Long Term Surveillance of Intraductal Papillary Mucinous Neoplasms
The Potential of Cyst Growth Rate to Predict Malignant Transformation

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A. Study Purpose and Rationale

The frequency of incidental pancreatic cyst findings during cross-sectional imaging has increased greatly over the last 15 years as the quality of imaging studies has improved. Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are potentially malignant epithelial neoplasms within main or branch ducts that are grossly visible and composed of mucin-producing columnar cells. They are associated with cyst formation, varying degrees of cellular atypia, and a time dependent longitudinal risk of malignancy.

While the risk of carcinoma in situ or invasive carcinoma in main duct IPMNs is established as approximately 70%[i], there exists conflicting data about the rate of malignant transformation in branch duct IPMNs. Studies cite ranges of 2-6% at 40 months[iiiii] and 10-40% at five years[iv], confirming the time dependent longitudinal risk of malignancy, however offering little consensus. Established predictors for malignancy in branch duct IPMNs include size (tumor diameter > 3 centimeters), older age, male gender, presence of symptoms, and presence of concerning radiographic features such as solid components, pancreatic ductal dilatation > 10 millimeters, or lymphadenopathy[vvi]. While not fully established as a risk factor, an increase in cyst size during follow-up has also been considered to be predictive of malignancy by many experts[iv].

Because of the high risk of malignant transformation, surgical resection via pancreaticoduodenectomy is recommended for all main duct IPMNs with ductal dilatation greater than 10 millimeters. Resection is likewise recommended for all branch duct IPMNs with such high risk stigmata as size greater than 3 cm, main duct dilatation greater than 10 millimeters, thick cyst walls, or mural nodules. For branch duct IPMNs that do not meet criteria for surgical resection, the Sendai Consensus Guidelines dictate interval surveillance according to size: 12 months for lesions less than 10 millimeters, 6-12 months for lesions 10-20 millimeters, and 3-6 months for lesions greater than 20 millimeters. Computed tomography (CT) using a pancreatic protocol or magnetic resonance cholangiopancreatography (MRCP) are typically used to follow patients. Data suggests the Sendai Consensus guidelines are highly sensitive for malignancy (95-100%) but less specific (25-30%). If there are no changes in the IPMN lesion within two years of follow-up, experts agree the surveillance interval can be lengthened – the amount by which, however, has not been established.

In an effort to better identify potential risk factors for malignant transformation in branch duct IPMNs initially selected for observation, this study will examine the initial rate of IPMN growth over a period of 12 months in patients with greater than five years surveillance. The hypothesis of this study is that IPMNs that exhibit growth over a period of 12 months are more likely to undergo malignant transformation at five years. The clinical implications of this study include a possible role for aggressive interventions in IPMNs that exhibit rapid growth during initial follow-up, including but not limited to early resection.

B. Study Design and Statistical Analysis

This study is retrospective and observational. It will identify a cohort of patients over the age of 18 who had (1) pancreatic cystic lesions identified by cross-sectional imaging between 2000 and 2014, and (2) interval follow-up by EUS, MRCP, or CT. Each chart will be retrospectively reviewed to identify patient demographics, baseline pancreatic cyst features (diameter, wall thickness, presence

of mural nodules), and interval cyst progression at six months, twelve months and five years (changes in diameter/wall thickness, quantity of mural nodules). An endpoint (surgery to remove the neoplasm(s), progression to malignancy, or the last imaging follow-up) will be identified for each patient in the study.

Based on the known number of pancreatic cysts diagnosed by cross-sectional imaging at Columbia University Medical Center since 2000, this study will aim to enroll 250 patients with documented branch duct IPMNs and greater than five-year follow-up by EUS, MRCP, or CT. Assuming a 10% rate of malignant transformation at five years based on the available literature, this study will hypothetically include 25 cases with documented cyst enlargement over 12 months and 225 controls with no evidence of cyst growth. Effect size will be expressed as the change in cyst diameter (in millimeters) per periods of 12 months. Power analysis using a paired t-test reveals a statistically significant difference of .6 standard deviations at a power of 80% and P=.05. Assuming a standard deviation of 4 millimeters/year, this study is powered to detect an effect size of 2.4 millimeters/year absolute change in cyst diameter.

C. Study Procedure

First, the Columbia University Medical Center radiology and endoscopy databases will be queried for reports containing the terms "intraductal papillary mucinous neoplasm, " "IPMN," and "pancreatic cysts." Second, the computerized records of all patients who had pancreatic cystic lesions identified by cross-sectional imaging between 2000 and 2014 will be cross-referenced to computerized records of patients who were found to have a pancreatic cyst that was followed for at least five years. Third, a thorough review of each patient's chart and imaging will identify pancreatic cyst characteristics and diameter at different intervals, as described in the study design. The progression of cyst growth will be documented and the incidence of malignant transformation at five years noted. This study will determine whether change in cyst diameter over a period of 12 months is associated with an increased risk of malignant transformation at five years follow-up.

D. Study Drugs

There are no drugs involved in this study.

E. Medical Device

There are no devices involved in this study.

F. Study Questionnaires

There are no questionnaires involved in this study.

G. Study Subjects

Inclusion criteria:
- All patients age >18 with:
    - Pancreatic cysts found on cross-sectional imaging (EUS, MRI, CT), and
    - Follow up time of at least five years from diagnosis

Exclusion criteria:
- Patients with known pancreatic adenocarcinoma.
- Patients with previous pancreatic surgery.
- Patients with history of pancreas transplant.

H. Recruitment of Subjects

Study subjects will be identified by reviewing existing medical records. No additional procedures will be performed and patients will not be contacted. No active recruitment is needed.

I. Confidentiality of Study Data

Research data will be obtained from medical records at Columbia University Medical Center. All patient identifiers will be removed and all study data coded. Study data will be maintained only on password-protected and/or encrypted computers and accessible only to the investigators.

J. Potential Conflict of Interest

There are no conflicts of interest to be disclosed.

K. Location of the Study

Research data will be obtained from medical records at Columbia University Medical Center using the same computer system as that used for clinical purposes.

L. Potential Risks

This study involves chart review. There is no more than minimal risk to the subjects.

M. Potential Benefits

On an individual level, there will be no immediate benefit to patients participating in this study. On a societal level, the implication that IPMNs that exhibit growth over a short time period of twelve months are more likely to undergo malignant transformation may alter screening guidelines and necessitate earlier aggressive intervention. However, if there is no significant change in cyst size over 12 months and consecutive interval imaging, long-term screening guidelines may be relaxed and extended, thereby reducing the amount of imaging procedures, cost, and radiation exposure.

N. Alternative Therapies

There are no therapies involved in this study.

O. Compensation to Subjects

There is no compensation offered in this study.

P. Costs to Subjects

Subjects will not incur any additional costs as a result of participating in this study.

Q. Minors as Research Subjects

This study does not involve participation of minors. All subjects must be over age 18.

R. Radiation or Radioactive Substances

There is no radiation or radioactive substances involved in this study.

[i] Tanaka M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology*. 2006; 6(1-2): 17.

[ii] Lafemina J, et al. Malignant progression in IPMN: a cohort analysis of patients initially selected for resection or observation. *Ann Surg Oncol.* 2013 Feb;20(2):440-7.

[iii] Ohno E, et al. Malignant transformation of branch duct-type intraductal papillary mucinous neoplasms of the pancreas based on contrast-enhanced endoscopic ultrasonography morphological changes: focus on malignant transformation of intraductal papillary mucinous neoplasm itself. *Pancreas.* 2012 Aug;41(6):855-62.

[iv] Kang M, et al. Cyst growth rate predicts malignancy in patients with branch duct intraductal papillary mucinous neoplasms. *Clin Gastroeneterol Hepatol*. 2011; 9 (1):87.

[v] Sugiyama M, et al. Predictive factors for malignancy in intraductal papillary-mucinous tumors of the pancreas. *Br J Surg.* 2003;90(10):1244.

[vi] Schmidt CM, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. *Ann Surg.* 2007;246(4):644.