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Natural history of patients followed radiographically with mucinous cysts of the pancreas

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Abstract

OBJECTIVE—The aim of this study was to evaluate the outcome of patients presumed to have mucinous cysts of the pancreas who were initially selected for radiographic surveillance.

METHODS—Patients with a pancreatic cyst and a measured cyst fluid CEA 192ng/mL were included. Patients were stratified by those who underwent initial resection, and those who were recommended for radiographic surveillance. The natural history of these two groups was examined.

RESULTS—From 1999–2014, 227 patients were identified who had a cyst fluid CEA 192ng/mL (median 961, range 192–300,000ng/mL). Immediate resection was performed on 63 patients (28%). Initial radiographic surveillance was recommended for 164 patients; 87% did not have main pancreatic duct dilation, and 87% met consensus criteria for radiographic surveillance. After a median follow-up of 56 months, 48 of the 164 patients (29%) had undergone resection. Ultimately, there were three cases (2%) of high-grade dysplasia, and two cases of invasive carcinoma (1%) within these 164 patients selected for observation. Three of the five cases of either high-grade dysplasia or invasive carcinoma were among the 22 patients followed outside of consensus guidelines.

CONCLUSIONS—Appropriately selected patients with mucinous pancreatic cysts can be safely followed with serial surveillance with a low risk of malignant progression.

Keywords

pancreatic cystic neoplasm; intraductal papillary mucinous neoplasm; mucinous cyst; pancreatic cyst

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Introduction

Cystic neoplasms of the pancreas are an increasingly recognized entity^{1–4}. This rising incidence is largely due to the increased use of high-resolution cross-sectional imaging, with many lesions found in otherwise asymptomatic patients during the work-up of other disease processes^{5–9}. Pancreatic cystic neoplasms encompass a wide range of lesions, ranging from benign to malignant. Within the group of cystic neoplasms, intraductal papillary mucinous neoplasms (IPMN) and the less common mucinous cystic neoplasm (MCN) require special consideration because they are considered premalignant, and usually require either resection or active surveillance. The most accurate test to discriminate between precancerous mucinous cysts and benign cystic neoplasms is cyst fluid carcinoembryonic antigen (CEA) level. When this level is greater than or equal to 192 ng/ml, the likelihood of the lesion being mucinous on endoscopic and/or surgical pathology is >90%^{10–13}.

Currently, most guidelines recommend resection for all main-duct intraductal papillary mucinous neoplasms (MD-IPMN), defined as main pancreatic duct dilation >5mm, and any branch-duct IPMN (BD-IPMN) 3 cm or larger in maximum cyst diameter with high-risk radiographic features, such as an enhancing solid component or main pancreatic duct dilation greater or equal to 10 mm¹⁴. Patients with lesions not meeting the above criteria have been shown to be at a lower risk for malignancy and may be monitored with serial radiographic surveillance. Multiple sets of guidelines have been developed, and these have been constructed using the outcomes from resected, pathologically-confirmed patients^{4, 15–20}. The natural history of patients with presumed mucinous cysts who undergo radiographic surveillance remains to be accurately characterized, particularly over a long-term period of follow-up.

The aim of this study was to examine and compare the natural history and disease progression of patients with presumed mucinous cysts (cyst fluid CEA ≥ 192 ng/mL) treated with immediate resection or initial serial surveillance.

Materials and Methods

Patients

This study was a single-center retrospective study of a prospectively-maintained database of patients diagnosed with pancreatic cysts who were evaluated at Memorial Sloan-Kettering Cancer Center (MSKCC) during a 15 year period (1999 to 2014). Patients were included in the MSKCC Pancreatic Cyst Registry if they were seen by either a gastroenterologist or surgeon and coded with a diagnosis of a pancreatic cyst (ICD-9 code 577.2). Patients included in this study had undergone EUS-FNA as part of their diagnostic work-up, either at MSKCC or an outside referring institution, with cyst fluid CEA levels ≥ 192 ng/mL, and had at least six months follow-up at our institution. This study was approved by the Institutional Review Board at MSKCC.

Patient demographic, radiographic, pathologic, operative, and follow-up data was collected. Immediate resection was defined as planned resection within six months of initial

radiographic diagnosis. International consensus guidelines were used to identify patients who were stratified to serial surveillance in accordance with these recommendations and those who were followed outside of these criteria. In general, resection was recommended for all MD-IPMNs and BD-IPMNs ≥ 3 cm with high-risk features on imaging, including solid component enhancement and main pancreatic duct dilation¹⁴. Post-operative complications were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 3.0²¹.

Radiologic and Pathologic Classification

Lesions were classified as main duct (MD), branch duct (BD), or mixed using radiographic imaging and pathology. MD-IPMNs had main pancreatic duct dilation >5 mm. BD-IPMNs had one or more cystic lesions without any main duct dilation. Mixed-type IPMNs demonstrated both cysts as well as main duct dilation. The maximum cyst diameter was defined as the largest dimension of the lesion being evaluated. If more than one lesion was being considered for treatment, the diameter of the largest lesion was recorded.

Resected specimens were classified by histopathologic sub-type. IPMN lesions were further characterized by highest level of dysplasia, as low, intermediate, high (including carcinoma-in-situ), and invasive. Microinvasive disease was included in the invasive group.

Statistical Analysis

Data analysis was performed using IBM SPSS version 22 and Microsoft Excel 2007. Patients were divided into two groups, those who underwent immediate resection versus initial serial surveillance. Chi-squared test was used to compare categorical variables and Mann-Whitney U test for continuous variables between these two patient groups. A p -value $<.05$ was considered significant.

Results

There were 2,326 patients who were initially identified from the MSKCC Pancreatic Cyst Registry, of which 280 patients had also undergone EUS-FNA with cyst CEA level ≥ 192 ng/mL. Fifty-three patients had a follow-up time at our institution of less than six months, and thus, 227 patients were ultimately selected for this study.

The median age at diagnosis was 65 years (range 29–85 years). The majority of patients did not have main pancreatic duct dilation (BD-IPMNs, 190/227, 84%). Twenty-six patients (11%) had MD-IPMNs, and 11 (5%) had mixed-type IPMNs. The median presenting main pancreatic duct size for MD-IPMNs was 2 cm (range .4–8 cm); the median presenting cyst diameter for BD-IPMNs was 2 cm (range .4–10.8 cm), and for mixed-type IPMNs 2.5 cm (range .7–7.5 cm). The median cyst fluid CEA was 979 ng/mL (range 192–300,000 ng/mL), and 56% of patients were asymptomatic. Patient demographics and presenting characteristics are summarized in Table 1.

Immediate resection was recommended for 63 patients (28%), and 164 patients (72%) were selected for initial serial surveillance. Within the group of 164 patients who were followed, 142 (87%) were followed in accordance with consensus guidelines. Reasons for surveillance

in those who met consensus criteria for resection included: initial treatment at an outside institution (n=8), significant medical comorbidities (n=6), patient refusal (n=5), and three were undergoing treatment for additional malignancies.

There were no differences between patients undergoing immediate resection and serial surveillance in age, gender, prevalence of active tobacco use, prevalence of diabetes mellitus, and cyst location (Table 1). There was no difference in the maximum diameter of MD-IPMNs but BD-IPMNs selected for immediate resection were larger in diameter than those recommended for surveillance ($p < .001$). Patients selected for immediate resection were more frequently symptomatic ($p = .01$), with abdominal pain as the most common complaint, and had higher cyst fluid CEA levels ($p = .01$). Patients with BD-IPMNs were more likely to be stratified to initial surveillance ($p = .02$). All 14 patients with active concurrent malignancies were stratified to the initial surveillance group. Comparison of these two treatment stratification groups is represented in Table 1.

The majority of patients who underwent initial resection underwent distal pancreatectomy with or without splenectomy (55 patients, 50%) or pancreaticoduodenectomy (37 patients, 33%). In the group of 63 patients who underwent immediate resection, 46 (73%) had mucinous cysts on pathologic examination, of which 33 had IPMNs and 13 had mucinous cystic neoplasms. High-grade dysplasia was present in three patients (9%), intermediate-grade dysplasia in 20 patients (61%), and low-grade dysplasia in 10 patients (30%). There were five cases of invasive carcinoma within this group of 63 patients (Figure 1). Other notable pathologies included five retention cysts (cyst fluid CEA range 1,428–60,000 ng/mL), one acinar cell cystadenoma (cyst fluid CEA 487 ng/mL), four benign simple cysts (cyst fluid CEA range 428–19,000 ng/mL), and two cases where no cystic lesion was identified.

The median follow-up at our institution for all patients was 56 months (range 6–171 months). Majority of patients (152/227, 67%) had more than 3 years of follow-up and nearly half of our study patients (107/227, 47%) had more than 5 years of follow-up. During this follow-up period, 48 of the 164 patients (29%) initially stratified to serial surveillance came to resection after a median of 22 months (range 7–146 months). Most common indications for resection in this group were radiographic changes in 69% (increasing cyst size, new or increasing main pancreatic duct dilation, new solid component) or subsequent repeat EUS-FNA demonstrating malignant or suspicious cytology (27%).

In the group of 48 patients who underwent resection after an initial period of surveillance, 38 (79%) had mucinous cysts on pathologic examination, of which 30 were IPMNs and eight were mucinous cystic neoplasms. High-grade dysplasia was present in 3 patients (10%), intermediate-grade dysplasia in 20 patients (67%), and low-grade dysplasia in 7 patients (23%). There were two cases of invasive carcinoma within this group of 48 patients (Figure 1). Both patients had developed concerning radiographic changes which prompted resection, including vessel abutment and new pancreatic duct dilation. Other notable pathologies included three retention cysts (cyst fluid CEA range 445–1,014 ng/mL), two pancreatic neuroendocrine neoplasms (cyst fluid CEA 354 ng/mL and 932 ng/mL), one microcystic

serous cystadenoma (cyst fluid CEA 218 ng/mL), and one squamoid cyst (cyst fluid CEA 2,136 ng/mL).

There were no post-operative mortalities following resection. There were 13 grade 3 adverse events that occurred in 11 patients (10%). Grade 3 complications included five pancreatic fistulae or leaks, four intra-abdominal fluid collections, one intestinal fistula, one gastrointestinal bleed, one case of metabolic acidosis requiring transfer to the intensive care unit, and one myocardial infarction. There were no grade 4 adverse events.

Among all patients in this study who underwent resection (n=111), at a median follow-up time of 38 months (range 0–152 months) from date of resection, two patients had developed IPMN-associated carcinoma and one patient developed non-IPMN-associated pancreatic adenocarcinoma in the pancreatic remnant. None of these three patients had high-risk pathologic lesions from the initial resection; two had IPMNs with intermediate-grade dysplasia, and one had a mucinous cystadenoma. One additional patient in the surveillance group who never underwent resection also developed non-IPMN-associated pancreatic ductal adenocarcinoma, at a separate site from the IPMN lesion that was being followed (Table 2).

Discussion

This study captures a longitudinal perspective of patients who presented with presumed mucinous cysts of the pancreas, with particular focus on those with lesions of low malignancy risk who were initially stratified to serial surveillance. This is a unique subset of the IPMN population for whom the risk of malignant transformation must be carefully weighed against the risks of operative resection. In particular, the long-term safety and potential failures of this follow-up strategy have yet to be accurately defined and quantified.

As the understanding of the pathogenesis of IPMNs evolves and the risk factors associated with malignancy are more clearly delineated, the management of IPMNs has trended away from routine resection towards non-operative management in select patients with low predicted risk of malignancy. Current consensus guidelines establishing the criteria for resection is based on cumulative reports of resected patients¹⁴. Resected patients, by nature of having undergone resection, tend to have lesions with high-risk or worrisome features. It is unknown if the disease progression and natural history of these patients can be applied to the remainder of patients with IPMN who lack these concerning features and may never reach resection.

Our current study is unique as it is the largest study to describe the actual risk of malignant progression in the group of patients with presumed mucinous cysts. In addition, it is our institutional practice to maintain long-term active surveillance on these patients regardless of resection status, and therefore longer term follow-up data are available. In expanding our study population to all patients with a presumed diagnosis of a mucinous cyst on initial presentation, this appropriately reflects the real-life heterogeneity in disease pathology that is encountered by a pancreatic specialist.

In the present study, 142 of the 164 patients who underwent initial conservative management with serial radiographic imaging were managed in accordance with consensus guidelines, of which only 1% developed lesions with high-grade dysplasia or invasive components after a median follow-up of 64 months. This is a much lower rate of invasive disease than reported in other published series, which have ranged from 8% to 40%^{17, 20, 22–26}. This is likely due to our focus on a low-risk study population, and the fact that some of these patients do not have IPMN. Only 16% of our patients had MPD involvement, compared with 34% to 70% in other series^{17, 20, 22, 25, 26}. In addition, all patients in our study had undergone EUS-FNA, which is often only offered in patients with lesions requiring further characterization, representing only 10% of the total number of pancreatic cyst patients we evaluate at our institution, and is bypassed in high-risk patients who are recommended for resection based on cross-sectional imaging alone, further narrowing our selected patient population to those with a low predicted malignancy risk.

In contrast to the relative low risk of high-grade dysplasia or carcinoma in patients followed within consensus guidelines, 14% of patients in this study who were followed outside of consensus guidelines (3/22) developed high-risk lesions. In a study of 35 patients with IPMNs who were followed outside of consensus criteria, Piciocchi et al. reported 8 patients (23%) who had subsequent death secondary to progression of disease at mean follow-up time of 32.5 months²⁷. As none of these patients underwent resection, the malignant nature of disease was inferred from either appearance of vascular invasion or metastatic disease on cross-sectional imaging. Kobayashi et al. reported findings of 53 BD-IPMNs also managed with serial surveillance outside of consensus guidelines²⁸. During median follow-up time of 42.4 months, 10 patients underwent resection for concerning radiographic changes and there was only one patient found to have high-grade dysplasia IPMN, and no incidences of invasive IPMN. While these studies are all limited to patients followed outside consensus guidelines, there are substantial differences in the presenting patient characteristics and lesion features of these populations. This is the most likely cause of the varied incidence of high-risk lesions between these two studies and the present study, in particular as these are all small study populations.

The development of carcinoma in the remnant pancreas after resection of an IPMN or in a region distinct from the IPMN in patients undergoing serial surveillance only emphasizes the “whole-gland” risk in these patients, and the need for sustained, long-term follow-up. Four of the 227 patients (1.8%) followed in this study developed invasive disease separate from the IPMN being followed. In an older series from our institution of 356 patients with radiographically and/or pathologically confirmed IPMNs, there were 10 cases (2.8%) of invasive disease that developed separate from the IPMN²⁶. These findings are consistent with reports from other institutions, with the incidence of invasive disease occurring in a region distinct from the IPMN ranging from .5–5.6%^{29–31}. While this highlights the importance of continued surveillance for this patient population, the incidence of recurrent or metachronous invasive disease was too low in our study population to develop specific recommendations on the appropriate length of time for continued surveillance.

Another interesting finding is the high false positive rate we found in the identification of mucinous cysts using cyst fluid CEA elevation. Prior studies have reported cyst fluid CEA

elevation as the most accurate test for the diagnosis of mucinous cysts of the pancreas, with sensitivity ranging from 60% to 81%, and specificity ranging from 65% to 98%^{10–13}. However, in the present study, 24% of patients with a cyst fluid CEA ≥ 192 ng/mL had pathologies other than mucinous cysts, such as retention cysts and pancreatic neuroendocrine tumors. Therefore the inclusion criteria utilized for this study, although better than imaging alone, continues to include additional non-mucinous entities. As a result, the reported risk of high-grade dysplasia and invasive carcinoma is lower than if our study was limited to IPMNs alone.

The main limitation of the study was the inclusion of only patients who had undergone EUS-FNA. As EUS-FNA is typically reserved for patients with borderline or questionable lesions that require additional work-up, this study inherently excludes many high-risk lesions that proceed directly to surgical resection without undergoing EUS-FNA, as well as patients with very small cysts for which EUS is not felt indicated. However, in constructing this uniquely selected study population, our study addresses the subset of patients with mucinous cysts that pose the greatest diagnostic and management dilemma to physicians. The extensive long-term follow-up of these patients also provides an accurate assessment of the true malignancy risk for those with both resected and unresected lesions.

Conclusion

In conclusion, this study proves a unique and comprehensive account of the natural history and disease progression of patients with presumed IPMNs. The serial surveillance of patients in accordance with consensus guidelines is safe and associated with a very low incidence of progression to a high-risk lesion. However, the risk of disease progression to high-grade dysplasia and/or invasive IPMN increases significantly when lesions are followed outside of consensus guideline recommendations. While this situation is at times unavoidable due to other patient factors and co-morbidities, this substantial increased risk of malignancy is important for clinicians to recognize and communicate when counseling patients in this situation.

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Figure 1.

Schema of 227 study patients, stratified by treatment and incidence of high-risk lesions.

IPMN indicates intraductal papillary neoplasm; CEA, carcinoembryonic antigen; HGD, high grade dysplasia

Table 1

Presenting patient demographics and cyst characteristics.

	All Patients N = 227	Immediate Resection N = 63	Initial Surveillance N = 164	p-value
Gender, Male	86 (38%)	20 (32%)	66 (40%)	.237
Age of diagnosis, years (range)	65 (29–85)	66 (33–85)	68 (29–85)	.332
Active tobacco use	13 (6%)	4 (6%)	9 (5%)	.803
Diabetes mellitus	46 (20%)	10 (16%)	36 (22%)	.308
Active concurrent malignancy	14 (6%)	0 (0%)	14 (9%)	.057
Presenting symptoms				.01
None	127 (56%)	24 (38%)	103 (63%)	
Abdominal pain	84 (37%)	33 (52%)	51 (21%)	
Pancreatitis	12 (5%)	4 (6%)	8 (5%)	
Jaundice	3 (1%)	1 (2%)	2 (1%)	
Elevated LFTs	1 (.4%)	1 (2%)	0	
FNA CEA level, ng/mL (range)	979 (192–300,000)	1424 (263–300,000)	813 (192–164,407)	.013
Cyst type				.021
MD	26 (11%)	9 (14%)	17 (10%)	
BD	190 (84%)	47 (75%)	143 (87%)	
Mixed	11 (5%)	7 (11%)	4 (2%)	
Cyst location				.643
Head/neck	69 (30%)	14 (22%)	55 (34%)	
Uncinate	23 (10%)	6 (10%)	17 (10%)	
Body	53 (23%)	18 (29%)	35 (21%)	
Tail	41 (18%)	13 (21%)	28 (17%)	
Diffuse	41 (18%)	12 (19%)	29 (18%)	
Maximum cyst diameter, cm (range)				
MD	2 (.4–8)	3 (.7–8)	1.8 (.4–4.1)	.148
BD	2 (.4–10.8)	2.9 (.68–8.9)	1.9 (.4–10.8)	<.001
Mixed	2.5 (.7–7.5)	2.6 (1.5–7.5)	2 (.7–3)	.164

LFTs indicates liver function tests; FNA, fine needle aspiration; CEA, carcinoembryonic antigen; MD, main duct; BD, branch duct

Table 2

Pathologic outcomes and long-term follow-up of all patients.

	Immediate Resection N = 63	Initial Surveillance N = 164
Maximum cyst diameter on pathology, cm (range)	2.5 (1–6)	2 (.3–23)
Highest dysplasia grade of IPMN		
Low	10 (16%)	7 (4%)
Intermediate	19 (30%)	20 (12%)
High	3 (5%)	3 (2%)
Invasive IPMN	5 (8%)	2 (1%)
Subsequent development of invasive IPMN/carcinoma during follow-up period	3 (5%)	1 (.6%)
Follow-up time since resection, months (range)	30 (1–150)	51 (0–152)
Follow-up time, months (range)	36 (6–151)	64 (6–171)

IPMN indicates intraductal papillary neoplasm.