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Surgery versus surveillance among patients with incidental, low- to medium-risk pancreatic cysts: a randomized trial

A. Study purpose and rationale

The rise of high definition cross-sectional imaging by CT scan or MRI has led to the discovery of increasing numbers of asymptomatic pancreatic cysts[i] but the best management of these cysts is not clear. A minority of cysts may harbor malignancy but autopsy studies have suggested that the majority of cystic lesions of the pancreas are benign[ii, iii] with incidental cysts occurring in up to 50% of older patients at autopsy after an unrelated death.[iv] Non-invasive imaging is unable to accurately differentiate malignant from benign lesions. Invasive diagnostics, primarily endoscopic ultrasonography with fine-needle aspiration (EUS-FNA) may add further information about cyst characteristics but is also frequently non-diagnostic. As a result, the best algorithm for the diagnosis of malignancy in pancreatic cysts remains undefined[v, vi] and optimal management is unclear.

Current practice is idiosyncratic and based on observational data from the era before widespread cross-sectional imaging.[vii] High risk lesions are resected or, if unresectable, the patient is considered for palliative therapy. When patients with low- to medium-risk lesions are operative candidates, they are often referred for consideration for EUS-FNA. Endoscopy is performed to look for high risk cyst features. Sensitivity and specificity of EUS-FNA for malignancy is imperfect but accepted high-risk features include dilated main pancreatic duct or mural nodules on EUS, elevated cyst fluid chorioembryonic antigen (CEA), and cyst fluid cytology showing atypical or malignant cells.[viii] Guidelines suggest that patients with these features should be referred for surgery. In the remaining patients, both surgery and surveillance are considered reasonable.[ix] When surgery is selected, definitive diagnosis is not available until post-operatively and pancreaticoduodenectomy (Whipple) procedure is frequently necessary to remove the lesion.[x, xi] When surveillance is selected, standard of care is non-invasive imaging (MRCP or CT scan) or EUS every 6 months to reassess for interval development of high risk features.[xii] Thus, among patients with low- to medium-risk pancreatic cysts, the current approach attempts to individualize care, carefully balancing the unknown risk of monitoring a cyst that may progress into lethal malignancy against the significant morbidity of an extremely complicated surgery.

Prior studies have retrospectively examined the strategies of surgery versus surveillance. A series of 256 patients who underwent resection for cystic lesions of mixed risk and median size from 2-3cm had one peri-operative death and 6 of 256 (2%) lesions containing adenocarcinoma.[xiii] A retrospective series of 81 patients who selected surveillance for low risk branch duct cystic lesions with median size 1-2cm showed 6 patients who went on to develop high risk features with 6/6 resected lesions benign.[xiv] Another retrospective series of 71 patients who selected surveillance for low risk main or branch duct IPMNs with median size 1-2cm showed 69 of 71 patients living after 3-4 years follow-up, with the 2 deaths judged to be unelated.[xv] It is difficult to compare these studies because they involve different populations and are retrospective; nonetheless, the low rates of adenocarcinoma in surgical series and high survival among patients selecting surveillance have led many experts to suggest that more patients may be appropriate for surveillance. There are several ongoing prospective studies of surveillance but, to our knowledge, no ongoing randomized trials.

This trial seeks to add clarity to the question of optimal management for patients with incidental, low- to medium-risk pancreatic cysts. We will randomize patients to surgery versus surveillance and prospectively follow patients who will not consent to randomization. The primary outcome will be mortality assessed after 2 years of follow-up. Secondary outcomes will be quality of life, function, and maintenance of pre-enrollment weight. Rate of progression to surgery will be assessed among participants randomized to surveillance.

B. Study design and statistical analysis

1. Recruitment
Recruitment will take place in the endoscopy suite among surgical candidates referred to a gastroenterologist for EUS-FNA. Consenting participants will be randomized 1: 1 via computer after non-invasive imaging but before endoscopy. (Pre-endoscopy randomization will be done to minimize possible selection bias – for example, the endoscopist might otherwise report high risk features in patients in whom surgery was preferred.) If endoscopy shows no high risk features, randomization envelopes will be opened and participants randomized to surgical referral versus surveillance.

2. Participant requirements
At 6, 12, and 24 months all participants will be asked to complete a short questionnaire related to health and general well being, the SF-36. They will be weighed at every clinical visit. No additional clinic visits will be required as part of study participation.

3. Statistical methods
Using a chi-squared approximation of Fisher's exact test that includes the continuity correction, we project n=240 participants needed for 80% power to detect $p < 0.05$ at two-year mortality rates of 12% for surveillance versus 2% for surgery. The 10% mortality benefit is selected as the minimal clinically significant difference necessary to justify the high morbidity of pancreatic surgery. Secondary outcomes of SF-36 score and weight changes will be analyzed as continuous variables with T-tests.

C. Study procedure

1. EUS-FNA
Prior to inclusion but after randomization, all patients will undergo EUS-FNA for better risk stratification of cysts. This is the current standard of care and EUS-FNA will be undertaken only among patients who had already been selected for the procedure rather than as part of the study itself. This is an endoscopic procedure that may involve general anesthesia. FNA will be performed when cysts are accessible; when FNA is performed, a single dose of prophylactic antibiotics will be given. Possible complications of EUS-FNA include infection, bowel perforation, sepsis, and death.

2. Surgical procedure
Surgical procedure and technique will be at the discretion of the surgeon. Patients will require general anesthesia and prophylactic antibiotics. Lesions in the tail of the pancreas may be resectable endoscopically. Lesions in the body or head of the pancreas will likely require laparotomy and up to half of patients may require pancreaticoduodenectomy (Whipple) procedure. Possible short-term complications of surgery include infection, abscess, biliary or pancreatic duct leak, sepsis, and death. Possible long-term complications of surgery include gastroparesis, weight loss, steatorrhea, and chronic pancreatitis. Pancreatic surgery is best performed at a high volume center such as CUMC.

3. Surveillance
Surveillance will be preferably via non-invasive imaging, either CT scan or MRI. In patients in whom non-invasive imaging is not possible -- for example, because elevated serum creatinine precludes use of intravenous contrast -- EUS will be used. Imaging will be conducted at 6, 12, and 24 months of follow-up and thereafter left to the discretion of the responsible physician. Patients who show interval development of high risk features will be referred for surgical evaluation. High risk features are growth of the cyst to over 3 cm in the largest dimension, dilation of the main pancreatic duct to more then 1.0 cm, or development of mural nodules.

D. Study drugs

Not applicable.

E. Medical devices

Not applicable.

F. Study questionnaires

Peri-operative mortality will be assessed from hospital records. Overall mortality will be assessed by a search of the social security death index. Participants will be asked to complete questionnaires at 6, 12, and 24 months of follow-up. Questionnaires will be mailed or given to subjects at appointments scheduled for usual care. If questionnaires are not completed within a reasonable time frame, participants will be telephoned as a reminder. The extensively validated SF-36[xvi] questionnaire will be used to assess general health and well being.

G. Study subjects.

The following table summarizes inclusion and exclusion criteria and are adapted from current guidelines.

Inclusion	Exclusion
18 to 75 years old	Serious comorbid condition
Surgical candidate	EUS characteristics
	Pancreatic duct 1 cm or more
	Intramural nodules
Low- to medium-risk cystic lesion of the pancreas	FNA or biopsy characteristics
	Bx showing malignancy
	Fluid CEA > 192 ng/cc
	Cytological atypia

More specifically, high cross-sectional imaging that would exclude patients would include lesion size > 3 cm, associated mass or other evidence of invasion, or metastatic disease. Serious comorbid conditions are those that would result in a life expectancy of under 10 years including congestive heart failure, severe obstructive or restrictive lung disease, end-stage renal disease, advanced cancer, advanced or uncontrolled AIDS, pancreatic insufficiency, and end-stage liver disease. Patients with jaundice or ascites will be assumed to have malignancy or other serious coexisting disease and will not be considered for the study.

H. Recruitment of subjects

Informed consent will be obtained among adult patients 18 to 75 years old and referred for consideration for EUS-FNA of incidental, low- to medium-risk pancreatic cysts. Recruitment will take place in the CUMC endoscopy suite. A study coordinator will assist participants with the forms and a gastroenterologist will be available to explain the study and all procedures and to answer questions. Patients reluctant to be randomized will be offered to be followed as study participants without randomization.

I. Confidentiality of subject data

Participants will be randomly assigned a code number and participant data will be stripped of all personal identifiers and stored by code number on a password-protected computer. Only IRB-approved study investigators will have access to the computer.

J. Potential conflict of interest

There are no conflicts of interest.

K. Location of the study

The study will be based at Columbia University Medical Center, Milstein Hospital Building, 177 Fort Washington Avenue, New York, NY, 10032. Recruitment of subjects and endoscopy will take place in the CUMC endoscopy suite in the Irving Pavilion, 161 Fort Washington Avenue.

L. Potential risks

The potential risks of surgery are described above and include sepsis and death. Peri-operative mortality rates range from 1 to 20%; rates at high volume centers such as CUMC are at the low end of this range.[xvii] The potential risks of surveillance include progression to lethal malignancy.

M. Potential benefits

All potential benefits would also be available without participation in the study. Long-term, participants may directly or indirectly benefit from knowledge gained about management of these lesions.

N. Alternative therapies

Non-participation is an option. Both surgery and surveillance are available to patients who do not desire randomization.

O. Compensation to subjects

Subjects will not be compensated for participation.

P. Costs to subjects

There will be no costs to subjects.

Q. Minors as research subjects

No one less than 18 years old will be recruited into this study.

R. Radiation or radioactive substances

Not applicable.

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