risk individuals. High-risk patients who are undergoing pancreatic cancer screening in accordance with national guidelines at participating study centers will be eligible for the study. Information regarding patient characteristics, findings at screening examination, and patient outcomes will be collected. Interested sites who would like to collaborate on this study with BIDMC will be approved by the BIDMC IRB through submitting an amendment. The collaborating site's data will be shared with BIDMC following obtaining BIDMC IRB approval and finalized executive data use agreement (DUA).

The following sites are the new collaborating sites which will share their data through the study REDCap managed by BIDMC. They includes Central Arkansas Veterans Healthcare System, Interventional Endoscopy at Wake Forest School of Medicine, and Division of Gastroenterology at Washington University School of Medicine (St. Louis, Missouri).

Moreover, RUSH University, Northwell Health System, and Veteran Affair Medical Center Salisbury would like to collaborate with BIDMC on this study.

The collaborating sites will share their data through the study REDCap.

Primary Outcome (Primary Aim):

To identify the proportion of patients who meet International Cancer of the Pancreas Screening Consortium screening criteria 3rd update (CAPS Jan 2020) who are found at screening to have high-risk pancreatic lesions amenable to treatment (definition of "high risk lesions amenable to treatment" is provided under section on study outcomes).

Secondary outcomes (Secondary Aims) will include (details are provided under section on study outcomes):

1- proportion of patients diagnosed with any stage pancreatic cancer

2- proportion of patients undergoing pancreatic surgery

3- Cancer related outcome, defined as cancer related death

4- proportion of patients experience harms, defined as any complications/adverse event due to screen related procedures

5- Comparison of cancer outcome, defined cancer related death, in screen-detected cancer with cancer outcomes reported by the SEERs population-based registry.

Study overview

Study type: prospective observational cohort

High risk patients who meet study inclusion criteria at study centers will be identified. Screening and patient follow-up will be performed at individual study centers per standard clinical practice. Patient characteristics, screening performed and screening results, clinical outcome data will be collected by individual study centers. This data will be stored and analyzed at central study REDCap located at BIDMC. The following sites are the new collaborating sites which will share their data through the study REDCap managed by BIDMC. They includes Central Arkansas Veterans Healthcare System, Interventional Endoscopy at Wake Forest School of Medicine, and Division of Gastroenterology at Washington University School of Medicine (St. Louis, Missouri).

Inclusion criteria

Inclusion criteria 1-3 are indications for pancreatic cancer screening as defined by the CAPS3 guidelines. Patients who do not meet these guidelines but are undergoing pancreatic cancer screening at the discretion of their treating physician at participating study centers will also be included in the study. Based upon indication for screening, patients will be categorized as either meeting CAPS3 screening criteria, or not meeting CAPS3 screening criteria.

1. Familial Pancreatic cancer kindred. This is defined as family history of pancreas cancer that meet the criteria listed below.
    a. If at least two affected relatives who are First degree relatives (FDR) to each other, of whom at least one is an FDR to the individual considered for surveillance
    b. If at least three affected relatives on the same side of the family, of whom at least one is an FDR to the individual considered for surveillance
    c. If at least two affected relatives on the same side of the family, of whom at least one is an FDR to the individual considered for surveillance

    Screening is usually initialed at age **50** years or 10 years younger than the youngest family member with pancreatic cancer

2. Patients with genetic susceptibility to pancreas cancer
    a. Patients with Peutz-Jeghers syndrome diagnosed with using clinical criteria or with deleterious mutation in LKB1/STK11. Screening is usually initiated at **age 40** years or later.
    b. Patients with Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM syndrome), diagnosed using clinical criteria or CDKN2A p16 mutation. Screening is usually initiated at age **45 years or 10** years younger than the youngest family member with pancreatic cancer.
    a. Hereditary Breast and Ovarian Cancer syndrome: diagnosed using clinical criteria or deleterious BRCA1, BRCA2, PALB2. Usual indication for screening is:

-BRCA1 mutation and at least one affected first degree relative with pancreatic cancer

-BRCA 2 mutation and at least one affected first degree relative, or at least two relatives of any degree with pancreatic cancer

-PALB2 mutation and at least one affected first degree relative with pancreatic cancer

Screening is usually initiated at age **45** or 10 years younger than the youngest family member with pancreatic cancer

b. Lynch syndrome or ATM mutations with at least one affected first degree relative (FDR). Lynch syndrome could be diagnosed either by using clinical criteria or MLH1, MSH2, MSH6, PMS2 or EPCAM mutation.

   Screening to be initiated at age **45** or 10 years younger than the youngest family member with pancreatic cancer.

c. Patients with hereditary pancreatitis diagnosed using clinical criteria or deleterious PRSS1 mutation. Screening is usually initiated at age **40** years or 10 years younger than the youngest family member with pancreatic cancer

3. New-onset diabetes, age > 50 years with weight loss.
4. Patients who do not meet these CAPS screening criteria but are determined by the site principal investigator to be high-risk for pancreatic cancer based upon family history or other risk factors, and are undergoing pancreatic cancer screening will also be included in the study. Indication for pancreatic cancer screening and age at which screening was initiated will be recorded.

Exclusion criteria

5. Patients presenting with symptoms suggestive of pancreatic cancer who are undergoing diagnostic EUS or MRCP e.g. acute recurrent pancreatitis, abnormal imaging

Pancreatic Cancer Screening protocol

1. All patients at the leading site (BIDMC) and the collaborating sites who present for pancreas cancer screening and meet the inclusion criteria will be prospectively enrolled in the study.
2. Indication of the screening and family history will be collected by the treating physician via the study screening form. The screen form will be redacted and uploaded to the study REDCap managed by BIDMC as the leading site.
3. Patient information will be collected by treating physician per clinical practice
4. Initial pancreatic cancer screening: will be performed per CAPS-3 guidelines or local institutional protocol. This will be done using MRI, EUS or CT scan per clinical protocol.
5. Follow-up screening: CAPS-3 guidelines recommend alternating between EUS and MRI yearly. Patient will be contacted by treating physician to arrange for follow-up screening yearly, as is standard clinical practice. At the time of yearly contact, medical and family history will be updated. Screening EUS, MRI or CT scan will be performed using standard clinical practice.
6. CAPS-3 guidelines recommend annual screening for new-onset diabetes. This will be done by obtaining fasting bleeding glucose or HbA1C, per local institutional protocol.
7. Results of all investigations and procedures that result from findings of screening studies will be recorded.
8. If patients undergo pancreatic surgery, type of surgery, surgical/patient outcomes and surgical pathology will be recorded.
9. Study duration: We estimated (see Data Analysis and sample size calculation for details) that it will take 3 years to enroll all patients into the study. We plan to follow each patient for 5 years after first screening to determine outcome of screening.

Data Collection

1. Data collected from BIDMC and the collaborating sites: patient demographic, family history, medical history, result of screening tests, results of imaging studies, surgeries, outcomes, new diagnosis will be collected.

2. All data will be stored in REDcap database at BIDMC.
3. Participation is study does NOT require any additional testing or procedures to be performed. All patient care will be standard clinical care per institution protocol.
4. Based upon indication for screening, patients will be categorized as either meeting CAPS3 screening criteria, or not meeting CAPS3 screening criteria.
5. Each collaborating site has access to its own database only. The screening form which is prospectively completed by the treating gastroenterologist, based on the available family and medical history, will be uploaded into the study REDCap after redaction of name and medical record.
6. No name or medical record will be entered in the study REDCap. Elements of date such as date of birth and date of procedure will be entered.

Possible benefits

Data analyzed through our study may have the following benefits:

(1) Quantify benefits of pancreas cancer screening

(2) Identify subgroup of patients who are most likely to benefit from pancreatic cancer screening

(3) Identify subgroup of patients who are most likely to be harmed by pancreatic cancer screening

(4) Determine optimal screening protocol

(5) Determine if screening is associated with improved cancer related outcomes

(6) Inform design for further clinical studies, including randomized trial comparing pancreatic cancer screening with no screening

Possible risks and analysis of risk/benefit ratio

Participation in this study does not require the patients to undergo any procedure or testing that is not part of standard clinical care. Decision to consider screening, type of screening modality to be used, and follow up with all be done at the discretion of the treating physician per standard clinical

care period. Therefore the only risk to patient of participation in the study is breach of data confidentiality.

Confidentiality and Data Safety Monitoring

Careful data monitoring and quality control will be maintained with all possible precautions taken to protect the confidentiality of study subjects. All information with patient identifiers will be coded using study IDs and anonymized by deletion of all printed information. Any hard copies of research records that include patient information with identifiers will be under lock-and key in a private and secure location at each site, with access only to the PI and research co-coordinator of the site. No participant will be identified from published reports and correspondence between investigators will not include patient names. All information will be reviewed in a private location and only by study staff delegated to review records.

Study outcomes (Study Aims)

Primary outcome (primary aim) is to identify the proportion of patients who meet International Cancer of the Pancreas Screening Consortium screening criteria (CAPS3 issued in Jan 2020) who are found at screening to have high-risk pancreatic lesions amenable to treatment. High-risk pancreatic lesions amenable to treatment will be defined as the followings:

1. Lesion with high-grade dysplasia (HGD)
2. High-grade pancreatic intra-epithelial neoplasia (panIN)
3. Resectable or borderline resectable pancreatic cancer. Pancreatic cancers that were staged T1-3, N0-2 and M0 designated as resectable or borderline resectable. Cancers that were staged as T4 or M1 were considered locally advanced or metastatic, and therefore designated as unresectable.
4. Main duct intra-ductal papillary mucinous neoplasm (IPMN). This will be defined per Fukuoko guidelines as dilation of main pancreatic duct ≥ 5 mm, after duct dilation due to other causes have been excluded (Tanaka et al., 2017).

5. Branch-duct IPMN with "worrisome features". Worrisome features will be defined per Fukuoka guidelines as: cyst ≥ 3 cm, cyst with enhancing mural nodule, cyst with thick or enhancing walls, cyst associated with abrupt change in main pancreatic duct caliber with pancreatic atrophy (Tanaka et al., 2017).
6. Neuroendocrine tumor ≥ 2 cm.

Secondary outcomes (Secondary Aims):

1. Yield of screening at initial screen and at each subsequent screen annually.
2. Proportion of patients undergoing pancreatic cancer screening who are found to have low or moderate-risk pancreatic lesions. Low or moderate-risk pancreatic lesions pancreatic lesions are defined as:
    a. Branch-duct IPMN without HGD
    b. Neuroendocrine tumor < 2 cm
    c. dilation of main pancreatic duct < 8 mm
    d. Chronic pancreatitis-like change
3. Proportion of patients who underwent further testing, such as FNA (fine needle aspiration), ERCP (endoscopic retrograde cholangiopancreatography), CT (Computerized Tomography), and/or abdominal ultra sound, as a result of screening test findings. Details of these tests will be recorded
4. Proportion of patients who undergo pancreatic surgery as a result of screening test results.
5. Proportion of patients who undergo "low-yield pancreatic surgery" as a result of screening test results. Low yield pancreatic surgery is defined surgery where surgical pathology does not yield high-risk pancreatic lesions. See primary outcome for definition of high-risk pancreatic lesions.
6. Proportion of patients who undergo non- pancreatic surgery as a result of screening test results.
7. Proportion of patients diagnosed with any stage pancreatic cancer

8. Proportion of patients undergoing screening who are found to have high risk lesions stratified by the following sub-groups: gender, family history of pancreatic cancer, genetic mutation. See primary outcome for definition of high-risk pancreatic lesions.
9. Compare proportion of patients undergoing screening who are found to have resectable or borderline resectable pancreatic cancer with those who are found to have symptom detected pancreatic cancer from the Surveillance Epidemiology and End Results Program (SEERs) population database.
10. Compare outcomes, defined as cancer related death, of screen-detected cancers, detected in this study, with symptomatic cancers from SEERs population database.
11. Proportion of patients who experienced any complications/adverse events due to the screen related procedures

Data Analysis and Sample size calculation

A recent meta-analysis showed by high-risk lesions were found in 1% of patients undergoing screening (Corral, Mareth, Riegert-Johnson, Das, & Wallace, 2019). To determine an estimate with margin of error as 2% with 95% confidence interval, such that confidence interval of the estimate does not cross 0, we estimate that approximately 400 patients will be needed for the study. We estimate that 20% patients will be non-complication with screening recommendations and an additional 5% will be lost to follow-up over the study duration. We therefore propose the enroll 500 patients in our study. We estimate that each center will enroll around 25 patients per year. We therefore estimate that 7 centers over 3 years will be needed to accrue total number of patients needed for the study. We plan to follow each patient for minimum of 5 years after first screening to determine outcome of screening. We plan to conduct interim analysis after enrolling 250 into the study.

The categorical variables will be presented by percentage. The continuous variables will be shown by mean, median and standard deviation. The univariate analysis between categorical and continuous variables will be conducted by t-test or Wilcoxon rank for parametric and non-parametric values accordingly. Chi square or Fisher exact test will be used for comparison between categorical variables, as needed.

Logistic regression model will be created. Dependent outcome will be patience with high risk pancreatic lesions found on screening. Independent variables will be patient characteristics, and screening modality. This will be used to determine subgroup of patients most likely to benefit from screening and optimal screening modality, while adjusting for other risk factors such as smoking and family history.

Survival analysis using Kaplan Meier curves will be conducted to assess outcomes of screen-detected cancers. This will be compared with results from SEERs database. Poisson's regression will be used to adjust for confounding variables.

New sample size estimation following interim analysis and after 3 years of enrollment at BIDMC- February 2024:

Results of interim analysis showed that high-risk lesions in pancreas found in patients undergoing pancreatic cancer screening were noted **at a lower rate than previously anticipated**. Therefore, we would like to increase the sample size for the study to be able to identified more high risk lesion.

The modified sample size analysis is as follows:

Proportion of high-risk lesions noted in patients undergoing pancreatic cancer screening = 0.45%. Using the following assumptions: alpha = 0.05, power = 0.8, to assess a difference (delta) of 0.55%, we estimate that a sample size of 1163 patients will be needed. Based on our interim analysis we assume that 10% of patients will be lost-to-follow up and also 10% of patients will have incomplete data. Therefore, we estimate a final sample size of (1163 + 232) 1395 patients.

So far, four (4) sites have joined to this multicenter study and have shared their data with us. There are two more collaborating sites who have been approved by the IRB to join the study. However, due to the slow process of DUA review at the SPC office, the DUAs of the aforementioned two sites have not been finalized yet to enable them to share their data with us. We hope if we extend 3 more years (until March 2027) to the study enrollment time period, we will not only be able to enroll more cases at BIDMC, but also will be able to add more collaborating sites with more potential subjects adding to the study.

So far, the total number of subjects have been included in this study are near 400 cases (388) at BIDMC and near 100 cases (95) at the collaborating sites.

Based on the above reasons we estimate we need three additional years to accrue the new estimated sample size of 1395 subjects. We therefore ask for a three-year extension (until March 2027) of enrollment period to accrue more patients into the study.

The duration of follow up of each patient will be remained the same as before which was at least 5 years.

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