Secretin-Stimulated MRCP as an Early Screening Modality in Patients at High Risk for Pancreatic Adenocarcinoma: A Pilot Study

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1. Study Purpose & Rationale

Pancreatic cancer remains the fourth leading cause of cancer-related death in the United States. The annual incidence of the disease approximates its annual mortality, largely due to the advanced stage at which most patients present. The lack of accurate and cost-effective screening techniques, technical difficulties in the attainment of tissue samples when a mass is identified, and the rapid progression of the disease, all contribute to this advanced presentation.[1]

Screening strategies to identify early disease will be critical in the struggle to improve patient outcomes, and is especially important for the estimated 10-20% of pancreatic cancers considered familial or syndromic. Several syndromes with known germline genetic defects are associated with increased lifetime risk of pancreatic cancer. These include the hereditary nonpolyposis colorectal carcinoma syndrome, the hereditary breast cancer syndrome due to BRCA1 or BRCA2, the familial atypical multiple mole melanoma syndrome, Peutz-Jeghers and Hereditary Pancreatitis.[2] The majority of familial pancreatic cancers, however, occur outside one of these syndromes, from as yet unidentified genes.

A sequential model of progression of preneoplastic lesions, pancreatic intraepithelial neoplasia (PanIN), has recently been described.[3-4] PanIN is morphologically characterized as grades I to III depending upon the severity of the neoplastic change. With this model in mind, it should theoretically be possible to identify patients at highest risk through the detection of these preneoplastic stages, allowing for surgical resection of the pancreas before a fatal tumor arises. In addition, it has been shown that resection of a tumor of less than 1cm is associated with near 100% 5-year survival rates,[5-6] perhaps indicating that even early detection of lesion that have already progressed to adenocarcinomas will significantly impact patient survival. Unfortunately, there is no existing screening strategy that is sensitive enough to identify early lesions, yet safe and cost-effective to apply to the general population. Until mass screening is possible, initial implementation of screeningg is likely to be most feasible and effective in the highest risk population.

Traditional radiological methods utilized to diagnose pancreatic cancer, such as ultrasound, CT and MRI lack sensitivity and resolution to detect small carcinomas and dysplasia.[7] Endoscopic techniques have proven more useful. Endoscopic retrograde cholangiopancreatography (ERCP) has a sensitivity and specificity for pancreatic carcinoma of 92% and 96%.[7] Endoscopic ultrasonography (EUS) is thought to have comparative sensitivity (93-98%) and is thus growing in popularity as the primary means of detection and staging of pancreatic carcinoma.[8]

The disadvantages of both ERCP and EUS are their invasiveness, dependency on technician, and limited availability to certain centers. Magnetic resonance cholangiopancreatography (MRCP) has emerged as a widely-accepted, noninvasive alternative with a 70-92% rate of concordance with ERCP.[9] MRCP, in conjunction with MRI (T1/T2-weighted and contrast-enhanced) and MRA, has demonstrated accuracy of 91% in distinguishing malignant from benign pancreatic lesions.[10,11]

Currently, there are no national guidelines regarding early detection of pancreas cancer or which tests should be performed. Given the recently demonstrated efficacy of lower risk procedures, ERCP is seldom used as a first line diagnostic tool, but is frequently reserved for patients with an abnormal MRCP or EUS in order to make decisions regarding surgical

intervention.[12] Therefore, at this institution, patients are screened with EUS and/or MRCP techniques and only undergo ERCP if one of these evaluations is abnormal.

MRCP has been further augmented by the use of secretin stimulation, which has been shown to improve visualization of the pancreatic duct as well as side branches often missed on traditional MRCP.[12,13] The utility of secretin-stimulated MRCP (S-MRCP) in detecting small and PanIN lesions has not been carefully studied. However, with recent evidence that PanIN lesions within small ducts can cause upstream (distal) duct irregularities, such as fat atrophy, we postulate that S-MRCP may demonstrate increased sensitivity in detecting early pancreatic lesions. If this is the case, S-MRCP may be especially important in the screening efforts of high-risk patients, in order to better identify patients who warrant further investigation or intervention with ERCP or surgery.

The aim of our study is evaluate the utility of S-MRCP in detecting carcinoma and precancerous lesions in patients with a significant familial history of pancreatic adenocarcinoma. S-MRCP will be conducted in conjunction with MRI with T1- and T2-weighted sequences and contrast enhancement as well as MRA. Radiological findings will be compared with pathological diagnosis when applicable. Secondarily, we will also look at the concordance of S-MRCP, EUS and ERCP in detecting early lesions in this high-risk population.

2. Study Design and Statistical Procedures

This is a prospective, observational study to evaluate the utility of a novel diagnostic test, S-MRCP, for screening asymptomatic patients with a significantly increased risk of pancreatic cancer. Patients from three tertiary referral gastroenterology centers will be identified by their treating physician as either having a positive family history for pancreatic cancer or fulfilling critiera (eg genetic testing or clinical criteria) for a syndrome associated with an increased risk of pancreatic cancer (as further specified below).

Screening will consist of two diagnostic imaging modalities. First, all patients will have S-MRCP in conjunction with contrast-enhanced MRI/MRA. All images will be independently analyzed by two radiologists who will be blinded to all patient identifiers and clinical data (other than known increased risk of pancreatic adenocarcinoma). Within thirty days, all patients will also undergo EUS. If the EUS shows abnormalities (such as echogenic foci, hypoechoic nodules, or an echogenic main duct), EUS-guided fine-needle aspiration will be performed.

If either S-MRCP or EUS demonstrate abnormalities, ERCP will then be performed. Biopsies or secretions may be collected during ERCP at the discretion of the endoscopist. Patients with abnormalities on ERCP (such as nobbing or irregularity of the small ducts) may then be offered total or subtotal pancreatectomy, as determined by the pancreatic surgeon and the current standard of care for high-risk individuals. Surgical pathology will be examined for dysplasia or neoplasia and these findings will be considered the gold standard.

The primary outcome measurement in this study will be the diagnostic yield of S-MRCP in detecting dysplastic or neoplastic pancreatic ductal abnormalities. In the subset of patients whom undergo pancreatectomy, S-MRCP results (negative if classified as benign or positive if classified as either suspicious or malignant) will be compared with postoperative histopathological findings (negative if classified as normal or positive if classified as dysplasia [PanIN 1A-3] or invasive adenocarcinoma). When appropriate, location and diameters of tumors will also be noted.

In order to determine the likelihood of our ability to detect a measurable outcome in this study, an estimate of the incidence of pancreatic dysplasia/adenocarcinoma in the high-risk population is needed. Though the prevalence of PanIN lesions as well as their natural history are unknown, the overall incidence of pancreatic adenocarcinoma in the general population is 8.8 in 100,000. There is a 2.8- to 18-fold increase in the risk of pancreatic cancer in patients with a positive family history and the relative risk in those with an inherited cancer syndrome is 10-100 fold that of the general population. The low incidence of pancreatic adenocarcinoma, even within the high-risk population, prevents the likelihood of large numbers of patients who will be able to provide the gold standard of surgical pathology for our primary outcome. In addition, the number of high-risk patients eligible for screening is also relatively limited. Thus, the sample size for this study will be determined primarily by the volume of patients seen at our three recruiting sites. It is estimated that approximately 60 patients can be recruited over a year period. With this sample size, to achieve 90% power that at least one case of pathologically-confirmed pancreatic dysplasia/neoplasm will be detected, the prevalence of pancreatic dysplasia/neoplasia will need to be at least 4% in the high-risk patient population.

$$\frac{\text{Log } \beta}{\text{Log } (1\text{-}p)} = N$$ where $1-\beta$ = power, p = prevalence of disease, N = sample size

Secondary analysis will include sensitivity, specificity, positive predictive value, and negative predictive values of S-MRCP. For secondary outcomes, negative ERCP and surgical pathology will be considered as indicative of no clinically significant pancreatic lesions present.

3. Study Procedures

Each of the 25 recruited subjects will undergo screening examinations with both S-EUS and S-ERCP. If either of these examinations demonstrate abnormalities, ERCP will be performed. Biopsies or secretions may be collected during ERCP at the discretion of the endoscopist.

Imaging procedures will be performed according to the following protocols:

a) MRI: All MR images will be obtained with a 1.5T superconducting magnet using a body array coil for signal reception and the standard body coil for signal transmission. All images will be obtained in a single breath-hold. An initial signal shot fast spin echo sequence will be performed in three planes to localize the pancreas and pancreatic duct. Pancreatic architecture will be evaluated using high-resolution 3D LAVA (T1- and T2-weighted) pulse sequence. A thick slab signal shot fast spin echo spin sequence will be positioned to cover the entire pancreatic duct in the coronal-oblique plane. Next, unenhanced MR angiography will be performed with coronal oblique sections.

A three-dimensional MRCP including pancreas and duodenum will then be performed to recreate the pancreatic ductal system. Both coronal-oblique and 3D-image sequences will be performed prior to secretin administration and then once per minute during and following secretin infusion for a total of 10 minutes. The final sequences will be dynamic 3D LAVA and MR angiography following injection of 300 ml gadolinium contrast agent. 3D LAVA sequences will be performed in axial and coronal planes and MRA in coronal oblique sections.

Images will be analyzed on a GE Advantage Window computer workstation by two independent radiologists. MRI will be analyzed for any masses or changes in pancreatic texture/architecture. When appropriate, the specific size and location of any abnormalities will be specified. In addition, the signal intensity pattern of the lesions (ie hyperintense, hypointense, or isointense as compared with adjacent pancreatic parenchyma) for the different sequences will be determined. MRCP images will be interpreted and assessed for the presence of pathological features of the common bile duct, pancreatic duct, and side branches. The presence of dilatations, stenoses, or obstructions will be recorded.

b) EUS: EUS will be performed following the administration of standard sedative medication. Imaging of the pancreatic duct and parenchyma will be imaged using an Olympus EM-160 radial echoendoscope. The endoscope will be inserted until the second portion of the duodenum and images of the pancreas and surrounding structures will be acquired as the scope is withdrawn through the duodenum and stomach. The maximal diameter of the pancreatic duct at the level of the confluence of the splenic vein and superior mesenteric vein will be determined. Pancreatic ducts and parenchyma will be examined for abnormalities such as echogenic foci and hypoechoic nodules. If such abnormalities are found, EUS-guided fine-needle aspiration will be performed through the esophageal, gastric or duodenal wall. All EUS images and all FNA specimens will be analyzed by endoscopists and pathologists who are blinded to all patient identifiers, other than increased genetic risk for pancreatic cancer.

c) ERCP: ERCP will be performed under conscious sedation by an endoscopist experienced in ERCP and using standard protocol. An Olympus diagnostic endoscope will be passed to the second part of the duodenum until the papilla is visualized. Cannulation with a papilla will be conducted utilizing a standard catheter, followed by injection of L-lysinamidotrizoate (Peritrast) to visualize the pancreatic and biliary ductal systems. ERCP will be examined for abnormalities of the major ducts (obstruction, strictures), small/side ducts (nobbing/irregularities) and parenchyma (fat atrophy, chronic pancreatitis).

4. Study Drugs or Devices

RG1068 (Synthetic Human Secretin, Repligen®).
Twenty-five patients will each undergo an S-MRCP and an S-EUS evaluation, at a dose of 0.2 ucg/kg per exam. Each study will require 16-32 ucg of secretin (1-2 vials).

5. Study Questionnaires

None

6. Study Subjects

Inclusion criteria:

1. 18 years of age and older.
2. At least two first- or second-degree relatives with pancreatic adenocarcinoma (diagnosed at an age 10 years or less than the study patient).

3. Fulfills criteria or has undergone genetic testing which confirms BRCA1, BRCA2, Familial Atypical Multiple Mole Melanoma, Peutz-Jeghers, HNPCC, Hereditary Pancreatitis, or ataxia-telangiectasia.

Exclusion criteria:

1. Any contraindication to MRI, including but not limited to implanted metal devices (e.g. pacemaker, berry aneurysm clips, neural stimulator or cochlear implants).
2. Known pancreatic malignancy or dysplasia.
3. Pregnancy
4. History of sensitivity to secretin.
5. Unwillingness or inability to provide informed consent.

7. Recruitment

Subjects will be recruited through a high-risk gastroenterology program at the Columbia University Medical Center One of the study investigators will obtain consent using Columbia University Medical Center IRB approved consent forms, which will be signed to indicate the participants' consent.

8. Confidentiality of Study Data

Confidentiality will be protected using standard CUMC clinical protocol procedures outlined by the CUMC IRB and HIPAA.

9. Potential Risks

Potential risks of MR imaging are minimal and include potential claustrophobia during examination. Synthetic human secretin product (RG1068) has been evaluated in FDA phase 1 trials and has demonstrated very few adverse effects. The only rare reported risk has been transient hypotension.

This is otherwise an observational study in which no additional procedures, tests or interventions will be requested as a result of study enrollment.

Discomfort of EUS is limited to that associated with the endoscopic procedure, including gagging from passage of the endoscope, feeling of distension from air introduced into stomach, and a tugging sensation from passage of scope from the stomach into the duodenum. Potential complications include those for standard EUS with fine needle aspiration. These are rare and include perforation of bowel, reaction to medications, infection, and bleeding. The overall complication rate for EUS is less than 1%. Similar risks exist for ERCP; in addition, this procedure carries a small but significant risk (between 2-30%) of post-ERCP pancreatitis.

Pancreatectomy is major surgery that usually requires extended hospitalization. The mortality rate for pancreatectomy has improved in recent years to 5-10%, depending on extent of surgery and experience of the surgeon. A study of 650 patients at Johns Hopkins Medical Center, found that only nine patients, or 1.4%, died from complications related to surgery. At Columbia University Medical Center, the mortality from pancreatic resection is 0.7%, well below the national average. There is still, however, a fairly high risk of complications following any form of

pancreatectomy. The Johns Hopkins study documented complications in 41% of cases. Potential complications include postoperative bleeding, infection, or anastomotic leaks. Following pancreatic resection, patients can also experience delayed gastric emptying (19% of patients in the Johns Hopkins study) and pancreatic exocrine/ endocrine insufficiency.

10. Potential Benefits

Subjects enrolled in this study are at increased rate of pancreatic cancer and participation in this pilot screening study may lead to earlier detection and increased risk of cure for pancreatic precancerous or cancerous lesions. Beyond any direct benefits to the participants, results from studies will give us insight on how to more effectively diagnose and screen patients at increased genetic risk of adenocarcinoma. In addition, these findings may help refine surveillance methodology that can be utilized in the general population.

11. Alternatives

Alternatives to participating in this study would be to not have screening for pancreatic lesions, or to be assessed by more readily available technologies, (CT, ultrasound). Some medical centers are also utilizing regular EUS as surveillance for patients with familial risk of pancreatic cancer.

12. Risks

Alternatives to participating in this study would be to not have screening for pancreatic lesions, or to be assessed by more readily available technologies as described above.

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