

ORIGINAL ARTICLE

## Determining the natural history of pancreatic cystic neoplasms: a Manitoban cohort study

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### Abstract

**Background:** Most pancreatic cystic neoplasms (PCN) are thought to harbor a low malignant potential. This historical cohort study attempts to describe the natural history of these lesions in a provincial cohort, to assess the safety of non-surgical management. Pathological diagnosis of malignancy was the primary outcome measure of interest.

**Methods:** All adult patients (age 18+) with PCN seen between 2000 and 2012 by the two main institutions in Manitoba were included in this study. PCN were graded as high and low risk, which dictated initial treatment plan (surgery or observation). Predictors of initial surgical treatment, delayed surgery in the observation group and the clinical/radiological predictors of malignancy were determined.

**Results:** 497 patients were included in this study. 43 (8.7%) high-risk lesions underwent initial surgery, with 13 (30.2%) cases of malignancy discovered. 450 (90.5%) low-risk cysts were observed for a median of 17.3 months (range: 0.00–142.3). 29 (6.4%) cases of delayed surgery occurred, with malignancy discovered in five (17.2%).

**Conclusions:** This study supports current selection criteria for management of PCNs. Due to the low incidence of malignancy in low-risk PCN, it appears that long-term observation is safe and should be the treatment modality of choice in the absence of high-risk features.

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### Introduction

Intraductal papillary mucinous neoplasms (IPMN's) of the pancreas are a relatively newly discovered entity, having first been described in 1982.<sup>1</sup> With the rapidly increasing resolution of modern computed tomography (CT) and magnetic resonance imaging (MRI) technology, these lesions are being detected with dramatically increasing frequency. In recent series, cystic lesions of the pancreas were incidentally discovered in 1.2%–2.6% of all CT or MRI scans being done.<sup>2,3</sup> Many of these cysts will prove to be IPMN's. This entity is expected to consume an ever-increasing amount of healthcare resources in the near future.

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It is well recognized that some of these lesions will harbor either in situ or invasive malignancy at the time of diagnosis, and the remainder carry a definite risk of malignant transformation in the future.<sup>3–6</sup> On the other hand, there does appear to be a subset of IPMN's in which the risk of malignant transformation is low. Given that the potential morbidity and mortality of major pancreatic surgery is high, there is likely a threshold below which the risk of malignant transformation in an IPMN is low enough to justify a watchful waiting approach. The dilemma facing hepatobiliary surgeons is to determine which of these IPMN's are truly low risk and may be safely observed and which lesions are high risk and therefore should proceed to surgery to remove malignancy or to prevent it from developing. Although much remains to be learned about these lesions, the body of knowledge is increasing. Current consensus guidelines, divide imaging

characteristics as either “high risk” (solid enhancing components and dilated pancreatic duct of more than 10 mm and obstructive jaundice) which are absolute indications for resection, or “worrisome” (including cyst size  $\geq 3$  cm, thickened walls and pancreatic duct dilatation of 5–9 mm), for which more conservative management is suggested.<sup>7</sup> This reflects a change from the previous criteria, which included cyst size  $\geq 3$  cm as an absolute indication for surgery.<sup>8</sup>

The safety of a non-operative approach to “low risk” side branch IPMN’s remains controversial. In part, this is because the natural history of such lesions is largely unknown. The available literature is not yet mature due to the recent appreciation of this entity.<sup>1</sup> Many authors advocate a selective approach to resecting side-branch IPMN’s and follow small lesions without other worrisome features, reporting a risk of either in situ or invasive malignancy in such low risk lesions of 3% or less.<sup>9–11</sup> This approximates the risk of operative mortality with major pancreatic resection. There are others who have recommended a more aggressive surgical approach.<sup>12,13</sup>

Although “low risk” IPMN’s make up the majority of new cases that are diagnosed, these lesions are premalignant and carry a real risk of malignant transformation. It is this risk that must be weighed against the potential morbidity and mortality of major pancreatic surgery.

## Objectives

The primary objective of this study was to describe the natural history of these cysts on a population basis. A secondary objective was to determine the rate of malignancy over time in the group of patients with “low-risk” lesions initially selected for observation in order to evaluate the safety of non-surgical management of these lesions.

## Hypothesis

It was believed that the Sendai criteria<sup>7</sup> would be appropriate for clinical decision-making guidelines with the Manitoba cohort and that small (<3 cm) side-branch IPMN’s without worrisome findings such as mural nodules, solid components or enhancement could be safely followed.

## Methods

Ethics approval for this study was obtained from the Health Research Ethics Board at the University of Manitoba.

This was a historical cohort study, consisting of patients with known or suspected cystic pancreatic neoplasm. Patients with suspected pancreatic pseudocysts were excluded based on clinical factors such as presentation with acute pancreatitis and imaging features consistent with pseudocysts that evolved over time. These diagnoses were based on the expert opinion of local radiologists and of the involved gastroenterologists or hepatobiliary surgeons. All other adult patients (age 18+) seen with pancreatic cystic neoplasms by the Hepatobiliary and Pancreatic Surgery Unit or

the Endoscopic Ultrasound and Pancreaticobiliary Endoscopy Unit at the University of Manitoba, between the period of January 2000 and December 2012, were eligible for inclusion in this study.

Patients were identified using clinic records and billing data for the specified period. This study used a historical cohort’s previously recorded demographic and clinical information to record patients’ diagnostic imaging findings and clinical status. Baseline statistics included patient comorbidities, which were standardized and graded using the Charlson Comorbidity Index (CCI).<sup>14</sup> The initial presentation and workup of the cystic lesions separated the cohort into those with high and low risk lesions. This distinction had been used clinically to determine which patients would be observed and which required immediate surgery.

The primary outcome measure was the rate of malignancy as defined by the presence of either invasive carcinoma or carcinoma-in-situ (CIS). This was determined by the final pathology. Patients were analyzed according to the initial treatment decision of either immediate surgery or observation. Pancreatic duct size was analyzed as over 6 mm and over 10 mm. Cyst size was also analyzed. Predictors of surgical treatment, predictors of malignancy among patients selected for immediate surgery, and predictors of delayed surgery amongst patients selected for initial non-operative management were determined. Postoperative complications were graded according to the classification system published by Dindo *et al.*<sup>15</sup>

Patient follow-up was at the discretion of the treating physicians, generally, this consisted of annual CT or MRI’s for small lesions without worrisome features, and every six to twelve months for lesions larger than 1 cm. Lesions larger than 2 cm were usually assessed by EUS for worrisome features not identified on CT or MRI; with serial EUS examinations at the discretion of the treating physicians.

Statistical analysis was performed using IBM SPSS Statistics (Armonk, NY: IBM Corp) and included numbers/proportions for categorical variables, and mean  $\pm$  standard deviation (SD) for continuous variables. Categorical variables were compared using either Pearson’s Chi-square test or Fisher’s exact test, when appropriate. Continuous variables were compared using either t-test or Mann–Whitney U test, depending on the distribution of the data. The long-rank test was used to compare survival curves analyzed by Kaplan–Meier survival analysis (Product-limit method). The multivariate analyses for categorical variables were done using logistic regression modeling, while Cox’s proportional hazard multivariate models were used in the case of time-to-failure analyses. For all analyses,  $p < 0.05$  was considered statistically significant.

## Results

A total of 496 patients diagnosed with pancreatic cystic neoplasms were included in this study. The majority of these patients were female (325, 65.4%) and the mean age at diagnosis was 65.2 years (SD = 13.3 years).

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